DOCTORAL THESIS

SOCIAL AND PSYCHOLOGICAL DETERMINANTS OF THE MISUSE OF ANTIBIOTICS AND TRANQUILIZERS IN THE GALICIAN AND LEBANESE POPULATIONS

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INTERNATIONAL DOCTORAL SCHOOL OF UNIVERSITY OF SANTIAGO DE COMPOSTELA

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DECLARACIÓN DO AUTOR/A DA TESE

D./Dna. **Narmeen Mallah**

Título da tese: **SOCIAL AND PSYCHOLOGICAL DETERMINANTS OF THE MISUSE OF ANTIBIOTICS AND TRANQUILIZERS IN THE GALICIAN AND LEBANESE POPULATIONS**

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Author Contribution

Article: Mallah N, Rodríguez-Cano R, Figueiras A, Takkouche B. Design, reliability and construct validity of a Knowledge, Attitude and Practice questionnaire on personal use of antibiotics in Spain. Sci Rep. 2020;10(1):20668. doi: 10.1038/s41598-020-77769-6

Narmeen Mallah performed the literature review, designed the questionnaire, collected, analyzed, and interpreted the data, and conceived and wrote the manuscript

Article: Mallah N, Rodríguez-Cano R, Figueiras A, Takkouche B. Development and validation of a knowledge, attitude and practice questionnaire of personal use of tranquilizers. Drug Alcohol Depend. 2021;224:108730. doi: 10.1016/j.drugalcdep.2021.108730.

Narmeen Mallah carried out the literature review, designed the questionnaire, collected, analyzed, and interpreted the data, and conceived and wrote the manuscript.

Article: Mallah N, Badro DA, Figueiras A, Takkouche B. Association of knowledge and beliefs with the misuse of antibiotics in parents: A study in Beirut (Lebanon). PLoS One. 2020;15(7):e0232464. doi: 10.1371/journal.pone.0232464.

Narmeen Mallah: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, writing- original draft, and writing- review and editing.

Article: Mallah N, Figueiras A, Takkouche B. Comparison of Longitudinal and Cross-Sectional Approaches in Studies About Knowledge, Attitude, and Practices Related to Antibiotic Misuse. Drug Saf. 2021. doi: 10.1007/s40264-021-01075-x.

Narmeen Mallah carried out the literature review, formulated the research idea, collected, analyzed, and interpreted the data, and conceived and wrote the manuscript

Article: Mallah N, Badro DA, Figueiras A, Takkouche B. Association of knowledge and attitudes with the misuse of tranquilizers in parents: a study in Beirut (Lebanon). Psychol Health. 2021. doi: 10.1080/08870446.2021.1912341.

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Article: Mallah N, Figueiras A, Heidarian Miri H, Takkouche B. Association of knowledge and attitudes with practices of misuse of tranquilizers: A cohort study in Spain. Drug and Alcohol Dependence. 2021;225:108793. doi: 10.1016/j.drugalcdep.2021.108793

Narmeen Mallah conceived the research idea, designed the study, collected, analyzed, and interpreted the data, and designed and wrote the manuscript.

Article: Mallah N, Tohidinik HR, Etminan M, Figueiras A, Takkouche B. Prenatal Exposure to Macrolides and Risk of Congenital Malformations: A Meta-Analysis. Drug Saf. 2020;43(3):211-221. doi: 10.1007/s40264-019-00884-5.

Narmeen Mallah: Conceptualization of the manuscript, review and synthesis of the literature, and data extraction and analysis.

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[SOCIAL AND PSYCHOLOGICAL DETERMINANTS OF THE MISUSE OF ANTIBIOTICS AND TRANQUILIZERS IN THE GALICIAN AND LEBANESE POPULATIONS]

D. Bahi Takkouche.....
D. Adolfo Figueiras.....

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Que a presente tese, correspóndese co traballo realizado por Dna. Narmeen Mallah, baixo a miña dirección/titorización, e autorizo a súa presentación, considerando que reúne os requisitos esixidos no Regulamento de Estudos de Doutoramento da USC, e que como director desta non incorre nas causas de abstención establecidas na Lei 40/2015.

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En....., ... de ..... de 20...

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DEDICATION

أهدي هذه الأطروحة إلى قدوتي ومثلي الأعلى، والديّ، أحمد وفاطمة، الذين ضحوا من أجلي دائمًا، وثقوا في إمكاناتي ودعموني في كل مرحلة من حياتي، وعلّموني أن أصنع القوة من الضعف.

إمتناني العميق إلى خالتي إبتسام (رحمها الله)، التي ستعيش في داخلي إلى الأبد، على رعايتها لي في صغري. كما أعرب عن إمتناني لأشقائي، علي، نيفين ونور، ولخالي فيصل ولأجدادي، علي وجانيت (رحمها الله)، على حبّهم ودعمهم.

Dedico esta tesis a Erich, mi alma gemela y compañero en la vida, con mi profundo agradecimiento, por ser él y por su apoyo continuo durante los años de preparación de esta tesis.

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"There are no limits of what you can accomplish, except the limits you place on your own thinking"
Brian Tracy

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Resumo

A resistencia aos antibióticos e a *dependencia e a adicción aos tranquilizantes* son dous problemas internacionais de saúde pública derivados do mal uso de *antibióticos* e *tranquilizantes*. Os fármacos considéranse mal usados cando se toman sen prescrición médica ou cando se utilizan en base dunha prescrición, pero sen adhesión ás instrucións do médico en termos de tempo, dose e duración.

1. **Resistencia aos antibióticos: un desafío multifacético**

Hai máis de dúas décadas, a comunidade científica comezou a alertar contra a pandemia de resistencia aos antibióticos, é dicir, a capacidade das bacterias para derrotar aos antibióticos deseñados para eliminalas. A resistencia aos antibióticos ten graves consecuencias para a saúde pública. Socava as terapias avanzadas, aumenta a incidencia de infeccións e, en consecuencia, ameaza a vida dun gran número de persoas de todo o mundo e de todas as idades. A resistencia aos antibióticos tamén afecta o manexo clínico durante o embarazo. Debido á resistencia aos antibióticos, a penicilina xa non se recomenda para tratar a bacteriuria asintomática. Os macrólidos, antibióticos de amplo espectro, recéitanse con frecuencia, pero a literatura non proporciona evidencia clara e consistente sobre a súa asociación con malformacións conxénitas. A resistencia aos antibióticos tamén ten un impacto considerable na economía que segue crecendo con cifras inquietantes.

A resistencia aos antibióticos viuse agravada en gran medida por prácticas como o mal uso de antibióticos. Só o 62% da poboación mundial informou que se adheriu ao réxime prescrito de antibióticos e o 29% declarou usar os restos de antibióticos non utilizados. O uso de antibióticos sen receita prodúcese en países con e sen lexislacións de antibióticos como España e Líbano, respectivamente, a pesar da diverxencia na estrutura dos sistemas sanitarios nestes países.

O mal uso de antibióticos asociouse con propiedades socioeconómicas como a idade (adultos-novos e anciáns> 65 anos), o sexo feminino e o difícil acceso á atención sanitaria. A literatura sobre a asociación da educación e os ingresos co mal uso de antibióticos mostrou resultados contraditorios. As prácticas do mal uso de antibióticos asociáronse con características psicosociais como ***Coñecementos*** e ***Actitudes***. O uso de antibióticos para pacientes ambulatorios varía amplamente entre países e suxeriuse que os determinantes culturais inflúen nas prácticas do uso destes medicamentos.

En ***Galicia*** e ***Líbano***, onde levou a cabo o presente proxecto de doutoramento, parece que **ningún** estudo previo avaliou a asociación de ***Coñecementos*** e ***Actitudes*** con ***Prácticas*** de mal uso de antibióticos a través de medidas de efecto.

2. **O mal uso de tranquilizantes, un problema de saúde pública cun crecemento exponencial pero que non está recoñecido o suficiente**

Os tranquilizantes utilízanse amplamente para reducir a ansiedade, a dor, a tensión e a axitación, relaxar os músculos, acougar ou sedar e durmir mellor. O uso de tranquilizantes é seguro e ben tolerado, pero pode afectar negativamente o sistema nervioso central e provocar dependencia, especialmente cando estes medicamentos se mal utilizan ou se consomen en doses altas. Os tranquilizantes, especialmente as benzodiazepinas, atópanse entre as drogas psicoactivas co máis alto índice de mal uso e cunha maior prevalencia de uso entre as mulleres que os homes. Son as segundas drogas máis incautadas despois dos opioides. As fontes dos tranquilizantes mal utilizados son a prescrición médica e os círculos sociais.

O uso simultáneo dos tranquilizantes con outras drogas ilícitas é un problema internacional destacado que está asociado cunha pesada carga para a saúde pública, a sociedade e a economía. O mal uso de tranquilizantes empeora a calidade de vida, complica o manexo de enfermidades comórbidas, aumenta a taxa de accidentes de tráfico e, en consecuencia, atribúese ao incremento das taxas de morbilidad e mortalidade.

En Europa, o mal uso de tranquilizantes segue unha tendencia ascendente e é máis frecuente que o do cannabis. España ocupa o primeiro lugar entre os países europeos no mal uso de tranquilizantes cunha prevalencia do 9% para o ano anterior e do 18% para o mal uso para sempre. En xeral, o consumo de tranquilizantes incrementouse en España na última década.

No Líbano, os tranquilizantes son as drogas medicinais que máis se consomen entre os estudantes de secundaria e universitarios, segundo os datos recompilados entre 1999 e 2001. Ao redor do 13% dos estudantes universitarios e o 3% dos estudantes das escolas informaron haber mal usado tranquilizantes e declararon que o acceso a estes medicamentos era fácil. Parece que non se realizaron outros estudos no país.

Os determinantes do mal uso de tranquilizantes non foron estudados suficientemente. Só uns poucos estudos examinaron a asociación de atributos sociodemográficos e psiquiátricos co mal uso de tranquilizantes. Os factores identificados incluíron a idade (adolescentes e adultos novos), o sexo feminino, o baixo nivel educativo, o desemprego, a inxesta de alcol, o tabaquismo, o uso de drogas ilícitas, a prescrición de tranquilizantes, a insatisfacción coas relacións, a presenza de enfermidades crónicas, a non percepción de risco destes fármacos e trastornos psiquiátricos.

A asociación do *Coñecementos* dos individuos e as súas *Actitudes* cara ás *Prácticas* de mal uso de tranquilizantes ***non se investigou anteriormente***.

3. Modelo de cuestionario de *Coñecementos, Actitudes* e *Prácticas* (CAP)

Os cuestionarios de modelo CAP aplícanse en gran medida na avaliación das propiedades psicosociais dunha ampla variedade de problemas relacionados coa saúde, como o mal uso de antibióticos. Os cuestionarios CAP consisten nunha serie de declaracións (ítems) que están deseñadas para recompilar información sobre o que a poboación sabe (é dicir, *Coñecementos*) e o que a poboación pensa (é dicir, *Actitudes*) sobre un tema específico. Os cuestionarios modelo CAP tamén implican un conxunto de preguntas sobre o desempeño dos enquisados cara ao tema estudado (é dicir, *Prácticas*). As conclusións obtidas dos estudos baseados en CAP poden axudar a determinar a necesidade de programas de intervención educativa, deseñar as intervencións e avaliar a súa eficiencia.

Ata a presente tese **non se dispoñía** de cuestionarios validados para medir o uso de antibióticos e / ou tranquilizantes. Na bibliografía atópanse dispoñibles moitos cuestionarios CAP sobre o uso de antibióticos por parte da poboación adulta en xeral. Con todo, ningún destes cuestionarios someteuse a un proceso de validación completo.

4. Obxectivos

Obxectivos principais:

a) Desenvolver e validar instrumentos en diferentes linguaxes e escenarios sobre a asociación de *Coñecementos* e *Actitudes* con *Prácticas* de mal uso de antibióticos e tranquilizantes.
b) Estudar os determinantes psicosociais e sociodemográficos do mal uso de antibióticos e tranquilizantes en ***Galicia*** e ***Líbano***.
c) Determinar as consecuencias do consumo de tipos específicos de antibióticos na saúde.

Obxectivos específicos

a) Desenvolver e validar un cuestionario CAP en galego, francés e árabe sobre o uso de antibióticos e tranquilizantes.
b) Estudar a asociación de *Coñecementos* e *Actitudes* con *Prácticas* de mal uso de antibióticos e tranquilizantes en Galicia e Líbano.
c) Verificar se os enfoques transversais producen resultados similares aos de estudos lonxitudinais sobre a asociación de *Coñecementos* e *Actitudes* con prácticas de uso indebido de antibióticos e tranquilizantes.
d) Resumir mediante un metaanálise de dose-resposta a asociación entre educación e ingresos co uso indebido de antibióticos.
e) Determinar mediante un metaaanálise se a exposición prenatal a macrólidos é un determinante de malformación conxénita.

5. Métodos e resultados

Poboación e contorna

Este traballo involucrou varios estudos que levaron a cabo en ***Galicia*** e ***Líbano***. Foi aprobado polo comité de ética correspondente e as autoridades de ambas as contornas.

No Líbano, a poboación de estudo consistiu en adultos (> 18 anos), pais de escolares. O árabe é o idioma nativo e oficial do Líbano. O francés considérase o segundo idioma do país. Os pais dos nenos matriculados nas escolas participantes recibiron unha copia impresa do cuestionario no idioma elixido pola escola (árabe ou francés). Os pais recibiron instrucións de que o cuestionario debe ser respondido só por un dos pais, é dicir, a nai ou o pai. Os cuestionarios recolléronse despois de cinco días.

En España, a poboación principal estivo constituída por adultos que acudían a consultas de atención primaria cun familiar no Complexo Hospitalario Universitario de Santiago de Compostela. O estudo foi presentado polo autor deste traballo a cada visitante adulto das clínicas de atención primaria pediátrica do Hospital. As persoas que aceptaron participar no estudo asinaron un formulario de consentimento. O cuestionario foi autocompletado. Recolleuse de novo nun sobre pechado, inmediatamente despois da súa finalización.

Desenvolvemento e validación de seis cuestionarios de Coñecementos, Actitudes e Prácticas (CAP) sobre antibióticos e tranquilizantes

Métodos

Seis cuestionarios modelo CAP foron desenvoltos e validados; CAP sobre antibióticos en galego, árabe e francés (3 cuestionarios), e CAP sobre tranquilizantes nos mesmos tres idiomas (3 cuestionarios). Os cuestionarios en galego validáronse en Galicia en 2019, mentres que os de árabe e francés validáronse en Líbano no mesmo ano. Cada un dos seis cuestionarios foi validado na súa totalidade.

Xeramos os ítems dos cuestionarios despois dunha revisión exhaustiva da literatura e sesións de grupos focales. Logo avaliamos a validez aparente e de contido, e probamos os cuestionarios de maneira piloto. Examinamos a fiabilidade de cada cuestionario mediante análise test-retest (tamaño da mostra (N) para o galego= 145, o árabe= 60 e o francés= 31). Distribuímos os cuestionarios a 879 persoas en Galicia e a 1421 adultos (N= 375 para o árabe e 1046 para o francés) no Líbano, probamos a validez de constructo a través da Análise Factorial Confirmatoria (AFC), medimos a súa confiabilidad xeral e determinamos a súa aceptabilidade.

Resultados

Para cada un dos seis cuestionarios, o índice de validez de contido do ítem (I- CVI) e a estatística Kappa modificada (K*) confirmaron a validez de contido das preguntas (0,78≤ I- CVI ≤1,00 e 0,78≤ K* ≤1,00). O estatístico S-CVI mostrou a validez de contido da escala (S- CVI / Ave ≥ 0,95). Despois da validez aparente e a proba piloto, a confiabilidad *Test- Retest* confirmou a confiabilidad das preguntas (coeficiente de correlación intraclase> 0.4). Realizamos AFC utilizando cargas cruzadas e índices de modificación para elixir o modelo máis adecuado nos datos recollidos de cada poboación. Estimamos os indicadores de axuste do modelo e demostramos que os modelos seleccionados teñen un axuste de bo a excelente, establecendo así a validez de constructo. Non se puido realizar a análise AFC para os cuestionarios en árabe debido á presenza de preguntas sen contestar que afectaron a estrutura dos datos recompilados. As versións finais dos cuestionarios en galego e francés foron moi aceptadas pola poboación adulta en Galicia e Líbano, como o reflicte a alta taxa de resposta (≥95%) e a baixa porcentaxe de preguntas sen resposta (0,1% -4,4%).

Asociación de Coñecementos e Actitudes con Prácticas do mal uso de antibióticos e tranquilizantes: catro estudos en Galicia e Líbano

Métodos

Utilizamos os cuestionarios validados para medir a asociación entre coñecementos e actitudes con prácticas do mal uso de antibióticos e tranquilizantes. Realizamos dous estudos transversais en Líbano (N= 1421) e dous estudos de cohortes en Galicia (N= 879) sobre o mal uso de cada un dos dous fármacos. A exposición definiuse como baixo nivel de *Coñecemento, Actitudes* médicamente inadecuadas cara aos antibióticos ou tranquilizantes, ou *Actitudes* negativas cara ao médico. Avaliáronse seis *desenlaces* de *Prácticas* de uso indebido: uso non prescrito, tratamento acurtado, sobras almacenadas, doses esquecidas duplicadas ou tomadas cando se lembran, dose modificada sen recomendación médica e un resultado composto: "calquera tipo de mal uso". As asociacións de *Coñecementos* e *Actitudes* co mal uso de antibióticos se modelaron utilizando regresión loxística múltiple para estudos transversais e modelos de regresión de Poisson e modelos mixtos lineais xeneralizados (GLMM) para estudos de cohortes.

Realizamos análise de sensibilidade para os estudos de cohortes. O axuste por posibles factores de confusión levou a cabo utilizando o método de cambio na estimación. Comparáronse os resultados dos enfoques transversais e de cohorte utilizando datos recompilados en Galicia dos mesmos individuos para verificar a utilidade dos enfoques transversais nos estudos CAP sobre antibióticos e tranquilizantes.

Resultados

Estudo transversal no Líbano sobre o mal uso de antibióticos: 277 participantes (16%) recoñeceron usar antibióticos no mes anterior, o 41% dos cales mostrou polo menos un comportamento de mal uso. A falta de *Coñecemento* e as *Actitudes* médicamente inadecuadas cara aos antibióticos aumentaron substancialmente as probabilidades do seu mal uso. Por exemplo, os participantes que pensaban que os antibióticos eran eficaces no tratamento contra o virus, arrefriados ou dor de garganta tiñan o dobre de probabilidades de mal usar os antibióticos [*Odds Ratio* intercuartil axustada (aIqOR): 2,08 (intervalos de confianza (IC) 95% IC: 1,32-3,19), aIqOR: 1,81 (95% IC: 1,41-2,29), aIqOR: 2,19 (95% IC: 1,61-2,93), respectivamente]. Os pais que manteñen antibióticos en casa para probable uso no futuro tiñan máis probabilidades de mal utilizar os antibióticos [aIqOR: 2,44 (95% IC: 1,68-3,46)].

Estudo transversal no Líbano sobre o mal uso de tranquilizantes: 63 (62,2%) de 91 pais que usaron tranquilizantes informaron polo menos un patrón de mal uso. Observáronse maiores probabilidades de "calquera mal uso" entre os pais que informaron que tomaban tranquilizantes para durmir mellor, para divertirse coas súas familias ou para traballar mellor [2,35 ≤aIqOR≤ 1,99]. O almacenamento de tranquilizantes para necesidades futuras asociouse fortemente co mal uso [aIqOR: 5,00 (95% IC: 3,30-7,59)]. Unha maior conciencia sobre os perigos dos tranquilizantes e a importancia do cumprimento terapéutico asociouse con menores probabilidades de patróns específicos de mal uso (0,50 ≤ aIqOR ≤ 0,72).

Estudo de cohorte en Galicia sobre mal uso de antibióticos: 747 adultos completaron o cuestionario basal e o de seguimento. Na análise transversal, 78 participantes mal utilizaron os antibióticos e observáronse fortes asociacións entre o acordo con varias declaracións de *Coñecementos* e *Actitudes* e as *Prácticas* do mal uso de antibióticos, con OR que oscilaron entre 1,94 e 5,66. Na análise de datos lonxitudinal mediante regresión de Poisson, detectáronse 46 eventos de mal uso de antibióticos. Non se observaron asociacións entre os *Coñecementos*, as *Actitudes* e as *Prácticas* de uso indebido, excepto por dúas afirmacións sobre a preferencia de almacenar antibióticos [índice de taxa de incidencia axustado (aIRR): 2,33 (95% IC: 1,20, 4,54)] e tomar antibióticos cando se arrefría [aIRR: 2,28 (95% IC: 1,24- 4,21)]. A magnitude destas asociacións foi menor que a observada na análise transversal. Os resultados da análise GLMM foron similares aos obtidos pola regresión de Poisson.

Estudo de cohorte en Galicia sobre o mal uso de tranquilizantes: as *Actitudes* persoais dos individuos cara aos tranquilizantes e médicos están fortemente asociadas co resultado "calquera mal uso" destes medicamentos. Estas *Actitudes* inclúen: a aceptación dos individuos de tomar tranquilizantes para mellorar o soño [aIRR: 5.10 (95% CI: 2.74-9.48)], para traballar mellor [aIRR: 2.04 (95% CI: 1.05-3.99)], ou con fins recreativos [aIRR: 1,85 (95% IC: 1,04-3,32)]; vontade de prolongar o curso do tratamento con tranquilizantes sen consulta médica [aIRR: 2,45 (95%IC: 1,46-4,13)]; aceptar o almacenamento de tranquilizantes para unha posible necesidade futura [aIRR: 5,07 (95% IC: 2,73-9,40)]; e desconfiar da decisión do médico sobre a prescrición de tranquilizantes [aIRR: 1,92 (95%IC: 1,12-3,30)]. O nivel de coñecemento asóciase marxinalmente co uso indebido de tranquilizantes. Hai diferenzas entre os enfoques

transversal e lonxitudinal. Só o enfoque lonxitudinal mostrou que o baixo nivel de *Coñecemento* sobre o efecto dos tranquilizantes sobre o comportamento [aOR: 3,24 (95% IC: 1,12-9,38)] e sobre o efecto negativo do seu consumo excesivo [aOR: 4,12 (95% CI: 1.5-11.33)] están asociados coa *Práctica* "almacenar / compartir tranquilizantes". Tanto as análises transversais como os lonxitudinais indicaron que as *Actitudes* persoais cara aos tranquilizantes e as *Actitudes* cara aos médicos están asociadas co mal uso de tranquilizantes, pero con diferentes graos de asociación. Tamén se observaron discrepancias entre os dous enfoques para tipos individuais de uso indebido.

Metaanálise de dose-resposta dos determinantes socioeconómicos do mal uso de antibióticos

Esta parte da tese levou a cabo durante unha estancia de tres meses no Department of Global Public Health, Karolinska Institutet, Estocolmo, Suecia. Levaron a cabo dúas revisións sistemáticas e metaanálises de doses-resposta para cuantificar a asociación do nivel de ingresos e o nivel educativo coas prácticas do mal uso de antibióticos.

Métodos

Identificamos os estudos pertinentes mediante unha procura nas bases de datos e a revisión manual das listas de referencias dos artigos seleccionados e os informes de revisión relacionados ao tema. Realizamos dous metaanálises de dose-resposta sobre a asociación de ingresos e de educación co mal uso de antibióticos. Presentamos enfoques continuos e categóricos do metaanálise de dose-resposta. Os ORs agrupados e os seus IC do 95% calculáronse mediante un modelo de efectos aleatorios.

Resultados

Metaanálise de dose-resposta de ingresos e mal uso de antibióticos: incluíronse 51 estudos de 22 países de diferentes clases económicas. En xeral, os datos están de acordo cunha asociación lineal plana entre os ingresos estandarizados segundo os indicadores socioeconómicos e o mal uso de antibióticos (OR por incremento de 1 unidade= 1,00, valor de p= 0,954, valor de p da non linealidad= 0,429). Os datos son compatibles con ningunha asociación entre niveis de ingresos medios e altos co mal uso de antibióticos en xeral [OR: 1,04 (95% IC: 0,89-1,20) e OR: 1,03 (95% IC: 0,82-1,29)]. Os ingresos medios asócianse cun 19% máis de probabilidades de almacenamento de antibióticos [OR: 1,19 (95% IC: 1,07-1,32)] e un 18% máis de probabilidades de calquera aspecto de mal uso de antibióticos nos estudos procedente de África [OR= 1,18 (95% IC: 1,00-1,39)]. Os ingresos altos asócianse cun 51% menos de probabilidades de non adherencia ao réxime de tratamento con antibióticos [OR: 0,49 (95% IC: 0,34-0,60)]. Os ingresos altos tamén se asocian cun 11% máis de probabilidades de calquera práctica de mal uso de antibióticos nos países de nivel de riqueza media-alta [OR: 1,11 (95% IC: 1,00-1,22)].

Metaanálise de dose-resposta de educación e mal uso de antibióticos: incluíronse 85 estudos de 42 países de diferentes niveis socioeconómicos. En comparación coa educación baixa (≤9 anos), a educación media (> 9-12 anos) asóciase cun 20% menos de probabilidades de mal uso de antibióticos nos países de ingresos altos [OR: 0,80 (95% IC: 0,66-0,97)], mentres que a educación superior (> 12 anos) asóciase cun 14% menos de probabilidades de calquera aspecto de mal uso de antibióticos [OR: 0,86 (95% IC: 0,72-1,03)]. A asociación é máis pronunciada en Oriente Medio [OR: 0,64 (95% IC: 0,42-1,00)] e países de economías medias baixas [OR: 0,67 (95% IC: 0,41-1,11)]. Á inversa, en Europa, a educación superior asóciase cun 25% máis de probabilidades de mal uso de antibióticos [OR: 1,25 (95% IC: 1,00-1,58)]. O incremento de

cada ano de educación asóciase cun 4% menos de probabilidades de calquera aspecto do mal uso de antibióticos nos países de nivel de riqueza media-baixa [OR: 0,96 (95% IC: 0,92-1,00)] e en Oriente Medio [OR: 0,96 (95% IC: 0,93, 1,00)]. Pola contra, asóciase cun 3% máis de probabilidades de almacenamento de antibióticos, un tipo específico de mal uso [OR: 1,03 (95% IC: 1,01-1,06)].

Metaanálise da asociación de macrólidos con malformacións conxénitas

Métodos

Realizáronse procuras en MEDLINE, EMBASE e outras bases de datos ata xuño de 2019. Avaliouse a calidade dos estudos e verificouse a heteroxeneidade e o rumbo de publicación. Realizamos tres análises diferentes e comparamos o efecto dos macrólidos con cada unha das seguintes poboacións non expostas: Grupo 1: fetos non expostos a ningún medicamento antes do nacemento, Grupo 2: fetos expostos a antibióticos non macrólidos / non teratógenos, e Grupo 3: poboación mixta do primeiro e dos segundo grupos de comparación.

Resultados

Observouse unha asociación débil entre os macrólidos e as malformacións conxénitas de calquera tipo cando se compararon os macrólidos coa poboación mixta [OR_{grupo3}: 1,06 (95% IC: 1,01-1,10)]. A análise de subgrupos mostra que esta asociación débil limítase á exposición do feto no primeiro trimestre do embarazo [OR: 1,06 (95% IC: 1,01-1,11)] e aos estudos de cohortes [OR: 1,07 (95% IC: 1,02-1,13). Atopouse que as malformacións do sistema dixestivo están levemente asociadas coa exposición prenatal a macrólidos [OR_{grupo3}: 1,14 (95% IC: 1,02, 1,26)]. Tamén se atopou que o sistema musculoesquelético está potencialmente afectado [OR_{grupo3}: 1,21 (95% IC: 1,08-1,35) e OR_{grupo3}: 1,15 (95% IC: 1,05-1,26)]. Os estudos europeos mostran unha asociación lixeiramente máis forte que os estudos estadounidenses nestas dúas comparacións.

6. Conclusions

1. Os instrumentos validados para medir a asociación de *Coñecementos* e *Actitudes* con *Prácticas* de mal uso de antibióticos e tranquilizantes xa están dispoñibles por primeira vez.
2. Os cuestionarios foron validados en tres idiomas: galego, árabe e francés, e probados en dous contextos socioeconómicos diferentes: Galicia e Líbano. Os cuestionarios foron moi aceptados pola poboación galega e libanesa.
3. O nivel baixo de *Coñecemento* e os conceptos erróneos sobre o papel dos antibióticos e os perigos dos tranquilizantes están asociados co *Prácticas* de mal uso destes medicamentos.
4. As *Actitudes* médicamente inadecuadas, incluída a tendencia para reducir ou estender a duración do tratamento doutro xeito que a prescrita, a tendencia de obter antibióticos e tranquilizantes sen receita e a aceptación de usar tranquilizantes para mellorar o soño, o traballo ou o estado de ánimo, asócianse con maiores probabilidades de *Prácticas* de mal uso de antibióticos e tranquilizantes.
5. As *Actitudes* negativas cara ao médico asócianse con maiores probabilidades de *Prácticas* de uso indebido de antibióticos e tranquilizantes.
6. A dispoñibilidade e accesibilidade aos medicamentos identificáronse como factores de risco do mal uso de medicamentos

7. O mal uso de antibióticos e tranquilizantes prodúcese en contornas sen un sistema sanitario centralizado, como no Líbano, así como en contornas con sistemas centralizados como Galicia.
8. Os enfoques transversais e lonxitudinais lanzan resultados distintos con respecto á asociación de *Coñecementos* e *Actitudes* con *Prácticas* de mal uso de antibióticos e tranquilizantes. Ningún está libre de rumbos e os resultados de ambos os enfoques deben analizarse coidadosamente para obter conclusións sólidas nos estudos CAP.
9. O metaanálise de dose-resposta revelou que o uso indebido de antibióticos ocorre por todas as persoas independentemente do seu nivel de ingresos e o seu nivel de educación.
10. Un metaanálise mostrou unha asociación marxinal entre a exposición prenatal a macrólidos e a malformación conxénita. Necesítase unha investigación de risco-beneficio para abordar a cuestión de se a prescrición de macrólidos debe restrinxirse durante o embarazo.

Abstract

The misuse of antibiotics and tranquilizers contributes to the development and exacerbation of antibiotic resistance, and dependence and addiction to tranquilizers, two international public health problems with heavy burdens. Antibiotic resistance has long been recognized as a global problem, yet fully validated tools to measure the psychosocial determinants, i.e., *Knowledge Attitudes*, and *Practices* of antibiotic misuse are unavailable. Furthermore, no longitudinal epidemiologic studies have been carried out so far. Dependence on tranquilizers is associated with alarming public health indicators, nonetheless related investigation has been limited to sociodemographic and psychiatric determinants. Drugs are deemed misused when taken without medical prescription or with medical advice but without adherence to the treatment regimen in terms of timing, dosage, and duration.

The present doctoral project aimed at uncovering the psychosocial and socioeconomic determinants of antibiotic and tranquilizer misuse. The project was carried out in Galicia and Lebanon and involved three stages: **1)** Development and validation of questionnaires on *Knowledge*, *Attitudes* and *Practices* (KAP) of antibiotic and tranquilizer misuse in Galician, Arabic and French; **2)** Application of the validated questionnaires in Galicia and Lebanon in various epidemiological studies to determine the association of *Knowledge* and *Attitudes* with *Practices* of antibiotic and tranquilizer misuse. This stage also encompassed comparison of findings from cross-sectional and longitudinal approaches related to KAP studies, using data collected from the same individuals, in order to assess and discuss biases associated with each design; and **3) a:** Dose-response meta-analyses to summarize inconsistent findings in the literature about the association of income level and education level with antibiotic misuse. **b:** Meta-analysis on *prenatal* exposure to macrolide antibiotics as a possible determinant of congenital malformation.

For the first time, the present doctoral project provided validated KAP instruments in three languages to be used in studies of antibiotic and tranquilizer misuse. These instruments are the backbone for assessing, designing, and evaluating prevention programs to improve the rationale use of these drugs. This doctoral project also uncovered culture-specific misconceptions and *Attitudes* towards these drugs in two settings, Galicia and Lebanon, with different socioeconomic characteristics and public health systems. Inconsistencies about the association of income and education with antibiotic misuse were also resolved. Understanding the psychosocial and socioeconomic determinants of antibiotic and tranquilizer misuse is crucial to control the progression of antibiotic resistance and tranquilizer dependence.

Keywords: Arabic; antibiotics; antibiotic resistance, cohort study; cross-sectional study; dependence; dose-response; French; Galicia; Galician; knowledge-attitude-practice; Lebanon; meta-analysis; misuse; questionnaire; tranquilizers; validation

SCIENTIFIC PRODUCTION OF THE THESIS

Thirteen articles have been derived from the present Doctoral Dissertation.

Seven articles have already been accepted for publication: 6 in journals of the first quartile of the JCR Ranking and one in the second quartile, due to the downranking of the journal between submission and publication of the article.
Three articles are currently under review by first quartile ranking journals.
Three articles are being prepared for their submission in the next few days.

1. **Mallah N**, Rodríguez-Cano R, Figueiras A, Takkouche B. Development and validation of a knowledge, attitude and practice questionnaire of personal use of tranquilizers. Drug and Alcohol Dependence 2021:108730 (**first JCR quartile)**

2. **Mallah N**, Figueiras A, Heidarian Miri H, Takkouche B. Association of knowledge and attitudes with practices of misuse of tranquilizers: A cohort study in Spain. Drug and Alcohol Dependence 2021 (in print) (**first JCR quartile)**

3. **Mallah N**, Badro DA, Figueiras A, Takkouche B. Association of knowledge and attitudes with the misuse of tranquilizers in parents: A study in Beirut (Lebanon). Psychology and Health 2021 (in print) (**first JCR quartile)**

4. **Mallah N**, Figueiras A, Takkouche B. Comparison of longitudinal and cross-sectional approaches in studies about knowledge, attitude and practices related to antibiotic misuse. Drug Safety 2021 (in print) (**first JCR quartile)**

5. **Mallah N**, Rodríguez-Cano R, Figueiras A, Takkouche B. Design, reliability and construct validity of a knowledge, attitude and practice questionnaire on personal use of antibiotics in Spain. Scientific Reports 2020, 10(1):20668. (**first JCR quartile)**

6. **Mallah N**, Tohidinik T, Etminan M, Figueiras A, Takkouche B. Prenatal exposure to macrolides and risk of congenital malformations: A meta-analysis. Drug Safety 2020, 43(3), 211-221. (**first JCR quartile)**

7. **Mallah N**, Badro DA, Figueiras A, Takkouche B. Association of knowledge and beliefs with the misuse of antibiotics in parents: A study in Beirut (Lebanon). Plos One 2020, 15(7): e0232464. (**second JCR quartile)**

8. **Mallah N,** Orsini N, Figueiras A, Takkouche B. Income level and antibiotic misuse: A systematic review and dose-response meta-analysis. (Manuscript under review by European Journal of Health Economics, **first JCR quartile**)

9. **Mallah N,** Orsini N, Figueiras A, Takkouche B. Education level and misuse of antibiotics. A systematic review and dose-response meta-analysis. (Manuscript under review by Antimicrobial Resistance and Infection Control, **first JCR quartile**)

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11. **Mallah N**, Rodríguez-Cano R, Badro DA, Figueiras A, Takkouche B. Development and validation of a knowledge, attitude and practice questionnaire on misuse of antibiotics in French language in Lebanon. (Manuscript under preparation for submission to International Journal of Antimicrobial Agents, **first JCR quartile**)

12. **Mallah N**, Rodríguez-Cano R, Badro DA, Figueiras A, Takkouche B. Development and validation of a knowledge, attitude and practice questionnaire on misuse of tranquilizers in French language in Lebanon. (Manuscript under preparation for submission to Journal of Clinical Medicine, **first JCR quartile**)

13. **Mallah N**, Figueiras A, Takkouche B. Epidemiology of antibiotic and tranquilizer misuse: a review of the evidence. (Manuscript under preparation for submission to Drug Safety, **first JCR quartile**)

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1. INTRODUCTION

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Introduction

Self-medication, as defined by the World Health Organization (WHO), is the use of medicinal products like vitamins and dietary supplements and of over-the-counter drugs to treat self-diagnosed disorders [1]. Responsible self-medication in a safe and proper way as recommended by a physician for a recurrent disorder or symptom currently represents an area in the management of minor diseases. *Practices* of self-medication can be associated with health risks due to side effects, drug interactions caused by polypharmacy and the simultaneous use of prescription drugs, as well as the intake of products at an inappropriate dosage and for an inadequate duration [2, 3].

Since terms such as self-medication or ***misuse*** of medicine by the patient are interchangeably used in the literature to refer to self-treatment with over-the-counter drugs or with prescription drugs without medical prescription, to avoid any ambiguity, in this document the term ***misuse*** will be used to refer to:

"the use of medicines requiring prescription without medical advice or the use of medicines prescribed by the physician but without compliance with the physician's instructions in terms of timing, dosage and duration" [4, 5].

Serious public health issues have been derived from the ***misuse*** of medicines [6]. Each misused medicine is associated with specific health consequences. This doctoral thesis will cover the ***misuse*** of the two drugs: ***antibiotics*** and ***tranquilizers***.

1.1. Antibiotic resistance: a multifaceted challenge

Historically, infectious diseases have been among the main contributors to morbidity and mortality, where in 1900 they ranked among the top ten leading causes of death and accounted for one-third of the deaths in the United States [7]. The discovery of penicillin by Alexander Fleming in 1928 and the subsequent discovery and introduction of other classes of antibiotics played a key role in substantially reducing the rate of mortality attributed to once fatal infections [7]. Antibiotics are currently among the most prescribed medicines worldwide [8], and they have become indispensable in basic and advanced medicine [9, 10].

With time, bacteria develop the ability to defeat antibiotics designed to kill them; a phenomenon known as *antibiotic resistance*. In 2004, it was estimated that, at least, 70% of the pathogenic bacteria are resistant to at least one drug [11]. This renders antibiotic treatment ineffective, undermines advanced therapies, increases the incidence of infections, and consequently threatens the lives of a large number of individuals from all over the world and at all ages.

Public health impact

More than two decades ago, the scientific community started to alert against the pandemic of *antibiotic resistance* [12]. The problem has been continuously growing around the world until it reached epidemic levels [13]. Currently, in 2021, antibiotic resistance causes at least 700,000 annual deaths worldwide [14]. Each year, in the United States, 2.8 million individuals get infected by antibiotic-resistant bacteria and more than 35,000 deaths occur as a direct cause [15]. The records are also high in Europe with 670,000 antibiotic-resistant infections and 33,000 directly attributable deaths, annually [16]. There is a shortage of surveillance about antibiotic-

resistant infections in developing countries, nonetheless it was reported that these infections are associated with a three-fold increase in the risk of death [17].

By 2050, it is estimated that the annual mortality rate from *antibiotic resistance* will reach 10 million deaths, exceeding that of cancer (8.2 million) and other major causes of death like diabetes (1.5 million), diarrhoeal disease (1.4 million), and road traffic accidents (1.2 million) [14].

Clinical impact

Antibiotic resistance sabotages decades of efforts to control infectious diseases of major concern like tuberculosis and malaria. Among the 700,000 people who die worldwide annually because of antibiotic-resistant infections, 230,000 die from multidrug-resistant tuberculosis [14]. The health burden of these infections in Europe is comparable to that of influenza, tuberculosis and human immunodeficiency virus (HIV/AIDS) combined [16]. In other countries where *antibiotic resistance* and infectious diseases are highly prevalent, the attributable mortality rates are even higher [9].

Antibiotic resistance compromises effective therapies, and the declining effectiveness of antibiotics has been recognized worldwide, though the associated impact might vary between countries [9]. Initial therapies might fail to treat an infection if the infecting bacteria are resistant to the chosen drug, and the application of a more effective therapy in the later stages might be limited or not available [18]. High-income countries are overcoming the decreased effectiveness of first-line antibiotics by using more expensive second- and third-line drugs [9]. Nonetheless, in low-income or lower-middle-income countries with limited resources and access to second- or third-line drugs, resistance to one or more first-line drugs would imply the inexistence of an effective therapy [9, 18].

The number of antibiotics in the research and development pipeline is decreasing because of challenges related to the time needed to obtain market approvals, elevated cost of clinical trials and diminished profits of pharmaceutical companies due to drug-resistance [10, 19]. Some antibiotics have been particularly scrutinized because they have been associated with disorders such as cardiac events and liver damage [19].

Limited access to antibiotics will increase again the mortality from treatable infectious diseases. In 2013, 6.3 million children younger than 5 years of age died of treatable and preventable infections [20]. It is estimated that in the same age category, only 27.5 million out of 40.4 million febrile episodes caused by common bacterial pathogens are treated with antibiotics, leaving behind 12.9 untreated children [9].

Socio-economic impact

Antibiotic resistance has a considerable impact on the economy that continues to grow with disturbing figures. United States health system is spending annually between 21 and 34 billion dollars because of antibiotic-resistant pathogens, in addition to 8 million extra hospital days [21]. In Europe, 1.5 billion euros are spent annually due to antibiotic-resistant infections and 2.7 million extra hospital days were registered in 2007 [22].

The impact of *antibiotic resistance* is not limited to health care expenditures. It also entails declining in employment rate, productivity, and income. The World Bank projects a shortfall of at least one trillion dollars in the global Growth Domestic Product after 2030, and a force up of 24.1 million individuals into extreme poverty, with low-income countries being the most affected [14, 23]. As a result, the Sustainable Development Goals set for 2030 such as ending hunger and poverty would be difficult to achieve [23]. By 2050, the losses provoked by *antibiotic resistance* will be as large as that of the 2008–2009 global financial crisis [23].

1.1.2. Determinants of antibiotic resistance

Although it is a natural phenomenon, the expansion of antibiotic-resistant bacteria has been greatly exacerbated by *Practices* such as the misuse of antibiotics, insufficient to poor public *Knowledge* about antibiotic resistance, poor quality medicines, shortage of resources including testing laboratories and research facilities, lack of effective policies to reduce infection rates and absence of standard guidelines to regulate the prescription and dispensing of antibiotics [13].

Throughout the present thesis, we focused on the determinants of ***antibiotic misuse*** by the general population.

1.1.3. Prevalence of antibiotic misuse

Worldwide, nonadherence to antibiotic therapy is highly prevalent, and only 62% of the global population reported adherence to the antibiotic treatment regimen and 29% reported using antibiotic leftover according to a meta-analysis published in 2005 [24]. Though antibiotic use without prescription is taking place worldwide, 19 to 100% of the unprescribed use takes place outside North America and North Europe [25].

Within the United States, the prevalence of antibiotic use without prescription ranges between 1% and 66% [26]. One-quarter of the Americans declared their intention to take antibiotics without prescription and between 14% and 48% of the population in the United States store antibiotics for future use [26].

In Europe, according to a Eurobarometer report in 2018, 7% of the consumed antibiotics were used without prescription [27].

In the Middle East, the pooled prevalence between 2000 and 2016, showed that the misuse of antibiotics is high in the region with a pooled estimate ranging between 19% and 82% [28].

In low- and middle-wealth countries, the overall prevalence of antibiotic use without prescription was 38.8% according to a meta-analysis of studies published between 2002 and 2012 that involved 31,340 participants [2]. A more recent report that involved 11 studies from Asia, Africa and South America reported a higher estimate of pooled prevalence of the use of antibiotics without prescription of 78% [29].

The prevalence of unprescribed use of antibiotics is also surprisingly high among highly educated populations. A review report of studies conducted between 2000 and 2018 about the use of antibiotics without prescription among university students from low- and middle-income countries estimated that the pooled prevalence of this *Practice* was 46.0%, with the highest

pooled prevalence (55.30%) of antibiotic use without prescription observed in Africa and the lowest prevalence (38.3%) in South America [30]. Among individual of low- and middle-wealth countries, the prevalence of antibiotic use without prescription among university students swayed from 11% in Brazil to 91% in Congo [30].

1.1.4. Determinants of antibiotic *misuse*

Lack of *Knowledge* and awareness about antibiotic

In its global action plan to counteract *antibiotic resistance*, WHO set in 2015 as an objective to improve the *Knowledge* and awareness of the community about *antibiotic resistance* through effective communication and education [31]. A meta-analysis about *Knowledge* and *Practices* towards antibiotic use and resistance reported that lack of *Knowledge* and *misuse* of these drugs in the general population is prevalent worldwide [32]. More than one-third (33.7%) of the world population did not know that antibiotics treat bacterial infections, 54% of the studied individuals did not recognize that antibiotics do not treat viral infections, more than one-fourth (26.9%) of the people was unaware that the *misuse* of antibiotics leads to *antibiotic resistance* and almost half of the population (47.1%) seized their antibiotic treatment once noted an improvement [32].

In 2018, only 25% of the European population answered correctly to all *Knowledge* questions about antibiotics in the Eurobarometer survey, with the highest average number of correct answers given by Finnish and Swedish and the lowest average by Latvian and Romanian citizens [27]. Spain and Portugal ranked 18th and 21st in the ranking of countries with correct answers on all the *Knowledge* questions [27]. In Spain, only 57% of the studied population knew that antibiotics are not effective against cold and 38% recognized that antibiotics do not kill viruses [27].

As expected, *antibiotic resistance* is more prevalent in countries with lower levels of awareness about the problem [33] and in communities with a higher prevalence of antibiotic use without prescription [25].

Outpatient antibiotic use varies widely across countries and it was suggested that cultural determinants influence individuals' *Practices* of use of these drugs [33, 34].

The most common reported health conditions for antibiotic use without prescription included urinary and upper respiratory tract infections that include symptoms such as sore throat, flu, common cold, runny nose, cough, headache, pain, fever, diarrhea and toothache [35-37].

Attitudes of patients towards antibiotics and towards their healthcare provider

Expectations of patients to receive antibiotics, the direct request for antibiotics and poor doctor-patient communication were identified as the main motives for over-prescription of antibiotics [38-40]. Patients' pressure to receive antibiotic prescription was reported not only in developing countries [41], but also in developed ones [38, 42], and healthcare providers contribute to the misuse of antibiotics when catering antibiotics for demanding patients [43]. For example, in Australia, more than half of the general practitioners declared that they prescribed antibiotics to meet the expectations of their patients [38].

The trust between patients and their healthcare providers was also identified as a factor to improve adherence to antibiotic therapy [44].

Sociodemographic and socioeconomic determinants of antibiotic *misuse*

The ***misuse*** of antibiotics was associated with age (young adults and elderly > 65 years), female gender, unemployment, difficult access to health care, unaffordable cost of clinical visits, long waiting periods in clinics and lack of time or transportation problems [2, 26-28, 35, 45].

Literature review regarding the association of education and income with antibiotic misuse showed controversial findings.
Some studies reported up to six fold increased odds of *antibiotic misuse* in high income individuals [46, 47], while other studies did not find any association between income and *antibiotic misuse* [48-50], or detected lower odds of *antibiotic misuse* in high income than in low income individuals [51, 52]. Likewise, several studies reported a negative association between low education and *antibiotic misuse* [53-55]. Inversely, other studies reported that high education level is associated with a greater risk of *antibiotic misuse* [56-60]. Some studies found no association between education and *antibiotic misuse* [61-63].
Furthermore, it is unclear whether the association of income and education with *antibiotic misuse* maintains in settings with various social classes, different levels of access to healthcare and diverse regulations of antibiotic dispensing.

1.1.5. Sources of antibiotics without prescription

Friends, families and use of leftover antibiotics were identified as common sources of unprescribed antibiotics in the low-, middle- and high-wealth countries [2, 26, 36, 45, 64].

In developing countries, where many of the available antibiotics are of poor quality and regulations related to the dispensing of these drugs are lacking or insufficiently enforced, pharmacies represent the major source of unprescribed antibiotics [2, 65, 66]. Even in those countries where the dispensing of antibiotics is strictly regulated, such as in the European Union, access to antibiotics without a prescription still takes place and differences between countries are observed when looking at the national picture. For instance, where overall 7% of the Europeans declared using antibiotics obtained without a prescription from a pharmacy or leftover from a previous course of antibiotics, 14% of Latvian and Bulgarian people obtained antibiotics without a prescription in comparison to only 1% of Dutch citizens [27]. Citizens of countries with antibiotic regulations may obtain antibiotics without a prescription from pharmacies, buy them from e-pharmacies via the internet or from other countries during a holiday, use antibiotic leftover or share these drugs with someone else [64].

1.1.6. *Antibiotic resistance* limits treatment options in critical situations like pregnancy

Appropriate medication during pregnancy is crucial to the safety of the foetus and the pregnant woman. It is estimated that 8% of pregnant women experience urinary tract infections which

accounts for 10% of clinical visits during pregnancy [67]. As a result, antibiotics are prescribed to prevent the negative consequences of those infections such as pyelonephritis and preterm labour [67]. Women from deprived areas are more likely to receive an antibiotic prescription than those women from wealthier regions [68]. Due to *antibiotic resistance*, penicillin and other cost-effective antibiotics are no longer recommended to treat asymptomatic bacteriuria [67]. Macrolides are wide-spectrum antibiotics that are prescribed with high frequency during pregnancy [68]. Some studies showed that the use of macrolides (excluding erythromycin) during early pregnancy increases the risk of spontaneous abortion between 1.65-fold (for azithromycin) and 2.72-fold (for quinolones) [69]. Nonetheless, the literature does not provide clear and consistent evidence about the association of macrolide prenatal exposure with birth defects [70-74].

Birth defects are principal contributors to infants' morbidity and mortality [75, 76]. Though it is a global problem, low- and middle-income countries are the most affected ones as more than 94% of births with serious congenital malformations and 95% of related deaths take place in these countries [75]. Congenital malformations of non-genetic origin can be prevented through adequate antenatal care and medication [76].

1.2. Lebanon and Spain: Examples of countries with different socioeconomic status and public health systems

1.2.1. Lebanon: Socioeconomic and sociodemographic indicators

The Lebanese Republic (commonly known as Lebanon) is a Middle Eastern country of 10,452 km^2 [77]. The population size in Lebanon is 6.85 million individuals, 1.79 million (26.14%) of whom are 14 years or younger, and 1.21 million (17.71%) are young adults (15-24 years) [78]. The literacy rate in Lebanon is 95.1% for individuals 15 years or older [79].

According to 2018 data, the life expectancy of the Lebanese at birth is 79 years and the mortality rate of children under five is 7% [78]. One-tenth of the Lebanese population lives in rural areas [78].

Lebanon is classified as an upper-middle income country by the World Bank [77], however, the country frequently experiences fragilities due to its vulnerability to political tensions and external financing instability. Wars in neighbouring countries and high immigration rates to Lebanon also affected its economy and health indicators. Since 2017, the economic situation in the country is on a downward spiral, where the Lebanese currency (LBP) to American dollars (USD) exchange rate has drastically decreased and left a huge consequence on the purchasing power.

1.2.2. Lebanon: Healthcare system

The healthcare system in Lebanon relies on private and public healthcare providers, with a predominance of private healthcare [80, 81]. It is considered among the most expensive systems in the world [81], with healthcare costs that cannot be sustained by many households [82]. Three-quarters of private healthcare expenditures are out-of-pocket [82]. The available hospital beds are concentrated in the capital (Beirut) and its suburbs at a ratio of 70 beds per 10,000 individuals, in comparison to 20 beds per 10,000 in poorer and rural regions [82].

The Lebanese healthcare system encompasses the following schemes [80]:

National Social Security fund (NSSF) under the tutelage of the Ministry of Labour: it covers the employees in the private sector and their dependents, and the population employed in the public sector but who do not benefit from the Civil Service Cooperative (CSC) scheme. The population covered by NSSF is relatively young, as individuals are expulsed upon retirement. Only half of the Lebanese are supported by NSSF, and this healthcare assistance scheme covers 90% of hospital care through direct payment to the hospitals and 85% of ambulatory care via reimbursement to the patient. NSSF is funded by contributions from employers, employees and the government.

Civil Servants Cooperative (CSC) under the tutelage of the presidency of the Council of Ministers: it provides healthcare assistance for the regular government staff and their dependents. CSC covers hospital care through direct payment to the hospitals (90% for the employee and 75% for the dependents) and ambulatory care via reimbursement to the patient (75% for the employee and 50% for the dependents). It is funded by the government.

Funds for the military and security forces under the tutelage of the Ministry of Defense: it provides healthcare assistance for uniformed staff members and their dependents. It covers hospital and ambulatory care through direct payment (100% for the member, 75% for the spouse and children and 50% for dependent parents). The funds for the military and security forces are supported by the government.

Ministry of Public Health (MoPH): it covers Lebanese individuals who neither have private insurance nor benefit from the above-mentioned schemes, upon request. MoPH covers hospital care through direct payment, provides expensive drugs for catastrophic illnesses and vaccines and essential drugs. It is funded by the government.

Private insurance under the tutelage of the Ministry of Economy and Trade: individuals are voluntary enrolled under this scheme. The covered expenses vary according to the health insurance company. It is supported by households and employers and employees for complementary insurance.

Mutual fund under the tutelage of the Ministry of Agriculture: individuals are voluntary enrolled under this scheme. The covered expenses vary according to the contracted company. It is supported by households and government subsidies.

1.2.3. Antibiotic *misuse* and *resistance* in Lebanon

Previous studies in Lebanon reported that antibiotic *misuse* is a frequent *Practice* in the country [83, 84], most of the surveyed individuals thought that antibiotics should be taken for the common cold [85], and did not know that antibiotics are not anti-viral medicines [83]. Use of antibiotics without prescription in Lebanon was associated with lower educational level [85], lack of time, gender and sore throat symptoms [84]. *Knowledge* and *Attitudes* of the Lebanese population towards antibiotics is influenced by income, education, place of residence, and access to healthcare [83]. Nonetheless, none of these studies examined the association of *Knowledge* and *Attitudes* with *Practices* antibiotic *misuse* through effect measures. Besides, all previous studies undertaken in the country relied on a limited sample recruited by convenience.

1.2.4. Spain: An example from the developed world

Spain has a national health system that provides free access to all Spanish citizens. The health system in Spain is regionalized, i.e., each of the 17 autonomous communities is responsible to provide equal access to healthcare to all the population. In Spain, public healthcare predominates over private healthcare services. The literacy rate in Spain is 98.1% [79].

In Galicia, the autonomous community where an important part of the present doctoral project took place, the public healthcare system is centralized, and medical prescriptions are provided electronically. The National Social Security supports hospital and ambulatory care.

1.2.5. Actions Taken in Lebanon and Spain to tackle *antibiotic resistance*

Surveillance system

Lebanon designed a national surveillance system for antibiotic use that includes monitoring the sales or the consumption of antibiotics in health services, but that system has **not** been implemented yet [86].

Spain **regularly** collects data (annually or biannually) and reports on antibiotic sales or consumption at the national level for human use as well as on the appropriateness of antibiotic prescriptions in public and private health facilities [86].

Awareness campaigns

Lebanon carried out a **limited or small-scale** *antibiotic resistance* awareness campaign that target some relevant stakeholders [86].

Spain carries out **government-supported activities** at the national scale which aim at improving the behaviour towards antibiotics in target groups in human health from public and private sectors. It evaluates the change in awareness and behaviour every five years. [86].

Dispensing of antibiotics

In Lebanon, dispensing antibiotics without a prescription is an unlawful action (Decision number 1/2636) [87], however, the related regulations are **not** enforced. A recent study reported that 31% of the surveyed pharmacies in Lebanon distribute antibiotics without a prescription and only 6% of the pharmacists referred their patients to a doctor [88].

In Spain, guidelines on optimizing antibiotic use are **implemented** for all major syndromes and data on the use of these drugs are systematically fed back to prescribers. Antibiotic dispensing without a medical prescription is prohibited by law in Spain (Real Decreto 1718/2010) [89], nonetheless, a study in 2017 showed that antibiotics are still supplied without a prescription in one-fifth of the surveyed pharmacies, especially in rural settings and under patient's pressure [90].

1.3. Tranquilizer *misuse*, an exponentially growing but insufficiently recognized public health issue

Besides antibiotics, the other class of drugs which are prone to worldwide misuse is represented by tranquilizers.

The term "tranquilizers" is a generic label for drugs that are used to reduce anxiety, pain, tension and agitation, relax muscles, calm or sedate, and help get a better sleep. Tranquilizer use is safe and well-tolerated, but it may negatively affect the central nervous system and lead to dependence, especially when these drugs are misused or consumed in high doses [91]. Almost half of the young adults who had already been prescribed tranquilizers but misused them experienced a non-fatal overdose [92]. In the United States, in 2019, one-quarter of opioid overdose deaths also involved benzodiazepines [93]. Tranquilizers, especially benzodiazepines, rank among the topmost misused psychoactive drugs, with a higher prevalence among women than men [94]. Tranquilizers are the second most seized drugs after opioids, with the difference that most tranquilizers are derived from legal sources [94].

1.3.1. Prevalence of tranquilizer *misuse*

The simultaneous use of tranquilizers with other illicit drugs is an internationally salient issue that is associated with heavy public health, sociologic and economic burdens.

In the United States, 4.6% of individuals 12 years of age or older who used illicit drugs in 2010 had started with misusing tranquilizers, a percentage that is higher than that of cocaine, heroin and hallucinogens combined [95]. In 2015, 1.4 million Americans of the same age were recent initiates of tranquilizer misuse [96]. In the same year, 15% of the Americans who reported past-year use of tranquilizers *misused* these drugs to relax and relieve tension (45%) and get help with sleep (20%) [96]. In 2017, the prevalence of *tranquilizer misuse* among Americans of the same age was 2.2%, and a higher prevalence was estimated among people of 18 to 25 years of age [94].

According to the 2019 World Drug Report, *tranquilizer misuse* in Europe is more frequent than that of cannabis with a prevalence ranging from as low as 1% in Portugal to around 20% in Czechia [94]. In 2014, the overall prevalence of *misuse* of sedatives, including tranquilizers, among Europeans from Denmark, Germany, Great Britain, Spain and Sweden aged 12 to 49 years was 6% for past-year and 11% for lifetime misuse [97]. This reveals an upward trend in *tranquilizer misuse* in Europe as a study involving 31 European countries had reported that the lifetime misuse of tranquilizers was practiced by 5.6% of European adolescents in 2003 [98].

Spain ranked the first among the European countries in misusing tranquilizers with a prevalence of 9% for past-year and 18% for lifetime misuse [97]. In general, the consumption of tranquilizers has increased in Spain in the last decade [99]. The prevalence of *tranquilizer misuse* among Spanish adolescents was 2.94% in 2014, with a higher prevalence among girls than boys [100]. The concurrent use of cannabis and tranquilizers was also reported among young Spanish adults (15-34 years) [101].

Tranquilizer misuse is also reported in countries of South America, Africa, North Africa and Asia, though survey data are limited [94, 102-106].

In **Lebanon**, tranquilizers are the most misused medicinal drugs among high school and university students according to data collected between 1999 and 2001 [107]. About 13% of the university students and 3% of school students reported ever misusing tranquilizers and declared that access to these drugs was easy [107]. To the best of our knowledge, no other studies were conducted in the country.

The reported sources of the misused tranquilizers are doctor prescription and social sources, i.e., sharing with family and friends who had been prescribed these drugs.

1.3.2. Public health impact of tranquilizer *misuse*

Tranquilizer misuse is associated with heavy consequences on public health, though the available information is limited to North America [108-110]. In the United States, deaths from drug overdose including tranquilizers have increased by ten folds during the last decade, and emergency room visits attributed to benzodiazepine overdose have doubled [108, 109].

1.3.3. Determinants of tranquilizer *misuse*

The determinants of *tranquilizer misuse* are understudied. Only a few studies have examined the association of sociodemographic and psychiatric attributes with *tranquilizer misuse* [100-102, 111-113]. Identified factors included age (adolescents and young adults), low educational level, unemployment, alcohol intake, tobacco smoking, use of illicit drugs, receipt of a tranquilizer prescription, dissatisfaction with relationships, presence of chronic diseases, lack of perception of health risks related to these drugs, and psychiatric disorders [98, 100-102, 111-114].

The odds of tranquilizer and sedative *misuse* is higher among adolescents who: received a prescription for tranquilizers (7 folds for girls, and 10 folds for boys), smoke tobacco (1.3 folds), drink alcohol (1.3 folds), consume illicit drugs (3.5 folds), skip classes (1.4 folds), have friends using tranquilizers (6 folds) and have siblings using tranquilizers (2.7 folds) [98].

The association of the *Knowledge* of the individuals and their *Attitudes* towards tranquilizer misuse *Practices* has **not been investigated** earlier.

1.4. The *Knowledge, Attitude* and *Practice* Questionnaire Model

Knowledge, *Attitude* and *Practice* (KAP) questionnaires are largely applied instruments in the assessment of psychosocial properties related to a wide variety of health-related issues such as pain [115], vaccination [116], diet [117], and misuse of medicines such as antibiotics [118]. KAP questionnaires consist of a series of declarative statements (items) that are designed to collect information about what the population knows (i.e., *Knowledge*) and what the population thinks about (i.e., *Attitudes*) a specific topic [119]. KAP model questionnaires also entail a set of questions about the respondents' performance toward the studied topic (i.e., *Practice*) [119]. Examples of *Practice* questions include whether the patient adheres to the treatment regimen. Conclusions obtained from KAP-based studies can help determine the need for educational intervention programs, design the interventions and assess their efficiency [120].

Until the present work, **validated** questionnaires to measure the use of antibiotics and/or tranquilizers were not available. Many KAP questionnaires on antibiotic use by the general adult population are available in the literature. Nevertheless, **none** of these questionnaires have undergone a full validation process. A recent review report about *Knowledge* and/or *Attitudes* towards antibiotic use by the general population concluded that 11 studies had tested the validity and the reliability of the used questionnaire [118], but the undertaken validity steps in those studies were limited to face and/or content validity, i.e., other essential validation steps such as construct validity and questionnaire acceptability were not examined. It is worth mentioning that Alumran and colleagues validated the construct of a questionnaire that intended to measure the perceptions of the parents on the use of antibiotics for their children with upper respiratory tract infections [121], however, this instrument cannot be applied to assess *Knowledge* and *Attitudes* of adults concerning their own use of antibiotics because: 1) the questions in that questionnaire are oriented toward children such as "Children with common colds get better faster when antibiotics are given" and "when I visit the doctor for my child's common cold, I expect prescription for medication including antibiotics", 2) parents are usually more judicious with antibiotic use for children than for themselves [122].

Concerning studies about the association of *Knowledge* and *Attitudes* of the general population with *Practices* of tranquilizer use, to the best of our knowledge, **no studies** were available in the literature before this thesis, with the exception of two studies from the past century that measured limited attitudes towards tranquilizers [123, 124]

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2. HYPOTHESES

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Hypotheses

a) *Knowledge* about antibiotics and tranquilizers is associated with their *misuse Practices*.

b) *Personal Attitudes* towards the use of antibiotics and tranquilizers are associated with their *misuse Practices*.

c) *Attitudes towards health-care providers* are associated with the *misuse Practices* of antibiotics and tranquilizers.

d) The socioeconomic level of the individuals is associated with antibiotic *misuse Practices*.

e) The use of antibiotics such as macrolides may be associated with negative health consequences.

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3. OBJECTIVES

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Objectives

3.3. Main objectives

a) To develop and validate instruments about the association of *Knowledge* and *Attitudes* with *Practices* of antibiotic and tranquilizer misuse.

b) To study the psychosocial and sociodemographic determinants of antibiotic and tranquilizer misuse in Galicia and Lebanon.

c) To determine the consequences of the consumption of specific types of antibiotics on health outcomes.

3.4. Specific objectives

a) To develop and validate a *Knowledge, Attitudes* and *Practice* (KAP) questionnaire in Galician, French and Arabic languages about antibiotic and tranquilizer use.

b) To study the association of *Knowledge* and *Attitudes* with *Practices* of antibiotic and tranquilizer misuse in Galicia and Lebanon.

c) To verify if cross-sectional approaches yield similar findings to those of longitudinal studies on the association of *Knowledge* and *Attitudes* with misuse *Practices* of antibiotics and tranquilizers.

d) To summarize through a dose-response meta-analysis the association between education and income with antibiotic misuse.

e) To determine through a meta-analysis whether prenatal exposure to macrolides is a determinant of congenital malformation.

4. METHODS

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Methods

4.1. Global Study Setting and Population

Lebanon

The study population in Lebanon consisted of adults (>18 years), parents of schoolchildren. Schools represent an administratively accessible population and thus, provide access to a sufficient number of adults. We compiled a list of all private and public schools in Beirut (the capital of Lebanon) and invited those schools to take part in the study. Thirteen schools accepted to participate.

In Lebanon, Arabic is the native and official language. French is totally or partially spoken by half of the Lebanese population and is considered the second language in the country [125]. It is the first teaching language in 70% of primary schools in Lebanon. In addition, almost three quarters of French educated individuals in Lebanon also know English as trilingual people [125].

Parents of children attending the participating schools were first informed about the study objectives via school administrations. They were then provided with a printed copy of the questionnaire, the study instrument, in the language chosen by the school (Arabic or French). Every household received the questionnaire in a sealed envelope given to only one child of the family attending the school. Parents were notified about the date of questionnaire delivery and were notified on the delivery day to confirm the receipt of the questionnaire. They also received an instruction that the questionnaire should be answered by only one of the parents, i.e., either the mother or the father. We extensively followed up with the schools to maximize the response rate. Questionnaires were collected back after five days.

Spain

The main population in Spain consisted of adults attending primary care clinics with a next-of-kin at the University Hospital Complex of Santiago de Compostela. The study was presented by the author of this work to each adult visitor of the pediatric primary care clinics at the Hospital. Individuals who accepted to participate in the study signed a consent form. The questionnaire was self-administered. It was collected back in a closed envelope, right after completion.

4.2. Ethics

Lebanon

The study was authorized by the Lebanese Ministry of Education and Higher Education and approved by the Institutional Review Board at the American University of Science and Technology (AUST-IRB-20180202-01). The participation of the parents in this project was voluntary and anonymous.

Spain

The study was approved by the ethics committee of the University of Santiago de Compostela (R00002, No. 2019/179), and authorized by the Spanish Agency for Medication and Healthcare Products (AEMPS, Reference AFG-ANT-2018-01). It also complied with the general requirements of the ethics committee and with the General Data Protection Regulation (Regulation (EU) 2016/679 and Organic Law 3/2018). A written informed consent form was obtained from the participants and the data were anonymized before analysis.

4.3. Development and validation of six *Knowledge*, *Attitudes* and *Practice* (KAP) questionnaires about antibiotics and tranquilizers

Six KAP-modeled questionnaires were developed and validated in the present thesis: **1)** KAP about antibiotics in Galician, **2)** KAP about antibiotics in Arabic, **3)** KAP about antibiotics in French, **4)** KAP about tranquilizers in Galician, **5)** KAP about tranquilizers in Arabic, and **6)** KAP about tranquilizers in French. The questionnaires in Galician were developed and validated in Galicia in 2019, whereas those in Arabic and French were developed and validated in Lebanon in the same year. Each of the six questionnaires was validated in full using the same validation procedure. Examples of flow chart summarizing the validation process of the questionnaires in Galicia are available in **Figure *1*** (antibiotic questionnaire) and **Figure *2*** (tranquilizer questionnaire).

The two studies undertaken in Galicia concerning the development of KAP questionnaires about antibiotics and tranquilizers have been published (Scientific Reports 2020, 10(1):20668 & Drug and Alcohol Dependence 2021:108730). The corresponding publications are available in Annex II pages 190 and 200.

4.3.1. Literature review and items generation

We thoroughly reviewed the literature to identify related studies in Medline and Conference Proceedings Citation Index-Science (CPCI-S). We also scrutinized the reference lists of relevant articles to ensure a comprehensive review. Medline and CPCI-S were searched from their inception until September 2018 without any language or date restrictions.

For the development of KAP questionnaire about antibiotics, we centered our literature search on previously published KAP questionnaires about the personal use of antibiotics in the general population. We used the following search strategy and keywords in Medline: (("Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents" [Pharmacological Action]) AND ("Surveys and Questionnaires"[Mesh]) AND ("Attitude to Health"[Mesh] OR "Health Knowledge, Attitudes, Practice"[Mesh] OR "Knowledge"[Mesh] OR beliefs OR perception OR "Health Behavior"[Mesh] OR "Awareness"[Mesh]) AND (misuse or overuse or use or abuse)). We also examined reports about self-medication and medicine *misuse* including antibiotics. After the literature search, we generated a pool of items about *Knowledge*, *Attitudes* and *Practices*. We selected relevant questions and tailored them to fit the study objective and population.

For the development of KAP questionnaire about tranquilizers, no questionnaire was available prior to our study. Therefore, we used the following search syntax: "(tranquilizers) AND ((misuse OR non-medical use OR self-prescription))", and also reviewed studies about self-medication and abuse of psychoactive drugs. In addition, we reviewed reports about self-medication and drug *misuse* in general.

4.3.2. Focus groups

Subsequent to literature review, we held three focus group sessions with adults from different sociodemographic characteristics in Galicia as well as in Lebanon to ***identify the reasons*** for the *misuse* of antibiotics and tranquilizers. Finally, we developed additional items in order to provide comprehensive questionnaires that fit with the properties of each of the two populations.

The questionnaires were originally written in English and then they were forward and backward translated into Arabic, French and Galician.

4.3.3. Format

The *Knowledge* and *Attitude* statements of the questionnaire were designed to be answered using a 0-10 Likert scale. Zero and ten represented the lowest and highest levels of agreement, respectively. For questions about *Practice* and sociodemographic characteristics the participants were asked to select among a set of provided choices of answers.

The questionnaires were designed using OMR Remark Office software (Remark Office OMR 2014, version 9.2.0.20, GRAVIC, PA, USA) that permits optical reading of the data.

The questionnaires developed in the present study are available in the four languages in Annex I page 168.

4.3.4. Population

***In Lebanon*:** Parents recruited from two of the 13 schools who accepted to participate in the study were involved in the test-retest reliability (N= 60 for Arabic and 31 for French). Data collected from the remaining eleven schools were used in the Confirmatory Factorial Analysis (CFA) (N= 375 for Arabic and 1046 for French). The validation tests are explained in the subsequent sections.

In Spain: Two different sources of population were used for the test-retest reliability and CFA in Spain. For test-retest reliability, adult individuals were recruited from the administrative staff of the University of Santiago de Compostela (N= 145). For CFA analysis, children caregivers attending primary care clinics at the University Hospital Complex of Santiago de Compostela were approached (N= 879).

4.3.5. Content validity

Content validity entails an assessment of the ***adequateness*** and the ***completeness*** of the items of the questionnaire to measure a target construct [126, 127]. It is routinely performed by a panel of three to ten experts who review the items of the questionnaire for their clarity and relatedness to the target dimension (i.e. *misuse* of antibiotics and tranquilizers) [126, 127].

Each of the six questionnaires (KAP-Antibiotics and KAP-Tranquilizers in Galician, Arabic and French) was reviewed by a panel of nine experts in Galician and Lebanon, who have experience in questionnaire design and who were specialized in one or more of the following fields: pharmacy, psychology, medicine, public health, and epidemiology.

The experts were native speakers to the language of the reviewed questionnaire (Galicia-Galician, Lebanese-Arabic and Lebanese-French). At first, the experts were asked to review the questionnaires, identify any ambiguous or unclear item, suggest new questions or choices of answers, and comment on the questionnaire length and format. The questionnaires were then amended accordingly and sent for a second formal evaluation by the experts. At this stage, the experts were asked to rate the clarity and relevancy of each item on a 1-4 Likert scale with one and four representing the lowest and highest levels of clarity and relevancy, respectively.

For each questionnaire, the following indexes of content validity were calculated:

Item Content Validity Index (I-CVI): is the number of experts rating an item ≥ 3 to the total number of experts [128]. For a panel of nine experts, items with I-CVI ≥ 0.78 are deemed clear and relevant [128].

Scale Content Validity Index (S-CVI/Ave): is the average of I-CVIs of all items of the scale [128]. In our questionnaires, the *Knowledge* and *Attitude* items represent a scale. S-CVI/Ave > 0.90 reflects a content-valid scale [128].

Modified Kappa (k*): this index is calculated to check if the agreement between the nine experts happened by chance [129]. The probability of agreement by chance (Pc) is estimated as follows: Pc= [N/A (N − A) * 0.5N]. N is the total number of experts. A is the number of experts who rated the item by ≥ 3. K* is then calculated using this formula: K* = [(I-CVI − Pc)/(1 − Pc)] [129].

4.3.6. Face validity

At this validation step the ***clarity*** and ***completeness*** of the questionnaire are examined. The research group determines whether the items retained in the questionnaire after content validity are appropriate and relevant and whether the questionnaire measures the target concept, i.e. *Knowledge*, *Attitudes* and *Practices* towards antibiotics and tranquilizers in their respective questionnaires [127].

4.3.7. Pilot testing

The six questionnaires were pilot tested in a sample of adults (N= 30 in Galicia, N= 20 for each questionnaire in Lebanon) from the general population. The participants were recruited by convenience from different non-medical disciplines and demographic characteristics. We collected the feedback of the participants about the clarity, the comprehensibility and the format

of the questions, the ease of answering as well as the time taken to completely answer the questionnaire.

4.3.8. Test-retest reliability

The ***reliability*** testing of the questionnaire aims at measuring the stability of the instrument over time [127, 130]. In other words, it examines the ability of the questionnaire to generate reproducible results. The stability or reproducibility of a questionnaire is explored using test-retest procedure.

We tested the reproducibility of each of the six questionnaires in their corresponding populations, i.e., Galician in Galicia and Arabic and French in Lebanon. We carried out the test-retest for *Knowledge* and *Attitude* questions as these parameters, unlike *Practice*, are known to be stable over time [130]. The questionnaires were administered on two-time occasions to the same participants within a four-week time interval. Participants were informed about the aim of the study and accepted to answer the questionnaire on two occasions.

Intraclass Correlation Coefficients (ICC) reflected the test-retest reliability index of each item of the questionnaire. Using data collected from the two test rounds, ICCs were calculated with their 95% Confidence Intervals (CIs) relative to the average measure of the two-way mixed-effects model [131]. Items with ICC values ≥ 0.4 were deemed reliable [132].

4.3.9. Confirmatory Factorial Analysis

Construct validity is an evaluation of the extent to which a questionnaire measures a target construct. In a questionnaire, the *construct* is defined as the set of items that represent the subject to be measured, such as *Knowledge* and *Attitudes* about antibiotics. The set of items that are designed to measure a specific parameter such as *Knowledge* are denoted *factor* (trait or dimension) [127]. A *construct* might encompass one or more *factors*.

An empirical assessment of the validity of the *construct* is carried out using factorial analysis. It is undertaken when the *construct* of the questionnaire is designed to measure more than one *factor*, such as the case of our questionnaires that were developed to measure *Knowledge* about the drug (antibiotics or tranquilizers) and *Attitudes* towards that drug.

For each of the six questionnaires, we carried out a Confirmatory Factorial Analysis (CFA) to examine the validity of the *Knowledge* and *Attitude* construct. CFA explores the relationships between the items and their corresponding *factor*. Items are allocated at first to a specific *factor* using theoretical and logical grounds. A matrix of correlations between the items is also useful to identify those items that might belong to the same *factor* or share content; however, the theoretical concepts should always prevail while assigning the items to their *factors*.

In the first stage, we assigned the items to their corresponding *factors*. Items that tested the *Knowledge* about the drug were assigned to the *Knowledge factor*, and those that explored the agreement of the participants about certain *Attitudes* towards the use of the drug and towards health care provider were attributed to the *Attitude* factor.

In the second stage, the normal distribution of the data of each item was checked and then CFA was undertaken using the Maximum Likelihood Robust Estimation method. Missing data were

handled by applying Full Information Maximum Likelihood (FIML). *Factors* were standardized by constraining them to a mean of 0 and a variance of 1. We assessed the standardized residual correlations between items and applied the modification indexes method to better select the items to be added to a *factor*, and consequently enhance the fit of the model [133, 134]. Standardized factor loading estimates represent the correlation between the items with their related *factors*.

For each questionnaire, we tested several models and examined the goodness of fit of each model to select the most appropriate one. We explored the goodness of fit of the models using the following statistics: Root Mean Squared Error Approximation (RSMEA, acceptable if <0.08), Comparative Fit Index (CFI, acceptable if ≥0.90), Tucker-Lewis Index (TLI, acceptable if ≥0.90) and Standardized Root Mean Square Residual (SRMR, acceptable if <0.08) [135]. In addition to these indicators, we compared Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and sample-size adjusted BIC (aBIC). AIC reveals the relative amount of information lost by a model. The lower AIC values the better the quality of the models is. BIC is an indicator similar to AIC, however it is more conservative (penalizes the model more) than AIC [136].

4.3.10. Questionnaire overall reliability

We examined the ***internal reliability*** of each of the six questionnaires by calculating Cronbach's coefficient alpha [130]. A questionnaire was considered to have acceptable internal reliability when an index ≥ 0.6 was obtained [137, 138].

4.3.11. Questionnaire acceptability

We tested the ***acceptability*** of each questionnaire by calculating the percentage of individuals who accepted answering the questionnaire. The item-response rate was also computed from the percentage of missing data for each item [139-142]

Statistical analyses of questionnaire validation were carried out using SPSS (SPSS Inc. Released 2011. SPSS for Windows, Version 20.0. Chicago), and R (version 4.0.0) and R package: lavaan (version 0.6–6).

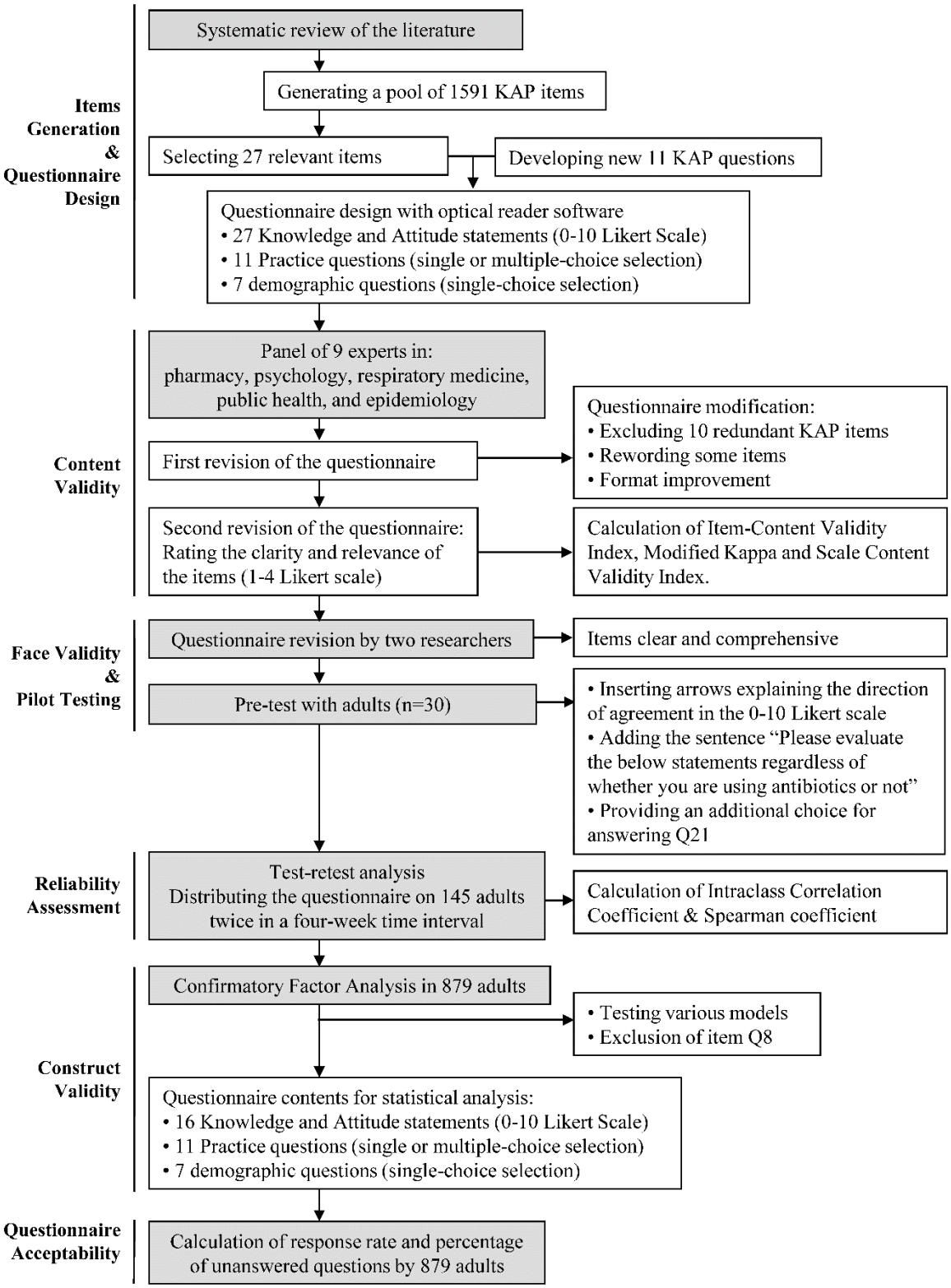

Figure 1 Flow diagram describing the steps followed to develop and validate the KAP questionnaire on antibiotic use in Galicia.

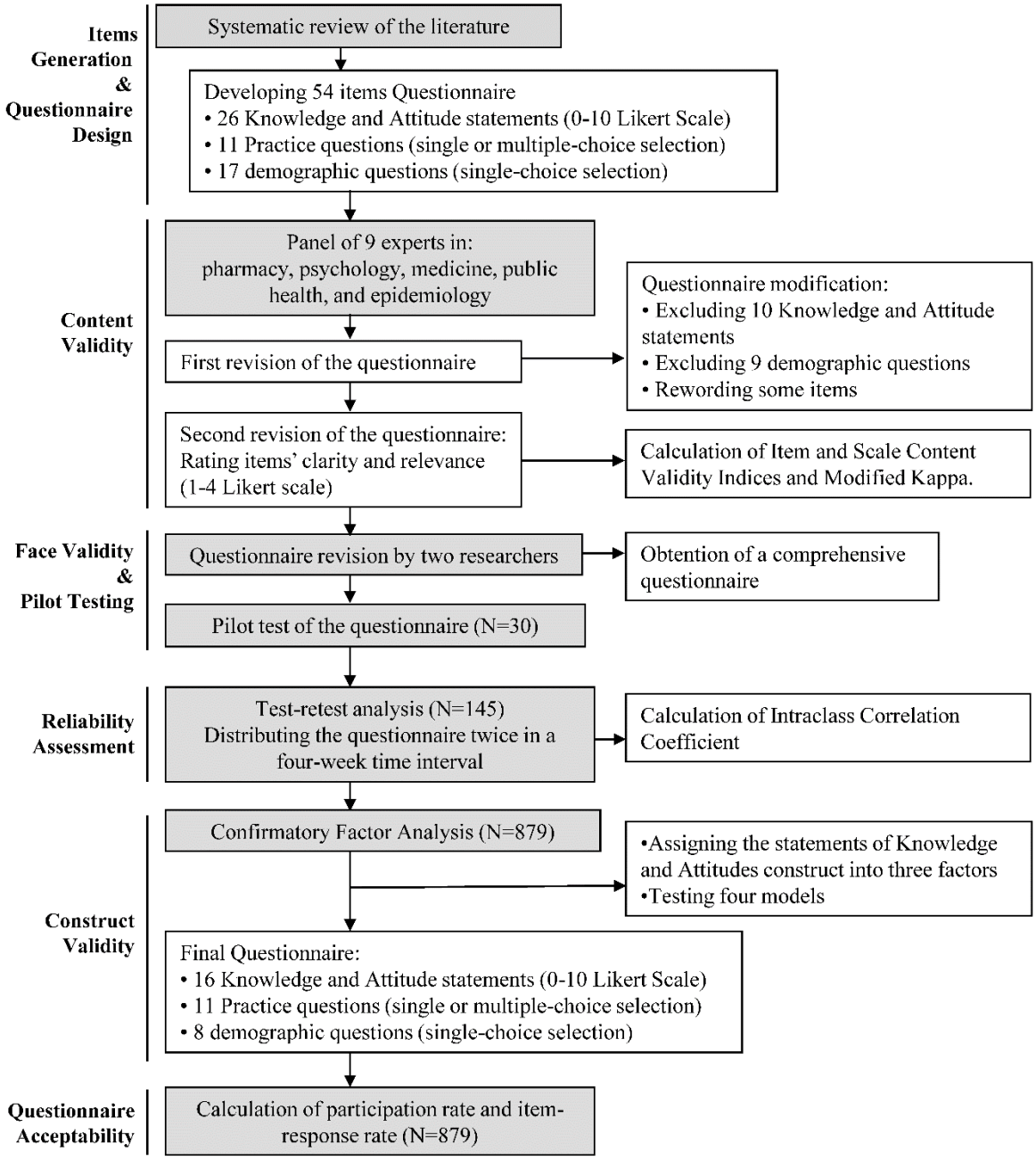

Figure 2 Flow diagram describing the steps followed to develop and validate the KAP questionnaire on tranquilizer use in Galicia.

4.4. Application of the validated KAP questionnaires

4.4.1. Association of *Knowledge* and *Attitudes* with antibiotic misuse *Practices*: two studies in Galicia and Lebanon

The two KAP studies about antibiotics in Galicia and Lebanon have been published (Drug Safety 2021 (in print) and Plos One 2020, 15(7): e0232464). The corresponding publications are available in Annex II page 209 and 221.

4.4.1.1. Study Design and Measures

We used the validated questionnaires to measure the association of *Knowledge* and *Attitudes* with *Practices* of antibiotic misuse in Galicia and Lebanon.

Lebanon: A cross-sectional study involving 1421 parents of schoolchildren was carried out between November 2018 and January 2019 to determine any misuse of antibiotics in the past month.

Spain: A cohort study involving 847 attendants of primary care clinics was undertaken between January and December 2019.

Individuals who answered the baseline questionnaire were followed-up by phone bimonthly to ask about their use of antibiotics in the past two months. Participant who reported using antibiotics were asked the questions of the *Practice* block of the questionnaire to ascertain the occurrence of misuse (Q19 to Q24 of the English version of the questionnaire available in Annex I page 168). The questionnaires used in Galicia and Lebanon in their respective languages are also available in Annex I. Individuals who did not participate in any follow-up questionnaire and who could not be reached after at least four attempts were excluded from the study.

4.4.1.2. Exposure

The exposure was defined as low level of *Knowledge*, medically inappropriate *Attitudes towards antibiotics*, or negative *Attitudes towards healthcare provider*. The exposure was ascertained using the items of the *Knowledge* and *Attitudes* of the questionnaire. Each of those items measured an independent exposure that was analyzed in a separate model.

4.4.1.3. Outcome

The outcome was the *misuse of antibiotics*. A misuse event was defined as the occurrence of any of the following five practices: **1)** use of antibiotics without prescription (Q19), **2)** shortening the course of treatment (Q20), **3)** storing antibiotic leftover or sharing them with someone else (Q21), **4)** not adhering to the treatment regimen regarding the timing and the dosage, i.e. skipping doses (Q22), doubling the dose when forgetting to take the previous dose or taking it when remembered (Q23), or **5)** changing the prescribed dose without medical advice (Q24). Each of those five *Practices* of misuse represented a separate outcome. A sixth composite outcome "any misuse of antibiotics" was generated if one or more of those five

Practices were presented. The cited question numbers correspond to the English version of the questionnaire available in Annex I page 168.

4.4.1.4. Potential confounding variables

We explored the effect of potentially confounding sociodemographic variables. These variables included age, gender, educational level, employment, family size, frequency of medical consultations in case of sickness and receiving a medical prescription over the phone. Besides these covariables, we additionally controlled for the following factors in the study carried out in Lebanon: income, having health insurance, availability of a healthcare facility close to the dwelling, marital status, spouse educational level and spouse employment status.

4.4.1.5. Statistical analysis

Cross-sectional study in Lebanon

Associations of *Knowledge* and *Attitudes* with *antibiotic misuse* were modelled using multiple logistic regression. Adjusted Interquartile Odds Ratios (aIqOR) and their 95% CIs were calculated to measure the effect of exposure change from the 25^{th} to the 75^{th} percentile.

Cohort study in Spain

The data of the cohort study were analysed using the following two approaches:

Person-time approach using Poisson regression: Each participant contributed to the study by a person-time value since the beginning of the study until the occurrence of the first *antibiotic misuse Practice*, drop-out, loss to follow-up or end of the study, whichever took place first. We estimated adjusted Incidence Rate Ratios (aIRRs) of *antibiotic misuse* and their 95% CIs using Poisson Regression models.

Longitudinal Approach using Generalized Linear Mixed Models (GLMM): GLMM analysis allows considering repeated observations contributed by the same individual during the follow-up periods. Using GLMM models fitted with the binomial family, adjusted ORs (aORs) of *antibiotic misuse Practices* and their 95% CIs were estimated.

In Poisson and GLMM analyses, the data was categorized per quantiles of the distribution of the exposure (*Knowledge* and *Attitude* items). The category the represented the highest level of *Knowledge* or the most medically approved *Attitude* was used as a referent.

Comparison of Cross-sectional and Longitudinal approaches

To compare findings from cross-sectional and longitudinal approaches of analysis of data collected from the same individuals, we analysed the data collected at the baseline of the cohort study. Only individuals who answered the baseline questionnaire and at least one follow-up assessment were included. aORs and 95%CI were estimated using multivariate logistic regression models.

For all statistical models, adjustment for potential confounders was carried out using the change-in-estimate method [143]. Covariables with p-value < 0.2 were introduced consecutively into the model, and those that modified the value of the measure of effect (OR or IRR) by at least 10% were retained in the final model.

Robustness Analyses

We undertook two robustness analyses to examine the effect of attrition bias due to loss to follow-up:

1) we used Multiple Imputations by Chained Equations (MICE) with 20 imputed data sets. We followed Rubin's rules to combine the results across the 20 imputed datasets [144, 145], and then re-estimated aIRRs and their 95%CIs from the imputed data using Poisson regression models.
2) we recalculated the originally estimated aIRRs and their 95%CIs under two extreme conditions. In the first assumption, we assumed that all individuals who were lost to follow-up had *misused* antibiotics (presented the outcome). In the second scenario, we supposed that none of the participants who were lost to follow-up had misused antibiotics (did not present the outcome). aIRRs and their 95%CIs were recalculated using Poisson regression models in both scenarios.

Statistical analyses were carried out using STATA v12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP.), and lme4 package of R Statistical Software (version 4.0.1).

4.4.2. Association of *Knowledge* and *Attitudes* with tranquilizer misuse *Practices*: two studies in Galicia and Lebanon

As in the study about antibiotics, we used the validated KAP questionnaires about tranquilizers to measure the association of *Knowledge* and *Attitudes* with *Practices* of tranquilizer misuse in Galicia and Lebanon.

We carried out a cross-sectional study in Lebanon and a cohort study in Galicia. We followed the same protocol as that of the study on antibiotics. We also compared cross-sectional and longitudinal approaches with respect to KAP studies on tranquilizer misuse.

In addition, for the cohort study in Galicia we carried out a validation sub-study to examine the robustness of our results to exposure misclassification [146]. We calculated the specificity and the sensitivity of the questionnaire using the data collected for the test-retest analysis during the questionnaire validation step, as no other superior instrument (gold standard) is available. We compared the ascertainment of the exposure (low level of *Knowledge* and medically disapproved *Attitudes*) by using the answers of the first round of the test-retest as a reference. We then applied the specificity and the sensitivity estimates to correct the previously computed relative risk measures. We compared ORs before and after correction assuming that there were no dropouts.

Statistical analyses were carried out using SPSS (SPSS Inc. Released 2011. SPSS for Windows, Version 20.0. Chicago), and mgcv package of R Statistical Software (version 4.0.5) [147].

The two KAP studies about tranquilizers in Galicia and Lebanon have been published [(Psychology and Health 2021 (in print) & Drug and Alcohol Dependence 2021 (in print)]. The corresponding publication of Drug and alcohol dependence is available in Annex II page 234. The article of Psychology and Health is not reproduced. Another manuscript about the comparison of cross-sectional and longitudinal approaches is currently under review by Journal of Clinical Medicine.

4.4.3. Dose-response meta-analyses of the socioeconomic determinants of antibiotic misuse

This part of the thesis was carried out during a three-month internship at the Department of Global Public Health, Karolinska Institutet, Stockholm, Sweden (Annex III page 246). Two systematic reviews and dose-response meta-analyses were undertaken to quantify the association of income and education with antibiotic misuse Practices.

We defined antibiotic misuse as the use or purchase of these drugs without medical prescription to treat oneself or another person, storage of antibiotics, and non-adherence to physicians' instructions in terms of dosage, timing, and duration of treatment.

4.4.3.1. Dose-response meta-analysis of the association of income with antibiotic *misuse Practices*

To date, there is no clear evidence of the association of income with antibiotic misuse, where divergent results were reported across studies. Therefore, we aimed to carry out a dose-response meta-analysis of **income** levels and *antibiotic misuse*. The protocol of this meta-analysis is registered in PROSPERO (Protocol ID: CRD42021233075).

Literature Search and Study Selection

We searched each of the following databases since their inception until January 19th, 2021 without any language or date restrictions: Medline, EMBASE, Conference Proceedings Citation Index-Science, the Open Access Theses and Dissertations, and the five regional bibliographic databases of the World Health Organization: African Index Medicus, Latin American and Caribbean Health Science Literature Database, Index Medicus for the Eastern Mediterranean Region, Index Medicus for South-East Asia Region and Western Pacific Region Index Medicus.

We used this search syntax in Medline (Socioeconomic Factors OR income) AND (antibiotic*) AND ((drug storage [MeSH]) OR (compliance) OR (adherence) OR (Nonprescription Drugs / administration & dosage* [MeSH]) OR (misuse) OR (irrational use) OR (left-over)) and adapted it for the other databases. To ensure the comprehensiveness of the search, we additionally reviewed the reference lists of related reviews and those of included studies.

We included studies that met the following criteria: **1)** providing at least two levels of monthly income as an exposure, with defined boundaries, **2)** measuring the association between **income** and *antibiotic misuse* by the general population, and **3)** reporting OR or Risk Ratio (RR) and their 95% CI, or data for their calculation. When more than one report corresponded to the same study population, we included the most complete one. Authors of related studies were contacted to inquire about any lacking information before deeming a variable missing or excluding any study due to lack of data.

Data Extraction and Synthesis

From each included study, we extracted:

1) **General study characteristics:** first author last name and year of publication, study period, participants' characteristics (age and gender), and country where the study took place.
2) **Exposure (dose):** levels of monthly income. We defined the dose as the midpoint of the upper and lower boundaries of a specific income category. When the lowest boundary was open-ended, it was set to zero, and when the upper boundary of a specific income level was not reported, we assumed that this level has the same amplitude as the adjacent level. Income that was reported on weekly or yearly basis was converted to monthly units.

   Standardizing the income level: to control for socioeconomic differences across countries, we standardized the income using the following two indicators as proxies of socioeconomic status:

   A) Gross domestic product (GDP) per capita based on purchasing power parity (PPP). GDP approximates the total value of all goods and services produced within a country for a defined period [148]. PPP is a currency conversion rate that equalises the purchasing power of different monetary units and thus permits comparing living standards and economic productivity across countries. [149].

   B) Adjusted net national income per capita (expressed in US dollars): is an indicator that complements gross national income (GNI) in evaluating economic progress by providing a broader measure of national income that accounts for the depletion of natural resources such as forest, energy, and mineral depletion. Depletion of natural resources reflects the decrease in asset values (i.e. stock) related to the extraction and harvesting of natural resources [148].

   We extracted the historical values of PPP, GDP per capita based on PPP, and adjusted net national income per capita that corresponds to the year of data collection in the studies included in the meta-analysis from their specific portals in World Bank [149-151].
3) **Measure of effect:** for each income level, we extracted the number of subjects who practiced *antibiotic misuse*, the total sample size, i.e., the total of subjects who practiced and who did not practice *antibiotic misuse*, adjusted OR or RR and 95% CIs, and restriction, adjustment, or matching variables. We used the OR or RR adjusted for the largest number of variables when possible.
4) **Multiple outcomes:** When data was provided for more than one outcome of *antibiotic misuse Practices* such as use without prescription and non-adherence to treatment regimen, we extracted the data of all *Practices*. In the dose-response analysis, each outcome was treated as a separate study.
5) **Countries classification by economy**: to stratify the studies according to countries wellness, we extracted the corresponding classification from the World Bank [152]. Country economies are categorized as Low income, Lower middle income, Upper middle income and High income. To avoid confusion throughout the text, we adopted the term "wellness" such as low wellness countries, instead of "income", when referring to a country.
6) **Countries classification by WHO region:** Countries are classified geographically by WHO into six regions [153]: African region, Eastern Mediterranean region, European region, Region of the Americas, South-East Asian region and Western Pacific region.

Quality Assessment

The methodological quality of studies included in the meta-analysis was evaluated using an adapted version of New Castle Ottawa Scale for cross-sectional studies [154]. We gave 1 point for the fulfilment of each of the following aspects: **1)** well-defined population (1 point), else (0 point); **2)** reported response rate (1 point), else (0 point); **3)** well described and appropriate statistical analysis (1 point), else (0 point); **4)** justified sample size (1 point), else (0 point); **5)** studies adjusted, matched or restricted for age, sex, educational level and household size (1 point), else (0 point); **6)** previously tested or validated questionnaire (1 point), else (0 point); and **7)** external assessment such as examination of prescription in addition to self-reporting was carried out to determine the outcome (1 point), else such as only self-report (0 point). When details on a specific item were not provided, we graded this item with 0 point. Finally, the points across the items were added to obtain a global quality score of maximum seven points.

Statistical Analysis

We undertook dose-response meta-analysis of income standardized to proxies of socioeconomic indicators: **1)** GDP per capita PPP and **2)** adjusted net national income per capita.

We carried out the dose-response meta-analysis using a one-stage mixed-effects model taking into account heterogeneity across studies [155, 156].

We first used a linear function to estimate a summary OR of *antibiotic misuse* associated with an increase of 1 unit in income. We next flexibly modelled the dose, standardized income, using restricted cubic splines with 3 knots fixed at 10^{th}, 50^{th} and 90^{th} percentiles of its distribution. We tested the departure of the second spline from non-linearity using Wald type test. Subsequently, we categorized the income into tertiles using the lowest as comparator to facilitate a tabular presentation of the summary ORs.

We performed a stratified analysis by: **1)** type of *antibiotic misuse Practice* (use without prescription, non-adherence to treatment, or storage/sharing of antibiotic leftover), **2)** WHO geographic classification, **3)** country economy, **4)** country literacy rate (≥90%, <90%); **5)** publication year (≤2015, >2015. 2015 is the year of WHO release to its global action plan to defeat antibiotic resistance [31]), **6)** method of exposure ascertainment (use of pretested/validated questionnaire; untested questionnaire or not reported); **7)** comparability (control for age, sex, educational level and household size; incomplete control); and **8)** Quality score (≤ 3 points, >3 points).

We checked for publication bias visually using funnel plot and formally through Egger's test [157], and the trim and fill method [158].

The manuscript of the meta-analysis of income and antibiotic misuse was submitted for publication and is currently under review by European Journal of Health Economics.

4.4.3.2. Dose-response meta-analysis of the association of education with *antibiotic misuse Practices*

We followed a similar strategy to that of the dose-response meta-analysis about income and antibiotic misuse. The protocol of the meta-analysis about **education** and *antibiotic misuse* is registered in Prospero (Protocol ID: CRD42021233425).

The search syntax used in Medline was: (Socioeconomic Factors OR education) AND (antibiotic*) AND ((drug storage [MeSH]) OR (compliance) OR (adherence) OR (Nonprescription Drugs / administration & dosage* [MeSH]) OR (misuse) OR (irrational use) OR (left-over)). It was tailored to complete the search in the databases: regional WHO databases, Conference Proceedings Citation Index-Science, and Open Access Theses. The electronic search was concluded in January 2021. The reference lists of included studies and of related review reports were manually checked to supplement the electronic search [2, 24-26, 28-30, 32, 35, 159].

Studies that met the following inclusion criteria were included: **1)** examined the association between **education** and any type of *antibiotic misuse Practices*, **2)** defined the education level, **3)** reported OR or RR and their 95% CIs or sufficient data for their calculation. Studies that compared university students to each other (such as 1st year versus 2nd year) were excluded.

As in the meta-analysis about income, we extracted the data of the following variables: general study characteristics and study population; measures of effect; adjustment, matching or restriction variables; and total number of subject and number of individuals with antibiotic misuse event per education level. Authors of published studies were contacted to inquire about any incompletely reported information.

We standardized the education levels across countries by transforming it to years of education according to the education system of each country [160]. Subsequently, we defined the **dose** as the midpoint of the upper and lower boundaries of each education level.

We performed a dose-response meta-analysis using a one-stage mixed-effects model [155, 156], and undertook categorical and continuous analyses.

In the categorical approach, in line with other studies [161], we categorized education into low (≤9 years), medium (>9-12 years), and high (>12 years) levels and used low education level as a referent.

In the continuous approach, we applied a linear function to estimate a summary OR of *antibiotic misuse* associated with an increase of 1 unit in **education**. Then, we flexibly modelled **education** using restricted cubic splines with 3 knots fixed at 10th, 50th and 90th percentiles of its distribution, and tested departure of the second spline from linearity.

We carried out various subgroup analyses and tested for publication bias.

We appraised the quality of the studies included in the meta-analysis using the Newcastle-Ottawa Scale for cohort and cross-sectional studies [154, 162]. Five criteria were common to cohort and cross-sectional designs: **1)** justified sample size; **2)** properly described and appropriate statistical analysis; **3)** determining *antibiotic misuse* through external assessment in addition to questionnaire; 4**)** ascertaining the education level through a previously tested or validated questionnaire; and **5)** comparability (adjusting, matching or restriction for age and gender). Two additional criteria were specific to study design, making a total of seven criteria. For cohort studies we inspected: **1)** if the study sample was representative of the general population and **2)** if the response rate was more than 50%. For cross-sectional studies we

checked **1)** if the study population was defined and **2)** if the response rate was reported. One point was attributed for the accomplishment of each criterion, and then the points were summed to obtain a quality score of a maximum of seven points.

The manuscript of the meta-analysis about education and antibiotic misuse was submitted for publication and is currently under review by Antimicrobial Resistance and Infection Control.

4.4.3.3. Meta-analysis of the association of macrolides with congenital malformation

Macrolides are frequently used during pregnancy, yet their safety to the foetus remains doubtful. Therefore, we carried out a meta-analysis to assess the association of prenatal exposure to this class of antibiotics and development of congenital malformations. The protocol of this meta-analysis is registered in PROSPERO (Reference: CRD42017055131).

Literature Search and Study Selection

Pertinent studies on prenatal exposure to macrolide antibiotics, i.e., use during pregnancy, and the occurrence of congenital malformation was obtained by searching MEDLINE, EMBASE, the five regional bibliographic databases of the WHO, the Open Access Thesis and Dissertations, and Conference Proceedings Citation Index-Science from inception through June 2019 without any language or date restrictions. The search syntax "(macrolide* OR erythromycin OR roxithromycin OR clarithromycin OR azithromycin OR macrolide [MeSH Terms]) AND ((birth defect*) OR (congenital) OR "congenital abnormalities" [MeSH Terms] OR fetal OR fetus)" used in MEDLINE and adapted for other databases. The search was complemented by using free-text words (birth defects, congenital malformation, congenital abnormalities, pregnancy, macrolides, cohort, case–control and incidence) and by manual checking of included studies and related review reports.

Studies that met the following criteria were included in the meta-analysis: **1)** original randomized clinical trials, case–control or cohort studies about macrolides prenatal exposure and congenital malformation, **2)** examining true macrolides as exposure, **3)** reporting ORs or RRs estimates along with their 95% CIs as a measure of association or providing sufficient data for their calculation. The study was restricted to congenital malformations in live births.
We excluded studies that: **1)** assessed drugs assimilated to macrolides such as ivermectin, nystatin, and natamycin, or **2)** investigated postnatal exposure to macrolides (maternal and/or infant).

When more than one publication was available on the same type of macrolides in the same study population, we considered the most updated report for the analysis. Studies carried out on different types of macrolides in the same population, were pooled together and treated as a single study.

Data Extraction and Synthesis

From each study that met the inclusion criteria, we extracted the following data: **1)** general study characteristics, **2)** study design, **3)** number of cases and controls in case-control studies or total sample size and number of events in cohort studies, **4)** type of control: unexposed to any medicine, exposed to non-macrolide antibiotics or to non-teratogens, or a mixed population

control involving foetuses unexposed to any medicine and others exposed to non-macrolides, **5)** method used to ascertain exposure to macrolide, **6)** dose of macrolides; **7)** exposure period (term of pregnancy), **8)** OR or RR and 95% CI or data for their calculation, **9)** adjustment, matching, and restriction variables, **10)** drop-out rate in cohort studies, **11)** response rate in case–control studies, **12)** macrolide type, and **13)** exposure to single or multiple types of macrolides. Authors were contacted to inquire about any needed data that was not reported in the publication.

Quality Assessment

Newcastle–Ottawa scale was adopted to evaluate the methodological quality of studies included in the meta-analysis. The scale was of seven points that were distributed according to the criteria fulfilment.

Common aspects between case-control and cohort studies (total: 5 points)

1) Exposure was ascertained using clinical records or any other documented proof (1 point), else (0 points).
2) Exposure was properly described: reported duration and determined dose (2 points, 1 point each), else (0 points).
3) Measures of association were adjusted for maternal age and urinary tract infections (2 points, 1 point each), else (0 points)

Specific aspects according to study design (total: 2 points):

1) Cohort studies: drop-out rate or losses to follow up: < 20% (2 points), 20–40% (1 point), and > 40% or not explained (0 points)
2) Case-control studies: participation rate for cases: > 80% (1 points), participation rate for controls: > 80% (1 point), < 80% or not reported (0 points).

Statistical analysis

Three analyses schemes were undertaken according to the characteristics of the comparison group:

1) comparison group 1: foetuses unexposed to any drug.
2) comparison group 2: foetuses exposed to non-macrolides or non-teratogenic drugs.
3) comparison group 3: mixed population involving foetuses of comparison groups 1 and 2.

We calculated pooled ORs and their 95% CI from cohort and case–control studies, by weighting the log RRs and log ORs by the inverse of their variance. ORs represent unbiased estimates of the RR [163]. We provided pooled ORs estimated using fixed and random effects models but considered the latter when heterogeneity was present. We inspected the presence of heterogeneity between studies using DerSimonian and Laird's *Q* test. Heterogeneity was quantified by calculating *Ri*, the proportion of the total variance due to between-study variance [164]. *Ri* values are interpreted as follows: substantial heterogeneity (*Ri* > 0.75), moderate heterogeneity ($0.40 \leq Ri < 0.75$) and low heterogeneity (*Ri* < 0.4).

We explored the origin of heterogeneity by stratifying the analysis by **1)** type of macrolide, **2)** exposure term of pregnancy, **3)** study design, **4)** geographic location, **5)** anatomical location of congenital malformations, **6)** adjustment variables, and **7)** quality score.

We examined the presence of publication bias visually using a funnel plot and formally using Egger's test [157] and the trim and fill method [158].

We carried out a sensitivity analysis under the assumption that case-control studies which show statistically non-significant results have low probability to be published. The originally estimated overall pooled OR was therefore recalculated under the following conditions: **1)** the case–control studies included in our meta-analysis represent only half of the studies of this design ever conducted on macrolides prenatal exposure and congenital malformation, **2)** the association was null (i.e. OR= 1) in those unpublished case–control studies, and **3)** the prevalence of congenital malformation in the unpublished case–control studies is equal to the average prevalence of the published studies.

The meta-analysis of macrolides and congenital malformation has been published (Drug Safety 2020, 43(3), 211-221) and the corresponding publication is available in Annex II page 235.

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5. RESULTS

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5.3. Development and validation of six *Knowledge*, *Attitude* and *Practice* (KAP) questionnaires about antibiotics and tranquilizers

The two studies undertaken in Galicia about the development of KAP questionnaire about antibiotics and tranquilizers have been published (Scientific Reports 2020, 10(1):20668 & Drug and Alcohol Dependence 2021:108730). The corresponding publications are available in Annex II pages 190 and 200.

5.3.1. Content validity

In Galicia as well as in Lebanon, nine native experts formally evaluated each of the six developed KAP questionnaires about antibiotics and tranquilizers in Galician, Arabic and French.

For all questionnaires:

The values of I-CVI ranged between 0.78 and 1.00, revealing that the experts found the retained items clear, easily comprehended, and relevant to the topic (KAP about antibiotic use and KAP about tranquilizer use).

K* statistic was > 0.75 for all items and equal to I-CVI, indicating that experts are unlikely to have agreed on rating the clarity and the relevancy of the items by chance.

S-CVI/Ave was ≥ 0.95, establishing the content validity of the scale.

5.3.2. Face validity and pilot testing

The research team evaluated the final form of each of the six questionnaires and concluded that they appear to measure what they are targeted to measure, indicating therefore their face validity.

The KAP questionnaire about antibiotic was pilot-tested in 30 adults in Galicia prior to the other five questionnaires. All volunteers completely answered the questionnaire. Two participants mentioned that they misunderstood the direction of 0-10 Likert scale. Accordingly, to improve the understanding of the scale and to remind the participants about the direction of agreement we added an explicative arrow-based indication and an answered example *"practicing sports benefits health"*. A participant reported that it was unclear if *Knowledge* and *Attitude* items should be answered in case of no use of antibiotics. Consequently, we added this indication *"Please evaluate the below statements REGARDLESS of whether you are using antibiotics OR NOT"*. Participants also suggested adding the option *"still using them"* for the question, *"The last time you had to take antibiotics, did you complete the course of treatment?"*.

These changes were also applied to the remaining five questionnaires before they were pilot tested. No further suggestions from the participants were received during the pilot testing of the other five questionnaires.

The completion of each questionnaire took between 8 and 10 minutes, and the participants reported satisfaction about the questionnaire length and format.

5.3.3. Test–retest reliability

In Galicia

One hundred forty individuals answered the KAP questionnaire about antibiotics on the two-occasions. **Table *1*** summarizes ICC values for the *Knowledge* and *Attitude* items towards antibiotics. All items showed acceptable reliability index (ICC ≥ 0.4), except Q5, Q10 and Q11. Low ICC values could be caused by the lack of sample heterogeneity for those items. Accordingly, to examine further the reliability of Q5, Q10 and Q11, we calculated their Spearman's correlation coefficient (r_s). The answers on Q5 on the two occasions were weakly correlated ($r_s = 0.193$; $p = 0.022$), and those on Q10 and Q11 were moderately correlated: Q10 ($r_s = 0.433$; $p < 0.0001$) and Q11 ($r_s = 0.405$; $p < 0.0001$).

One-hundred thirty-seven adults completed twice the KAP questionnaire about tranquilizers. **Table *2*** represents ICC estimates for the *Knowledge* and *Attitude* statements about tranquilizers. All ICC values were >0.5, proving the reliability (reproducibility) of these items.

In Lebanon

Sixty Lebanese adults answered the two rounds of the KAP questionnaire about antibiotics and tranquilizers in Arabic, and other 31 individuals answered twice the questionnaires in French. **Table *1*** and **Table *2*** represent ICC estimates for the *Knowledge* and *Attitude* statements in the Arabic and French questionnaires about antibiotics and tranquilizers, respectively. In the four questionnaires, ICC values were >0.5, demonstrating the reproducibility of the *Knowledge* and *Attitude* items.

5.3.4. Construct validity of KAP questionnaire about antibiotic use in Galicia

Model 1: According to theoretical grounds, the 17 items of the *Knowledge* and *Attitude* construct were distributed into two factors: Knowledge about antibiotics (*Knowledge*), and Attitude towards antibiotics (*Attitude*). The structure of this initial 2-*factor* model (***Model 1***) was tested by CFA. As shown in **Table *3***, the goodness of fit indicators of ***Model 1*** did not present an acceptable fit.

Model 2: In ***Model 1***, Q8 *"Antibiotics can kill the bacteria that normally live on the skin and in the gut"* did not load significantly in the *Knowledge* factor. Besides, the items "Q10, Q13, Q15-Q17" loaded negatively in the *Attitude* factor. The items "Q10, Q13, Q15-Q17" examined the patient-health care provider relationship with respect to antibiotics, hence they were assigned to a third factor (Attitude-Healthcare provider) in a new model named ***Model 2***.

Model 2 consisted of three factors: **1)** *Knowledge*: "Q1, Q2, Q4, Q6-Q8 and Q11", **2)** *Attitude-Personal*: "Q3, Q5, Q9, Q12, Q14" and **3)** *Attitude-Healthcare provider*: "Q10, Q13, Q15-Q17". The goodness of fit indicators of ***Model 2*** are represented in **Table *3***. They were better than those of ***Model 1***, yet the model was not acceptable.

Model 3: To improve the structure of ***Model 2***, various iterations were made based on cross-loadings and modification indexes. Correlations between item residuals were also analyzed in order to enhance further the goodness of fit. As a result, Q8 *"Antibiotics can kill the bacteria that normally live on the skin and in the gut"* was removed from ***Model 2***, and the modified

model was called ***Model 3***. **Table *4*** summarizes the loadings of the 16 preserved KAP items on their respective factors. As shown in **Figure 3**, there was significant correlations between the residuals of Q4 and Q7 (r= 0.12, p-value= 0.001), Q10 and Q13 (r= 0.18, p < 0.0001), Q11 and Q10 (r= 0.20, p-value < 0.0001) and Q13 and Q14 (r= − 0.13, p-value= 0.001).

Model 3 represented an adequate fit as concluded from indicators of the goodness of fit assessment: RMSEA= 0.044; CFI= 0.92; TLI= 0.90; SRMR= 0.047 (**Table *3***). There was a statistically significant difference between ***Model 2*** and ***Model 3*** as revealed by $\chi 2$ test ($\Delta \chi 2$= 331.97, Δdf= 22, p= 0.0001). As compared to the other models, ***Model 3*** showed the lowest AIC, BIC and aBICR values. Therefore, ***Model 3*** was adopted for the questionnaire in the Galician adult population.

There was a statistically significant positive correlation between the two factors: *Knowledge* and *Attitude-Personal* (r= 0.56, p < 0.0001). *Knowledge* and *Attitude-Healthcare provider* were not correlated (r= 0.04, p= 0.417). A weak negative correlation existed between *Attitude-Personal* and *Attitude-Healthcare provider* (r= − 0.11, p= 0.023) (**Figure 3**).

5.3.5. Construct validity of KAP questionnaire about antibiotics in French in Lebanon

Model 1: In the initial model (***Model 1***) we followed the structure of the model validated earlier in the Galician population to allocate the *Knowledge* and *Attitudes* items into three factors: *Knowledge* (Q1, Q2, Q4, Q6-8 and Q11), *Attitude-Personal* (Q3, Q5, Q9, Q12 and Q14) and *Attitude-Healthcare provider* (Q10, Q13, Q15-17). The fit indicators of ***Model 1*** were poor (**Table *5***).

Model 2: To improve the model fit, we applied modification indexes which suggested the inclusion of Q10 in the *Attitude-Personal* (***Model 2***). In this model, items Q7 *"Each type of infection needs a different antibiotic"* and Q9 *"If I feel side effects during a course of treatment of antibiotics, I should stop taking them as soon as possible"* did not significantly load on their respective factors. The fit indicators improved but they remained outside the acceptable range.

Model 3: Q7 and Q9 were removed from the model and the residuals of the items Q10 and Q13 were correlated as it was suggested by the analysis of the correlations between item residuals. The new model (***Model 3***) yielded better fit indicators than that of ***Model 2***, but the model was not adequately fit yet.

Model 4: Accordingly, in ***Model 4***, we additionally correlated items Q11 with Q10, and Q1 with Q3 and Q8. The fit indicators of the model enhanced, but they could be improved further.

Model 5: Based on various iterations, we moved item Q6 "When I have a sore throat, I prefer to use an antibiotic" to the factor *Attitude-Personal* and correlated Q3 with Q2 and Q12.

There was a statistically significant difference between ***Model 5*** and ***Model 4*** as revealed by $\chi 2$ test ($\Delta \chi 2$= 70.15, Δdf= 3, p < 0.0001). AIC, BIC and aBICR were the lowest for ***Model 5*** as compared to the other models. In ***Model 5,*** all items loaded significantly on their corresponding factors (**Table *6***), and significant correlations were observed between Q10 and Q13 (r= 0.196; p-value< 0.0001), Q11 and Q10 (r= 0.192; p-value< 0.0001); Q1 and Q3 (r= 0.236, p-value< 0.0001); Q1 and Q8 (r= -0.186, p-value< 0.0001); Q3 and Q12 (r= -0.135, p-value< 0.0001); and Q2 and Q3 (r= 0.247, p-value< 0.0001). ***Model 5*** showed adequate fit: RMSEA= 0.043; CFI= 0.926; TLI= 0.901; SRMR= 0.042. Therefore, ***Model 5*** was adopted for the French questionnaire about antibiotics in the Lebanese population **(Figure *4***). *Knowledge* factor was

positively correlated with *Attitude-Personal* (r= 0.434, p-value<0.0001), but not with *Attitude-Healthcare provider* (r= 0.057, p-value= 0.181). The two factors *Attitude-Personal* and *Attitude-Healthcare provider* also did not correlate (r= -0.026, p-value= 0.574).

5.3.6. Construct validity of KAP questionnaire about tranquilizers in Galicia

Model 1: The 16 *Knowledge* and *Attitude* items about tranquilizers were initially assigned to two factors: *Knowledge* and *Attitudes*. The *Attitude* factor englobed items that were designed to measure *attitudes* of the patients towards tranquilizers as well as towards the healthcare provider. **Table *7*** shows that ***Model 1*** had poor fit indicators. The inspection of the factor loadings of this model indicated that items Q9 and Q14-Q16 did not load significantly on the Attitude factor. These items were specifically designed to measure *attitudes* of the patients towards the healthcare provider. A further evaluation of the item content and the correlation matrix suggested the addition of a third factor to ***Model 1***.

Model 2: Accordingly, the *Attitude* items were allocated into two factors: *Attitude-Personal* which encompassed Q1-Q4, Q11 and Q13 and *Attitude-Healthcare provider* that included Q9, Q12 and Q14-Q16 (***Model 2***). The items loaded significantly on their corresponding factors (*Knowledge*, *Attitude-Personal*, and *Attitude-Healthcare provider*), and the fit indicators of ***Model 2*** were better than that of ***Model 1***, but they were not acceptable yet (**Table *7***).

Therefore, we explored the modification statistics which suggested correlating the residuals of certain items within the factors to enhance the specification of the model.

Model 3: The new model (***Model 3***), has the same structure as ***Model 2*** but the residuals of the following items were correlated: Q3-Q4 ($r_{Q14\text{-}Q15}$= 0.76, p-value< 0.001) and Q14-Q16 ($r_{Q14\text{-}Q16}$= 0.34, and $r_{Q15\text{-}Q16}$= 0.35, both p-value< 0.001).

The magnitude of χ^2 statistic importantly reduced and ***Model 3*** showed better fit indicators than ***Model 2*** (**Table *7***), yet the model required to be better specified.

Model 4: An additional analysis relying on item content and modification statistics suggested the creation of a new model (***Model 4***) with a cross-load of item Q13 on the two factors: *Attitude-Personal* and *Attitude-Healthcare provider*. This modification to the model structure was appropriate since the content of Q13 *"If I believe that I need a tranquilizer and the doctor did not prescribe it, I will get it at the pharmacy without a prescription"* includes information related to both *Attitude* factors.

Model 4 showed acceptable fit indicators CFI= 0.93, TLI= 0.92, RSMEA= 0.054 and SRMR= 0.05) (**Table *7***). The χ^2 Difference Test showed a significant decrease in the magnitude of χ^2 with respect to **Model 3** ($\Delta\ \chi2$= 67.66, Δdf= 1, p-value< 0.001). **Model 4** also had the lowest AIC, BIC and aBIC values as compared to the other models (**Table *7***). In **Model 4**, all items loaded significantly on their corresponding factors (**Table *8***). Therefore, **Model 4** was selected for the Galician adult population (**Figure *5***).

There was a negative relation between *Knowledge* and *Attitude-Personal* factors (r= -0.60, p-value< 0.0001), and a positive relation between *Attitude-Personal* and *Attitude-Healthcare provider* (r= 0.24, p-value< 0.038).

5.3.7. Construct validity of KAP questionnaire about tranquilizers in French in Lebanon

Model 1: Following the structure of the model adopted in Galicia, we assigned the 16 *Knowledge* and *Attitude* items to three factors: *Knowledge* (Q5-Q8 and Q10); *Attitude-Personal* (Q1-4 and Q11); *Attitude-Healthcare* provider (Q9, and Q12-Q16). ***Model 1*** had poor fit indicators (**Table *9***) and item Q13 *"If I believe that I need a tranquilizer and the doctor did not prescribe it, I will get it at the pharmacy without a prescription"* did not significantly load on the factor **"***Attitude-Healthcare provider*".

Model 2: Based on modification indexes, item Q13 was moved to factor *Attitude-Personal* (***Model 2***). All items loaded significantly on their respective factors and the model fit indicators improved but they were still not in the acceptable range (**Table *9***).

Model 3: As suggested by the modification indexes, we correlated the residuals of items Q3 and Q4 and those of Q11 and Q13. ***Model 3*** showed an adequate fit; CFI= 0.93, TLI= 0.91 RSMEA= 0.059 and SRMR= 0.055 (**Table *9***). The items loaded significantly on their corresponding factors (**Table *10***). The magnitude of χ^2 *statistic, AIC, BIC and aBIC was the lowest for* ***Model 3*** (**Table *9***).

Therefore, ***Model 3*** was adopted for the Lebanese population (**Figure 6**). The factors *Knowledge* and *Attitude-Personal* showed a negative correlation ($r= -0.261$, $p< 0.0001$). There was a weak but positive relation between *Knowledge* and *Attitude-Healthcare provider* ($r= 0.151$, $p< 0.001$). No relation was observed between *Attitude-Personal* and *Attitude-Healthcare provider* ($r= 0.046$, $p< 0.218$).

5.3.8. Questionnaire and item acceptability

In Galicia, out of 879 individuals, 844 (96%) and 836 (95%) completed the KAP questionnaires on antibiotics and tranquilizers, respectively, revealing a high acceptability of these questionnaires by the Galician population. The proportion of the unanswered questions in the KAP questionnaire on antibiotics was between 0.4% and 2.7%, and that in the KAP questionnaire on tranquilizers ranged between 1% and 4%, indicating an elevated item-response rate.

In Lebanon, out of 1046 individuals, 1016 (97.1%) and 1015 (97.0%) completed the KAP questionnaires in French about antibiotics and tranquilizers, respectively. The proportion of unanswered questions in the antibiotic questionnaire was between 0.1% and 4.4%, and that in the tranquilizer questionnaire ranged between 0.1% and 3.1%, indicating an elevated item-response rate.

Accordingly, the four questionnaires were deemed highly accepted by the general adult population in Galicia and Lebanon.

5.3.9. Questionnaire overall reliability

Using data of the returned questionnaires, the reliability of the questionnaires in Galician and French languages about antibiotics and tranquilizers were assessed.

Concerning the questionnaires in Galician, the KAP questionnaire about antibiotics had a Cronbach's alpha= 0.62. For KAP questionnaire about tranquilizers, the Cronbach's alpha was 0.65 for the *Knowledge* factor, 0.72 for *Attitude-Personal* factor, and 0.65 for *Attitude-Healthcare* provider factor. The two instruments validated in Galicia showed an acceptable reliability index.

Regarding the questionnaires in French, the Cronbach's alpha was low (0.54) for the KAP questionnaire on antibiotics, but acceptable for KAP questionnaire about tranquilizers (0.67).

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Table 1 Intraclass Correlation Coefficients (ICCs) and 95% Confidence Intervals (CIs) of the *Knowledge* and *Attitude* items of the Galician, Arabic and French versions of the questionnaire on antibiotic use

Item	ICC (95%CI)		
	Galician (№=140)	**Arabic (№=60)**	**French (№=31)**
Q1. Antibiotics are effective against viruses	0.82 (0.75, 0.87)	0.74 (0.57, 0.85)	0.94 (0.86, 0.97)
Q2. When I get a cold, I take antibiotics to help me feel better faster	0.62 (0.48, 0.73)	0.72 (0.53, 0.83)	0.94 (0.88, 0.97)
Q3. If I feel better after a few days, I sometimes stop taking my antibiotics before completing the course of treatment	0.40 (0.17, 0.57)	0.83 (0.72, 9.00)	0.79 (0.56, 0.90)
Q4. I expect my doctor to prescribe antibiotics if I suffer from common cold or flu symptoms	0.68 (0.55, 0.77)	0.60 (0.33, 0.76)	0.82 (0.62, 0.91)
Q5. It is good to be able to get antibiotics from relatives or friends without having to see a medical doctor	0.06 (-0.32, 0.32)	0.81 (0.69, 0.89)	0.84 (0.67, 0.92)
Q6. When I have a sore throat, I prefer to use an antibiotic	0.62 (0.46, 0.73)	0.84 (0.73, 0.90)	0.96 (0.91, 0.98)
Q7. Each type of infection needs a different antibiotic	0.67 (0.54, 0.77)	0.75 (0.60, 0.85)	0.78 (0.52, 0.89)
Q8. Antibiotics can kill the bacteria that normally live on the skin and in the gut	0.67 (0.54, 0.77)	0.66 (0.42, 0.79)	0.84 (0.67, 0.92)
Q9. If I feel side effects during a course of treatment of antibiotics, I should stop taking them as soon as possible	0.60 (0.44, 0.72)	0.73 (0.54, 0.84)	0.95 (0.90, 0.98)
Q10. I take the antibiotics according to the doctor's instructions	0.36 (0.10, 0.54)	0.65 (0.41, 0.79)	0.84 (0.67, 0.92)
Q11. If antibiotics are consumed in excess, they will not work when they are really needed	0.19 (0.14, 0.42)	0.71 (0.51, 0.83)	0.67 (0.31, 0.84)
Q12. I prefer to keep antibiotics at home in case there is a need for them later	0.58 (0.41, 0.70)	0.76 (0.60, 0.86)	0.87 (0.73, 0.94)
Q13. I trust the doctor's decision if s/he decides to prescribe or not prescribe antibiotics	0.50 (0.29, 0.64)	0.64 (0.39, 0.78)	0.52 (0.01, 0.77)
Q14. If I believe that I need an antibiotic and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	0.50 (0.29, 0.64)	0.67 (0.45, 0.80)	0.85 (0.68, 0.93)
Q15. Doctors often explain clearly to the patient the reasons for prescribing or not prescribing antibiotics	0.70 (0.58, 0.79)	0.77 (0.62, 0.86)	0.78 (0.55, 0.90)
Q16. Doctors often explain clearly to the patient the instructions for the use of antibiotics	0.65 (0.51, 0.75)	0.82 (0.70, 0.89)	0.76 (0.49, 0.89)
Q17. When you buy antibiotics, the pharmacist tells you about the importance of correct therapeutic compliance/adherence	0.63 (0.48, 0.74)	0.90 (0.83, 0.94)	0.67 (0.38, 0.86)

№: number of participants who answered the KAP questionnaire on antibiotics on two occasions. The questionnaire in Galician was tested in Galicia, while those in Arabic and French were tested in Lebanon.

Table 2 Intraclass Correlation Coefficients (ICCs) and 95% Confidence Intervals (CIs) of *Knowledge* and *Attitude* items of the Galician, Arabic and French versions of the questionnaire on tranquilizer use

Item	ICC (95%CI)		
	Galician (№= 137)	**Arabic (№= 60)**	**French (№= 31)**
Q1. I would agree to take tranquilizers in order to sleep better	0.84 (0.77, 0.88)	0.74 (0.57, 0.85)	0.86 (0.71, 0.93)
Q2. If I feel better after a few days, I will keep taking my tranquilizers even after completing the prescribed course of treatment	0.72 (0.60, 0.80)	0.78 (0.62, 0.87)	0.69 (0.35, 0.85)
Q3. I would take tranquilizers in order to enjoy myself with my family	0.77 (0.67, 0.83)	0.76 (0.60, 0.89)	0.76 (0.50, 0.88)
Q4. I would agree to take tranquilizers when I feel down and sad in order to work better	0.73 (0.62, 0.81)	0.77 (0.61, 0.86)	0.77 (0.52, 0.89)
Q5. Tranquilizers reduce people's control over what they do	0.68 (0.55, 0.78)	0.63 (0.38, 0.78)	0.68 (0.34, 0.85)
Q6. People taking tranquilizers are at increased risk of traffic accidents	0.71 (0.59, 0.79)	0.54 (0.23, 0.73)	0.77 (0.52, 0.89)
Q7. Psychotropic drugs (such as tranquilizers) may affect children's learning abilities when prescribed to them	0.71 (0.59, 0.80)	0.70 (0.50, 0.82)	0.88 (0.75, 0.94)
Q8. If I feel side effects during a course of treatment of tranquilizers, I should stop taking it as soon as possible	0.60 (0.43, 0.71)	0.57 (0.28, 0.74)	0.94 (0.87, 0.97)
Q9. I would take the tranquilizers according to the doctor's instructions	0.77 (0.67, 0.84)	0.66 (0.43, 0.80)	0.88 (0.75, 0.94)
Q10. If tranquilizers are consumed in excess, they won´t work when they are really needed	0.59 (0.42, 0.71)	0.75 (0.59, 0.85)	0.82 (0.63, 0.91)
Q11. I prefer to keep tranquilizers at home in case there is a need for them later	0.69 (0.56, 0.78)	0.65 (0.42, 0.79)	0.92 (0.83, 0.96)
Q12. I will trust the doctor's decision if s/he decides to prescribe or not prescribe tranquilizers	0.82 (0.74, 0.87)	0.66 (0.43, 0.70)	0.75 (0.47, 0.88)
Q13. If I believe that I need a tranquilizer and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	0.53 (0.34, 0.67)	0.68 (0.47, 0.81)	0.88 (0.75, 0.94)
Q14. I think that doctors often explain clearly to the patients the reasons for prescribing or not prescribing tranquilizers	0.65 (0.51, 0.75)	0.67 (0.45, 0.81)	0.72 (0.43, 0.87)
Q15. I think that doctors often explain clearly to the patients the instructions for the use of tranquilizers	0.63 (0.47, 0.74)	0.82 (0.69, 0.89)	0.88 (0.75, 0.94)
Q16. I think that, when dispensing tranquilizers, the pharmacists tell the customers about the importance of correct therapeutic compliance/adherence	0.65 (0.51, 0.76)	0.76 (0.59, 0.86)	0.78 (0.55, 0.90)

№: number of participants who answered the KAP questionnaire on tranquilizers on two occasions. The questionnaire in Galician was tested in Galicia, while those in Arabic and French were tested in Lebanon.

Table 3 Comparison of the goodness of fit parameters between models of *Knowledge, Attitudes* and *Practice* questionnaire on antibiotic use in the Galician adult population

Indicator	Model 1	Model 2	Model 3
χ 2	1037.074	580.45	248.49
df	118	116	94
p	<0.0001	<0.0001	<0.0001
RSMEA (90% CI)	0.096 (0.091, 0.102)	0.069 (0.063, 0.075)	0.044 (0.038, 0.051)
CFI	0.55	0.77	0.92
TLI	0.49	0.74	0.90
AIC	67594.035	67141.414	62873.317
BIC	67840.296	67397.146	63147.993
aBIC	67675.160	67225.659	62963.803
SRMR	0.088	0.073	0.047

Model 1 encompassed two factors (*Knowledge and Attitude*), ***Model 2*** consisted of three factors (*Knowledge, Attitude-Personal and Attitude-Healthcare provider*) and ***Model 3*** involved the same factors as ***Model 2*** but excluding Q8. $\chi^{2:}$ Chi-square value; df: Degree of Freedom; p: p-value (Chi-square); RSMEA: Root Mean Squared Error Approximation; CFI: Comparative Fit Index; TLI: Tucker-Lewis Index; AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion; aBIC: sample-size adjusted BIC; SRMR: Standardized Root Mean Square Residual

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Table 4 Factor loadings and standard errors from the three-factor model (Model 3) of the *Knowledge*, *Attitudes* and *Practice* questionnaire on antibiotic use in Galicia

Item	Loading estimate	Standard Error	P-value	Standard loading estimate
Knowledge				
Q1. Antibiotics are effective against viruses	1.65	0.09	<0.0001	0.60
Q2. When I get a cold, I take antibiotics to help me feel better faster	1.46	0.08	<0.0001	0.81
Q4. I expect my doctor to prescribe antibiotics if I suffer from common cold or flu symptoms	1.22	0.09	<0.0001	0.40
Q6. When I have a sore throat, I prefer to use an antibiotic	0.49	0.09	<0.0001	0.26
Q7. Each type of infection needs a different antibiotic	0.12	0.08	0.014	0.09
Q11. If antibiotics are consumed in excess, they will not work when they are really needed	-0.38	0.06	<0.0001	-0.25
Attitude-Personal				
Q3. If I feel better after a few days, I sometimes stop taking my antibiotics before completing the course of treatment	1.55	0.09	<0.0001	0.55
Q5. It is good to be able to get antibiotics from relatives or friends without having to see a medical doctor	0.66	0.05	<0.0001	0.56
Q6. When I have a sore throat, I prefer to use an antibiotic	0.84	0.12	<0.0001	0.37
Q9. If I feel side effects during a course of treatment of antibiotics, I should stop taking them as soon as possible	0.62	0.11	<0.0001	0.21
Q10. I take the antibiotics according to the doctor's instructions	-0.40	0.05	<0.0001	-0.39
Q12. I prefer to keep antibiotics at home in case there is a need for them later	1.28	0.09	<0.0001	0.48
Q13. I trust the doctor's decision if s/he decides to prescribe or not prescribe antibiotics	-0.34	0.08	<0.0001	-0.18
Q14. If I believe that I need an antibiotic and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	0.90	0.06	<0.0001	0.54
Attitude-Healthcare provider				
Q10. I take the antibiotics according to the doctor's instructions	0.12	0.04	0.004	0.11
Q13. I trust the doctor's decision if s/he decides to prescribe or not prescribe antibiotics	0.39	0.06	<0.0001	0.23
Q15. Doctors often explain clearly to the patient the reasons for prescribing or not prescribing antibiotics	1.76	0.08	<0.0001	0.77
Q16. Doctors often explain clearly to the patient the instructions for the use of antibiotics	1.69	0.08	<0.0001	0.82
Q17. When you buy antibiotics, the pharmacist tells you about the importance of correct therapeutic compliance/adherence	1.05	0.07	<0.0001	0.41

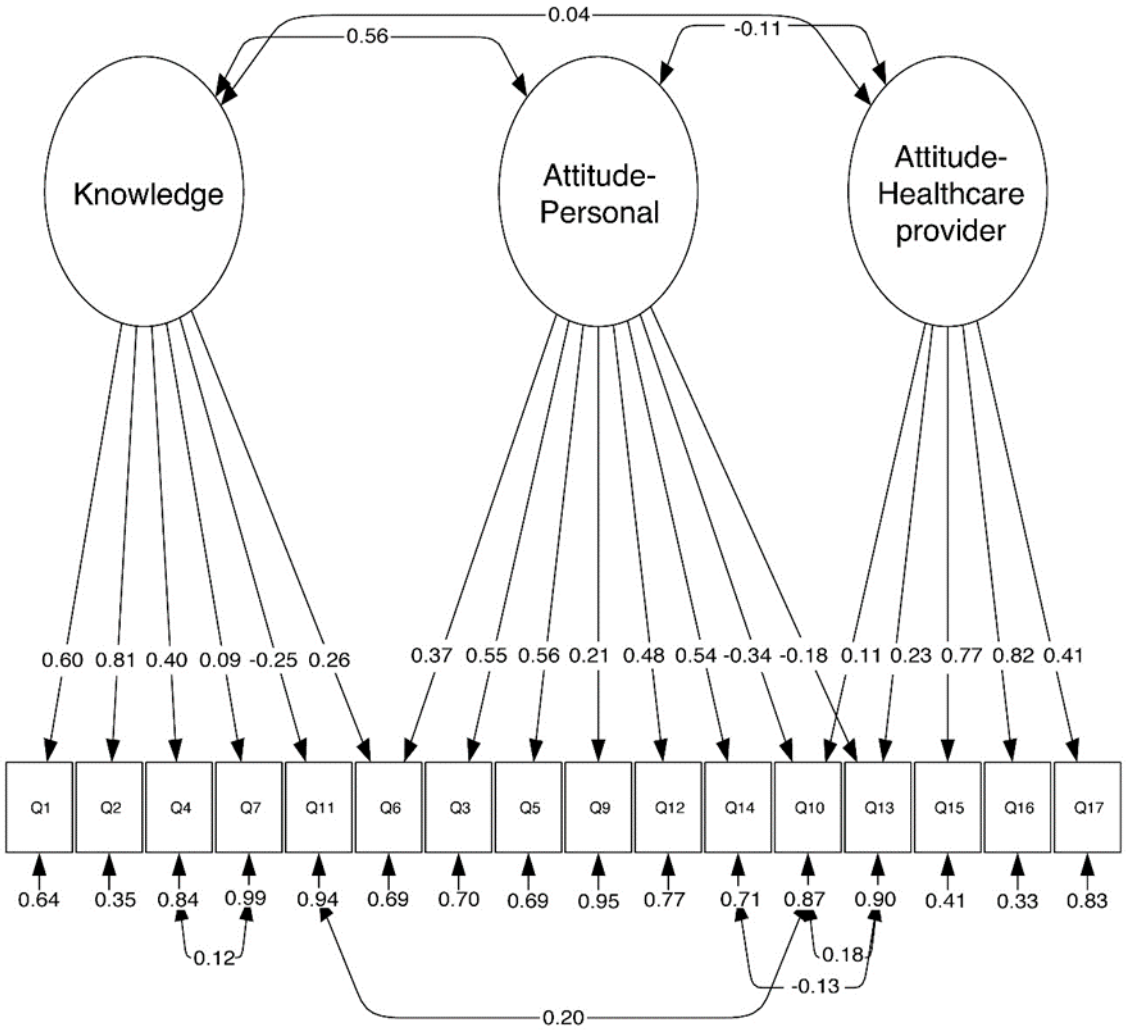

Figure 3 Representation of the model selected by CFA analysis (Model 3) for the *Knowledge* and *Attitude* construct of the KAP questionnaire on antibiotic use in the Galician adult population.
Each of the three factors (*Knowledge*, *Attitude-Personal* and *Attitude-Healthcare provider*) is represented with its corresponding standardized items loadings and their residuals. *Knowledge* includes items that explore the knowledge of the adults towards antibiotics. *Attitude-Personal* encompasses statements about attitudes towards the personal use of antibiotics. *Attitude-Healthcare provider* involves phrases about the patient-healthcare provider relationship with respect to antibiotics. The double-sided arrows represent correlations between the variables. Q1-Q7 and Q9-Q17 are items of the Knowledge and Attitude construct (Q8 was deleted in a previous step). The single headed arrows represent the correlation of the items and their respective factors.

Table 5 Comparison of the goodness of fit parameters between models of *Knowledge, Attitudes* and *Practice* questionnaire on antibiotic use in French language tested in the Lebanese adult population

Indicator	Model 1	Model 2	Model 3	Model 4	Model 5
χ 2	651.37	540.06	394.54	300.18	230.02
df	116	114	85	82	79
p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
RSMEA (90% CI)	0.067 (0.062, 0.072)	0.061 (0.056, 0.066)	0.060 (0.054, 0.066)	0.051 (0.045, 0.057)	0.043 (0.037, 0.050)
CFI	0.75	0.801	0.847	0.892	0.926
TLI	0.71	0.763	0.811	0.862	0.901
AIC	78330.024	78222.720	68620.373	68532.006	68467.852
BIC	78595.900	78498.443	68866.555	68792.959	68743.575
aBIC	78424.391	78320.582	68707.750	68624.626	68565.714
SRMR	0.067	0.059	0.052	0.046	0.042

Model 1 consisted of three factors (*Knowledge*, *Attitude-Personal* and *Attitude-Healthcare provider*) and items were allocated based on the model adopted for Galicia. ***Model 2*** differed from Model 1 by the inclusion of Q10 in the factor *Attitude-Personal*. In ***Model 3*** items Q7 and Q9 were excluded and residuals of item Q10 and Q13 were correlated. In ***Model 4*** additional correlations between item residuals were applied. In ***Model 4*** item Q6 was moved to *Attitude-Personal* factor and additional item residuals were correlated. $\chi^{2:}$ Chi-square value; df: Degree of Freedom; p: p-value (Chi-square); RSMEA: Root Mean Squared Error Approximation; CFI: Comparative Fit Index; TLI: Tucker-Lewis Index; AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion; aBIC: sample-size adjusted BIC; SRMR: Standardized Root Mean Square Residual

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Table 6 Factor loadings and standard errors from the three-factors model (Model 5) of the *Knowledge, Attitudes* and *Practice* questionnaire in French on antibiotic use in Lebanon

Item	Loading estimate	Standard Error	P-value	Standard loading estimate
Knowledge				
Q1. Antibiotics are effective against viruses	1.227	0.065	<0.0001	0.524
Q2. When I get a cold, I take antibiotics to help me feel better faster	1.136	0.065	<0.0001	0.811
Q4. I expect my doctor to prescribe antibiotics if I suffer from common cold or flu symptoms	0.970	0.081	<0.0001	0.335
Q6. When I have a sore throat, I prefer to use an antibiotic	0.667	0.055	<0.0001	0.434
Q8. Antibiotics can kill the bacteria that normally live on the skin and in the gut	-0.145	0.072	0.044	-0.075
Q11. If antibiotics are consumed in excess, they will not work when they are really needed	-0.252	0.054	<0.0001	-0.173
Attitude-Personal				
Q3. If I feel better after a few days, I sometimes stop taking my antibiotics before completing the course of treatment	0.757	0.075	<0.0001	0.353
Q5. It is good to be able to get antibiotics from relatives or friends without having to see a medical doctor	0.818	0.052	<0.0001	0.603
Q6. When I have a sore throat, I prefer to use an antibiotic	0.503	0.085	<0.0001	0.257
Q10. I take the antibiotics according to the doctor's instructions	-0.317	0.043	<0.0001	-0.282
Q12. I prefer to keep antibiotics at home in case there is a need for them later	1.374	0.084	<0.0001	0.472
Q14. If I believe that I need an antibiotic and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	1.051	0.064	<0.0001	0.579
Attitude-Healthcare provider				
Q10. I take the antibiotics according to the doctor's instructions	0.146	0.036	<0.0001	0.139
Q13. I trust the doctor's decision if s/he decides to prescribe or not prescribe antibiotics	0.573	0.055	<0.0001	0.328
Q15. Doctors often explain clearly to the patient the reasons for prescribing or not prescribing antibiotics	1.718	0.082	<0.0001	0.778
Q16. Doctors often explain clearly to the patient the instructions for the use of antibiotics	1.508	0.074	<0.0001	0.711
Q17. When you buy antibiotics, the pharmacist tells you about the importance of correct therapeutic compliance/adherence	1.054	0.071	<0.0001	0.441

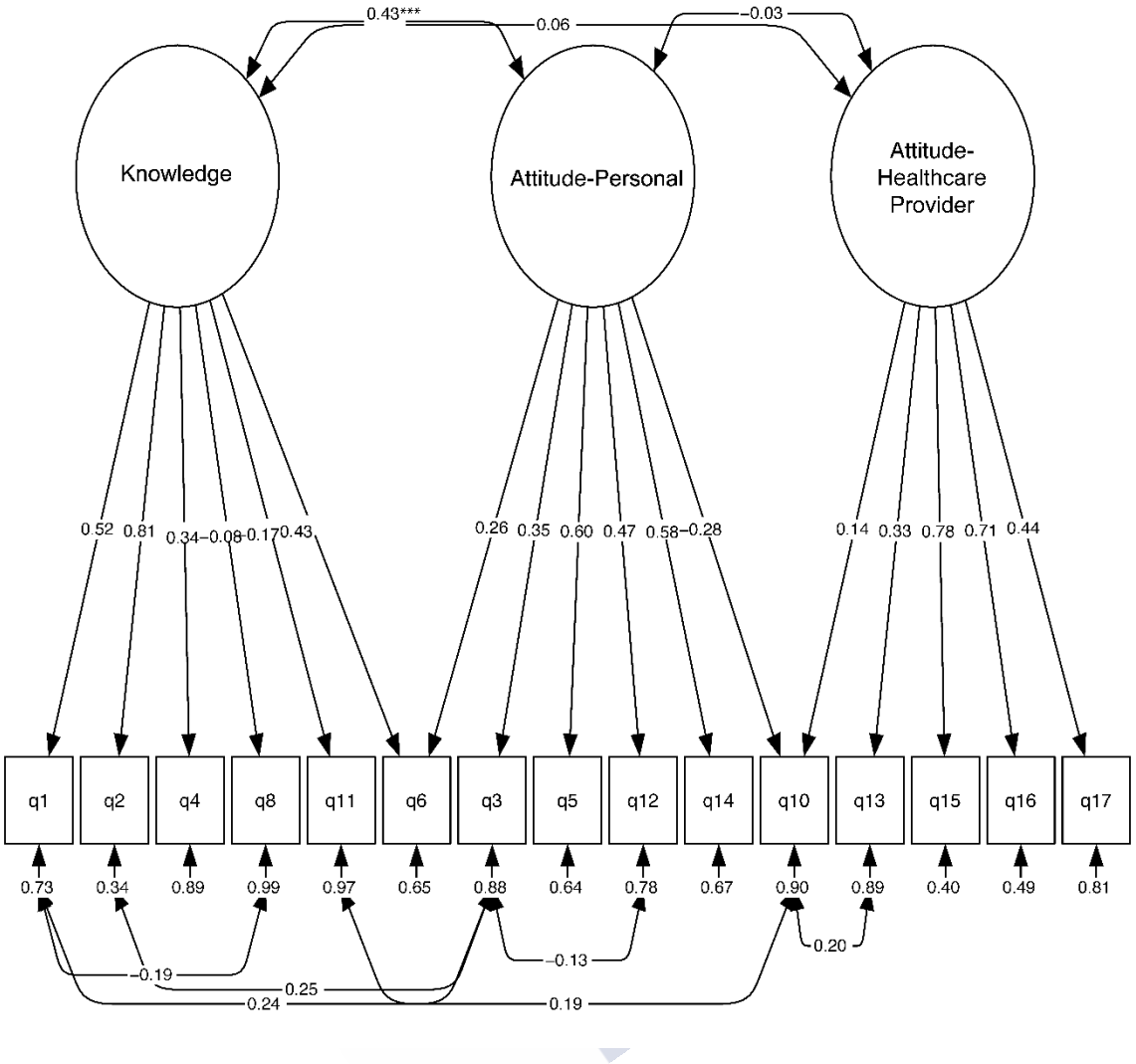

Figure 4 Representation of the model selected by CFA analysis (Model 5) for the *Knowledge* and *Attitude* construct of the questionnaire in French on antibiotic use in the Lebanese adult population.
The model includes three factors (*Knowledge*, *Attitude-personal* and *Attitude-Healthcare provider*) that are represented with their corresponding items, the standardized loading of these items and their residuals. The correlation between an item and its corresponding factor(s) is represented by a single headed arrow. The correlation between factors is indicated by double-sided arrows. *** corresponds to p-values< 0.0001.

Table 7 Comparison of the goodness of fit parameters between models of KAP questionnaire on tranquilizer use in Galicia

Indicator	Model 1	Model 2	Model 3	Model 4
χ 2	1939.22	613.21	400.25	332.59
df	103	101	97	96
p	<0.001	<0.001	<0.001	<0.001
RSMEA (90% CI)	0.146 (0.140, 0.152)	0.078 (0.072, 0.084)	0.061 (0.055, 0.067)	0.054 (0.048, 0.061)
CFI	0.47	0.85	0.91	0.93
TLI	0.39	0.83	0.89	0.92
AIC	63586	62264	62059	61994
BIC	63818	62505	62319	62258
aBIC	63662	62343	62145	62081
SRMR	0.13	0.07	0.06	0.05

Model 1 included two factors: *Knowledge* and *Attitudes.* ***Model 2*** encompassed three factors: *Knowledge, Attitude-Personal* and *Attitudes-Healthcare provider*. ***Model 3*** consisted of the three factors and residuals of similar items were correlated. ***Model 4*** also comprised the three factors, with correlation of residuals between similar items and cross loading of item q13. $\chi^{2;}$ Chi-square value; df: Degree of freedom; CFI: Comparative Fit Index; TLI: Tucker-Lewis Index; RSMEA: Root Mean Square Error Approximation; CI: Confidence Interval; SRMR: Standardized Root Mean Square Residual; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; aBIC: Sample-size adjusted BIC.

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Table 8 Standard loading estimates of the *Knowledge* and *Attitude* items of the tranquilizer questionnaire in Galician on their respective factors (Model 4)

Item	Loading estimate	Standard Error	P-value	Standard loading estimate
Knowledge				
Q5. Tranquilizers reduce people's control over what they do	1.32	0.07	<0.0001	0.64
Q6. People taking tranquilizers are at increased risk of traffic accidents	1.31	0.06	<0.0001	0.74
Q7. Psychotropic drugs (such as tranquilizers) may affect children's learning abilities when prescribed to them	1.15	0.06	<0.0001	0.67
Q8. If I feel side effects during a course of treatment of tranquilizers, I should stop taking it as soon as possible	0.57	0.08	<0.0001	0.26
Q10. If tranquilizers are consumed in excess, they won´t work when they are really needed	0.65	0.06	<0.0001	0.37
Attitude-Personal				
Q1. I would agree to take tranquilizers in order to sleep better	1.38	0.08	<0.0001	0.64
Q2. If I feel better after a few days, I will keep taking my tranquilizers even after completing the prescribed course of treatment	0.71	0.06	<0.0001	0.45
Q3. I would take tranquilizers in order to enjoy myself with my family	0.96	0.06	<0.0001	0.50
Q4. I would agree to take tranquilizers when I feel down and sad in order to work better	1.10	0.06	<0.0001	0.55
Q11. I prefer to keep tranquilizers at home in case there is a need for them later	1.20	0.08	<0.0001	0.54
Q13. If I believe that I need a tranquilizer and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	0.66	0.06	<0.0001	0.47
Attitude-Healthcare provider				
Q9. I would take the tranquilizers according to the doctor's instructions	0.88	0.08	<0.0001	0.48
Q12. I will trust the doctor's decision if s/he decides to prescribe or not prescribe tranquilizers	1.60	0.13	<0.0001	0.81
Q13. If I believe that I need a tranquilizer and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	-0.55	0.07	<0.0001	-0.33
Q14. I think that doctors often explain clearly to the patients the reasons for prescribing or not prescribing tranquilizers	1.03	0.06	<0.0001	0.48
Q15. I think that doctors often explain clearly to the patients the instructions for the use of tranquilizers	0.92	0.06	<0.0001	0.44
Q16. I think that, when dispensing tranquilizers, the pharmacists tell the customers about the importance of correct therapeutic compliance/adherence	0.61	0.08	<0.0001	0.26

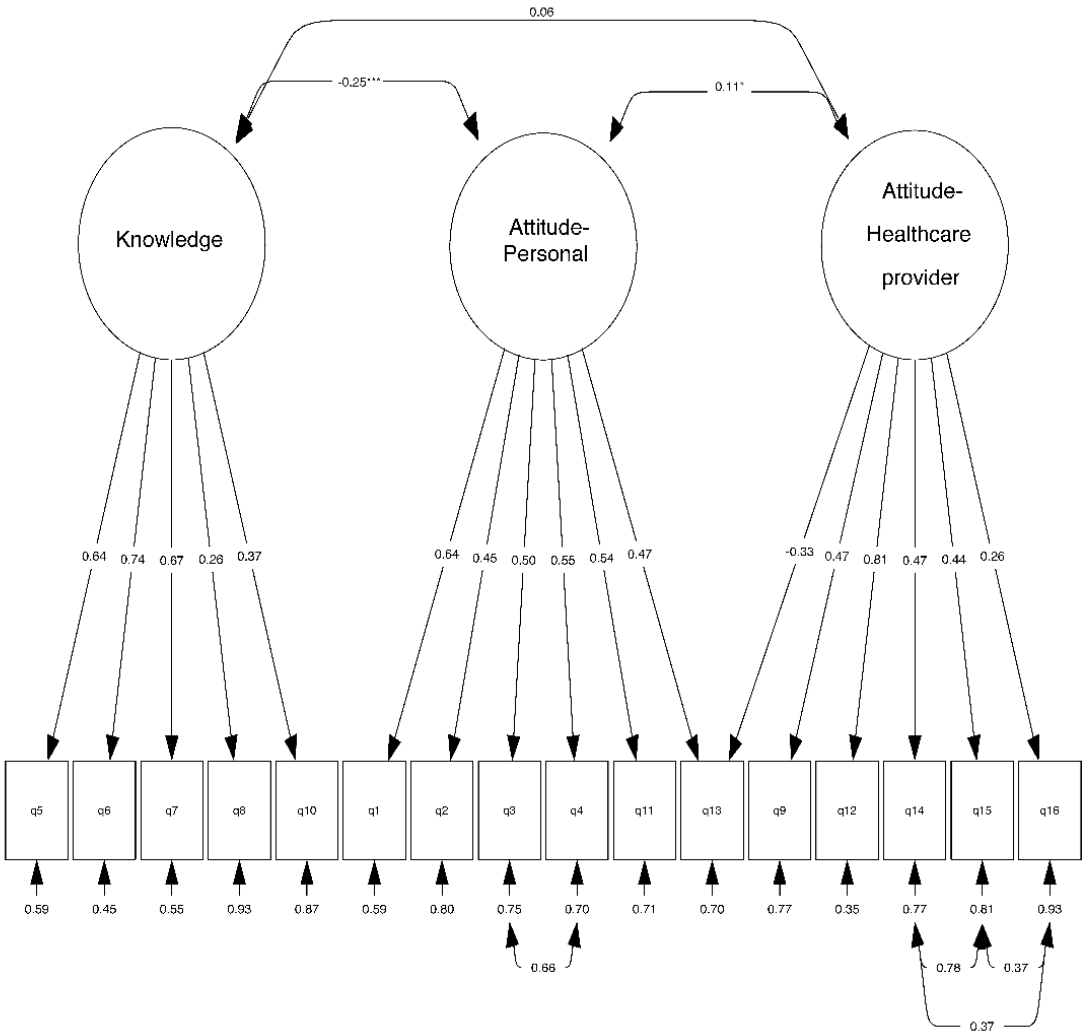

Figure 5 Confirmatory Factorial Analysis model (Model 4) of the *Knowledge* and *Attitudes* construct of the of the questionnaire on tranquilizer use in the Galician adult population.
The model includes three factors (*Knowledge*, *Attitude-Personal* and *Attitude-Healthcare provider*) that are represented with their corresponding items, the standardized loading of these items and their residuals. The correlation between an item and its corresponding factor(s) is represented by a single headed arrow. The correlation between factors is indicated by double-sided arrows. The asterisks represent the level of significance: *** and * correspond to p-values < 0.0001 and < 0.01, respectively.

Table 9 Comparison of the goodness of fit parameters between models of *Knowledge, Attitude* and *Practice* questionnaire on tranquilizer use in French language tested in the Lebanese adult population

Indicator	Model 1	Model 2	Model 3
χ 2	801.956	610.044	451.471
df	101	101	99
p	<0.0001	<0.0001	<0.0001
RSMEA (90% CI)	0.083 (0.077, 0.088)	0.070 (0.065, 0.076)	0.059 (0.054, 0.065)
CFI	0.86	0.90	0.927
TLI	0.83	0.88	0.912
AIC	71168.874	70976.962	70822.388
BIC	71419.929	71228.017	71083.288
aBIC	71257.948	71066.036	70914.956
SRMR	0.087	0.059	0.055

Model 1 consisted of three factors (*Knowledge*, *Attitude-Personal* and *Attitude-Healthcare provider*) and items were allocated based on the model adopted for Galicia. ***Model 2*** differed from Model 1 by the inclusion of Q13 in the factor *Attitude-Personal*. ***Model 3*** had the same structure as ***Model 2*** but residuals of similar items were correlated. $\chi^{2:}$ Chi-square value; df: Degree of freedom; CFI: Comparative Fit Index; TLI: Tucker-Lewis Index; RSMEA: Root Mean Square Error Approximation; CI: Confidence Interval; SRMR: Standardized Root Mean Square Residual; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; aBIC: Sample-size adjusted BIC

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Table 10 Standard loading estimates of the *Knowledge* and *Attitude* items of the tranquilizer questionnaire (Model 3) in French on their respective factors

Item	Loading estimate	Standard Error	P-value	Standard loading estimate
Knowledge				
Q5. Tranquilizers reduce people's control over what they do	1.435	0.052	<0.0001	0.713
Q6. People taking tranquilizers are at increased risk of traffic accidents	1.481	0.053	<0.0001	0.836
Q7. Psychotropic drugs (such as tranquilizers) may affect children's learning abilities when prescribed to them	1.015	0.045	<0.0001	0.612
Q8. If I feel side effects during a course of treatment of tranquilizers, I should stop taking it as soon as possible	0.502	0.065	<0.0001	0.243
Q10. If tranquilizers are consumed in excess, they won´t work when they are really needed	0.568	0.050	<0.0001	0.350
Attitude-Personal				
Q1. I would agree to take tranquilizers in order to sleep better	1.190	0.043	<0.0001	0.719
Q2. If I feel better after a few days, I will keep taking my tranquilizers even after completing the prescribed course of treatment	0.755	0.032	<0.0001	0.664
Q3. I would take tranquilizers in order to enjoy myself with my family	1.045	0.040	<0.0001	0.671
Q4. I would agree to take tranquilizers when I feel down and sad in order to work better	1.210	0.042	<0.0001	0.708
Q11. I prefer to keep tranquilizers at home in case there is a need for them later	1.195	0.052	<0.0001	0.584
Q13. If I believe that I need a tranquilizer and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	0.604	0.037	<0.0001	0.482
Attitude-Healthcare provider				
Q9. I would take the tranquilizers according to the doctor's instructions	0.429	0.042	<0.0001	0.305
Q12. I will trust the doctor's decision if s/he decides to prescribe or not prescribe tranquilizers	0.763	0.048	<0.0001	0.419
Q14. I think that doctors often explain clearly to the patients the reasons for prescribing or not prescribing tranquilizers	1.396	0.034	<0.0001	0.870
Q15. I think that doctors often explain clearly to the patients the instructions for the use of tranquilizers	1.445	0.035	<0.0001	0.918
Q16. I think that, when dispensing tranquilizers, the pharmacists tell the customers about the importance of correct therapeutic compliance/adherence	0.967	0.041	<0.0001	0.568

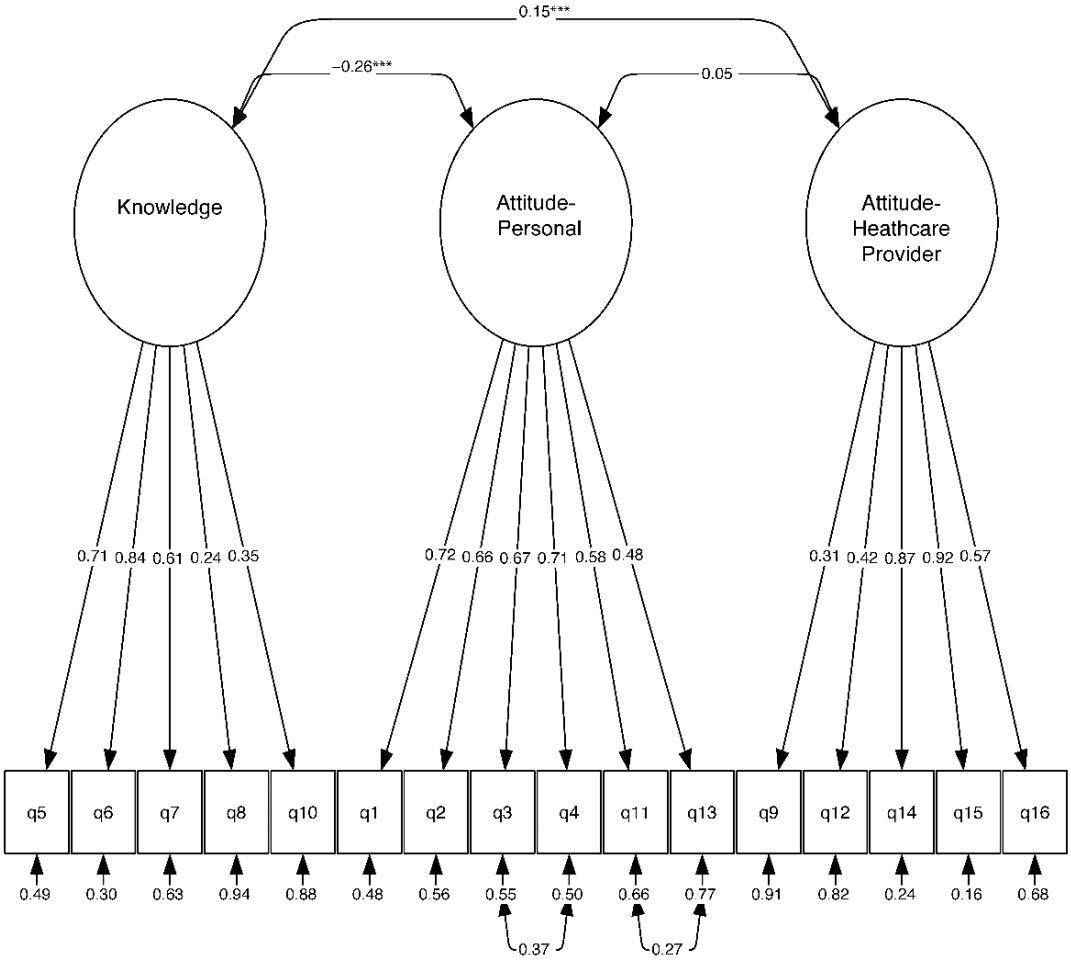

Figure 6 Confirmatory Factorial Analysis model *(Model 3)* of the *Knowledge* and *Attitudes* construct of the KAP questionnaire in French on tranquilizer use in the Lebanese adult population.
The model includes three factors (*Knowledge*, *Attitude-personal* and *Attitude-Healthcare provider*) that are represented with their corresponding items, the standardized loading of these items and their residuals. The correlation between an item and its corresponding factor(s) is represented by a single headed arrow. The correlation between factors is indicated by double-sided arrows. *** corresponds to p-values < 0.0001.

5.4. Association of *Knowledge* and *Attitudes* with *Practices* of antibiotic misuse

The two KAP studies about antibiotics in Galicia and Lebanon have been published (Drug Safety 2021 (in print) and Plos One 2020, 15(7): e0232464). The corresponding publications are available in Annex II page 209 and 221.

5.4.1. Cross-sectional study in Lebanon

Participants' socio-demographic characteristics

One-thousand four-hundred twenty-one individuals completed the KAP questionnaire on antibiotics in Lebanon and were included in the analysis. The demographic characteristics of the participants are represented in **Table *11***. Almost two-thirds (64.1%) of the participants reported not always visiting a physician in case of illness; 34.3% due to lack of time, 27% declared that it was unnecessary to always consult a physician, and 8.9% because of financial reasons. A similar fraction (60%) mentioned having consulted a doctor over the phone.

Patterns of antibiotic misuse

In the month preceding the study, more than one-quarter of study participants (16%, N=277) had used antibiotics and 41.4% of them (N=94) showed signs of at least one *antibiotic misuse Practice*. The most common *misuse Practices* involved non-prescribed use of antibiotics (22.5%), storing antibiotic leftover for future need and/or sharing the leftover with someone else (22%), and doubling the prescribed dose of antibiotics or taking the skipped dose when recalled, in case of forgetting to take the previous dose (10.6%).

Association of Knowledge about antibiotics with the misuse Practices of these drugs

Individuals who did not know that antibiotics are not effective against viruses had twice the odds to present any antibiotic misuse *Practice* [**Q1** aIqOR: 2.08 (95% CI: 1.32, 3.19)] (**Table *12***). In specific, they had higher chance of using antibiotics without medical prescription [aIqOR: 2.83 (95% CI: 1.61, 5.33)], seizing the course of treatment before completion [aIqOR: 2.66 (95% CI: 1.07, 6.27)], and changing the prescribed dose without medical advice [aIqOR: 5.94 (95% CI: 1.23, 28.04)] (**Table *13***).

Individuals who ignored that antibiotics do not treat colds had substantial higher odds of the outcome "*any misuse Practice*" of antibiotics than those who had better knowledge [**Q5** aIqOR: 1.81 (95% CI: 1.41, 2.29)] (**Table *12***). Specifically, they had more than two-fold higher chance to use antibiotics without prescription [**Q5** aIqOR: 2.29 (95% CI: 1.69, 3.22)], shorten the course of antibiotic treatment [**Q5** aIqOR: 2.36 (95% CI: 1.52, 3.73)], store or share antibiotic leftover [**Q5** aIqOR: 2.22 (95% CI: 1.57, 3.04)] and modify the prescribed dose of antibiotics without medical approval [**Q5** aIqOR: 4.42 (95% CI: 2.14, 9.38)]. These individuals also had considerable higher odds of doubling the subsequent dose of antibiotics or taking it when remembered when a previous dose was forgotten [**Q5** aIqOR: 1.94 (95% CI: 1.26, 3.13)] (**Table *13***).

Association of Attitudes towards antibiotics with the misuse Practices of these drugs

Individuals who preferred to use antibiotics to treat sore throat had more than twice higher odds of misusing antibiotics than those who did not prefer to take antibiotics for this purpose [**Q7** aIqOR: 2.19 (95% CI: 1.61, 2.93)] (**Table *12***). In concrete, they had three times the chance to self-prescribe antibiotics [**Q7** aIqOR: 3.30 (95% CI: 2.29, 5.00)], were more likely to curtail the treatment course [**Q7** aIqOR: 2.19 (95% CI: 1.22, 3.86)], store or share antibiotic leftover [**Q7** aIqOR: 2.10 (95% CI: 1.40, 3.05)], and modify the prescribed dose without medical advice [**Q7** aIqOR: 4.01 (95% CI: 1.69, 9.54)] (**Table *13***).

Individuals who preferred to store antibiotics at home for potential need in the future had substantial odds of misusing these drugs [**Q11** aIqOR: 2.44 (95% CI: 1.68, 3.46)] (**Table *12***). In particular, they had more than three-fold the odds of using unprescribed antibiotics [**Q11** aIqOR: 3.64 (95% CI: 2.19, 6.05)], and five-fold higher chance of changing the prescribed dose of antibiotics without medical approval [**Q11** aIqOR: 5.05 (95% CI: 1.59, 16.78)] (**Table *13***).

Similar findings were obtained for individuals who showed their agreement on statements about buying unprescribed antibiotics in case they think that they need an antibiotic, but the physician did not prescribe it **(Q13)** (**Table *12*** and **Table *13***).

Association of Attitudes toward healthcare provider with the misuse Practices of antibiotics

Individuals who agreed that the physician clearly explains to the patient the reasons for prescribing or not prescribing antibiotics had lower odds to use antibiotics without medical prescription [**Q14** aIqOR: 0.63 (95% CI: 0.43, 0.92)] (**Table *13***).

Similar findings were observed for individuals who agreed that the physician clearly explains the instructions of use of antibiotics **(Q15)**. These individuals had reduced odds of the outcome "any antibiotic misuse practice" [**Q15** aIqOR: 0.66 (95% CI: 0.47, 0.90)] and especially, they are less likely to use unprescribed antibiotics [**Q15** aIqOR: 0.59 (95% CI: 0.37, 0.90)] (**Table *12*** and **Table *13***).

Table 11 Demographic characteristics of individuals participated in the cross-sectional study about the association of *Knowledge* and *Attitudes* with *Practices* of antibiotic misuse in Lebanon

Characteristic	Total (№= 1421)	Any Misuse in the last month (№= 94)*
Gender		
Male	276 (19.4%)	22 (23.4%)
Female	1092 (76.8%)	69 (73.4%)
Missing	53 (3.7%)	3 (3.2%)
Age		
<38 years	355 (25.0%)	37 (39.4%)
39 -42 years	227 (16.0%)	14 (14.9%)
43 - 47 years	313 (22.0%)	13 (13.8%)
>= 48 years	259 (18.2%)	14 (14.9%)
Missing	267 (18.8%)	16 (17.0%)
Marital status		
Married	1327 (93.4%)	87 (92.6%)
Other	74 (5.2%)	6 (6.4%)
Missing	20 (1.4%)	1 (1.1%)
Educational level		
Until high school	252 (17.7%)	31 (33.0%)
University	1157 (81.4%)	62 (66.0%)
Missing	12 (0.8%)	1 (1.0%)
Spouse educational level		
Until high school	313 (22.0%)	36 (38.3%)
University	1028 (72.3%)	53 (56.4%)
Missing	80 (5.6%)	5 (5.3%)
Number of family members		
2-4	555 (39.1%)	36 (38.3%)
5-6	715 (50.3%)	50 (53.2%)
>6	129 (9.1%)	6 (6.4%)
Missing	22 (1.5%)	2 (2.1%)
Family income		
<500$	21 (1.5%)	2 (2.1%)
500$ - 1499$	260 (18.3%)	34 (36.2%)
1500 - 2500$	223 (15.7%)	17 (18.1%)
>2500$	808 (56.9%)	36 (38.3%)
Missing	109 (7.7%)	5 (5.3%)
Consulting a doctor		
Rarely or never	155 (10.9%)	8 (8.5%)
Sometimes	756 (53.2%)	63 (67.0%)
Always	493 (34.7%)	22 (23.4%)
Missing	17 (1.2%)	1 (1.1%)
Reasons for not always consulting a doctor		
No need	390 (27.4%)	24 (25.5%)
Fear	29 (2.0%)	2 (2.1%)
No money	127 (8.9%)	20 (21.3%)
No time	321 (22.6%)	26 (27.7%)
Long waiting time	166 (11.7%)	15 (16%)
No near clinic	53 (3.7%)	4 (4.3%)
Ever received medical consultation over the phone		
No	491 (34.6%)	30 (31.9%)
Yes	892 (62.8%)	62 (66%)
Missing	38 (2.7%)	2 (2.1%)

*: the outcome “any misuse” encompasses one or more of the following Practices: use without prescription, shortened treatment, modified dose, doubling a skipped dose, or taking it when remembered.

Table 12 Association of *Knowledge* and *Attitudes* with the outcome "any misuse" *Practice* of antibiotics in 1392 Lebanese parents of schoolchildren

Knowledge or attitude statements	Percentile of responses			No misuse №	Any Misuse №	alqOR** (95%CI)
	25%	50%	75%			
Q1. Antibiotics are effective against viruses	0	4	7	1171	86	2.08 (1.32, 3.19)
Q2. Each type of infection needs a different antibiotic	8	10	10	1174	87	1.17 (0.94, 1.44)
Q3. Antibiotics can kill the bacteria that normally live on the skin and in the gut	5	8	10	1138	85	1.16 (0.77, 1.61)
Q4. If antibiotics are consumed in excess, they won't work when they are really needed	8	10	10	1168	85	0.96 (0.81, 1.14)
Q5. When I get a cold, I take antibiotics to help me feel better faster	0	0	4	1187	88	1.81 (1.41, 2.29)
Q6. I expect my doctor to prescribe antibiotics if I suffer from common cold or flu symptoms	0	5	9	1180	88	1.42 (0.91, 2.36)
Q7. When I have a sore throat, I prefer to use an antibiotic	0	0	5	1187	88	2.19 (1.61, 2.93)
Q8. If I feel side effects during a course of treatment of antibiotics, I should stop taking them as soon as possible	5	9	10	1170	86	1.40 (0.95, 2.01)
Q9. It is good to be able to get antibiotics from relatives or friends without having to see a medical doctor	0	0	0	1186	88	1.00 (1.00, 1.00)
Q10. I take the antibiotics according to the doctor's instructions	10	10	10	1186	86	1.00 (1.00, 1.00)
Q11. I prefer to keep antibiotics at home in case there is a need for them later	0	2	6	1181	86	2.44 (1.68, 3.46)
Q12. I trust the doctor's decision if s/he decides to prescribe or not prescribe antibiotics	8	9	10	1183	87	0.88 (0.76, 1.04)
Q13. If I believe that I need an antibiotic and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	0	0	2	1180	87	1.51 (1.35, 1.72)
Q14. Doctors often explain clearly to the patient the reasons for prescribing or not prescribing antibiotics	5	7	9	1180	86	0.75 (0.57, 1.00)
Q15. Doctors often explain clearly to the patient the instructions for the use of antibiotics	5	8	10	1179	86	0.66 (0.47, 0.90)
Q16. When you buy antibiotics, the pharmacist tells you about the importance of correct therapeutic compliance/adherence	3	6	9	1181	87	1.27 (0.83, 1.87)

№: number of events; aIqOR: adjusted interquartile Odds Ratio; *: the outcome "any misuse" encompasses one or more of the following Practices: use without prescription, shortened treatment, modified dose, doubling a skipped dose, or taking it when remembered; **: adjusted for gender and age

Table 13 Association of *Knowledge* and *Attitudes* with specific aspects of antibiotic misuse *Practices* in Lebanese parents of schoolchildren

Knowledge and Attitude statements	Use without prescription (№=1361)		Shortened treatment (№=1376)		Changed dose (№= 1293)		Improper action when skipping a dose (№= 1295)		Stored or shared leftovers (№= 1298)	
	№	alqOR* (95%CI)	№	alqOR* (95%CI)	№	alqOR* (95%CI)	№	alqOR* (95%CI)	№	alqOR* (95%CI)
Q1. Antibiotics are effective against viruses	47	2.83 (1.61, 5.33)	23	2.66 (1.07, 6.27)	10	5.94 (1.23, 28.04)	24	1.71 (0.75, 3.58)	46	1.71 (1.00, 3.19)
Q2. Each type of infection needs a different antibiotic	49	1.17 (0.86, 1.59)	23	1.28 (0.77, 2.07)	11	0.77 (0.52, 1.17)	24	1.14 (0.76, 1.77)	46	1.06 (0.81, 1.42)
Q3. Antibiotics can kill the bacteria that normally live on the skin and in the gut	49	0.86 (0.53, 1.40)	22	0.86 (0.73, 1.76)	11	0.70 (0.25, 1.84)	24	1.16 (0.56, 2.49)	45	1.40 (0.82, 2.49)
Q4. If antibiotics are consumed in excess, they won't work when they are really needed	45	0.94 (0.76, 1.17)	21	0.86 (0.64, 1.17)	9	0.72 (0.50, 1.04)	22	1.08 (0.72, 1.59)	43	0.98 (0.76, 1.21)
Q5. When I get a cold, I take antibiotics to help me feel better faster	49	2.29 (1.69, 3.22)	23	2.36 (1.52, 3.73)	11	4.42 (2.14, 9.38)	24	1.94 (1.26, 3.13)	46	2.22 (1.57, 3.04)
Q6. I expect my doctor to prescribe antibiotics if I suffer from common cold or flu symptoms	49	1.42 (0.76, 2.77)	23	3.52 (1.30, 10.60)	11	1.20 (0.29, 4.79)	24	1.20 (0.52, 3.00)	47	1.42 (0.76, 2.77)
Q7. When I have a sore throat, I prefer to use an antibiotic	49	3.30 (2.29, 5.00)	23	2.19 (1.22, 3.86)	11	4.01 (1.69, 9.54)	24	1.34 (0.73, 2.39)	47	2.10 (1.40, 3.05)
Q8. If I feel side effects during a course of treatment of antibiotics, I should stop taking them as soon as possible	47	2.49 (1.28, 4.83)	23	2.70 (1.00, 7.59)	10	1.28 (0.42, 3.86)	24	1.05 (0.56, 2.10)	46	1.16 (0.70, 1.84)
Q9. It is good to be able to get antibiotics from relatives or friends without having to see a medical doctor	49	1.00 (1.00, 1.00)	23	1.00 (1.00, 1.00)	11	1.00 (1.00, 1.00)	24	1.00 (1.00, 1.00)	47	1.00 (1.00, 1.00)
Q10. I take the antibiotics according to the doctor's instructions	47	1.00 (1.00, 1.00)	23	1.00 (1.00, 1.00)	10	1.00 (1.00, 1.00)	24	1.00 (1.00, 1.00)	50	1.00 (1.00, 1.00)
Q11. I prefer to keep antibiotics at home in case there is a need for them later	47	3.64 (2.19, 6.05)	23	2.08 (1.06, 4.00)	10	5.05 (1.59, 16.78)	24	1.06 (0.53, 2.08)	46	3.30 (1.97, 5.29)
Q12. I trust the doctor's decision if s/he decides to prescribe or not prescribe antibiotics	48	0.86 (0.71, 1.08)	23	0.83 (0.61, 1.12)	11	0.59 (0.41, 0.85)	24	0.89 (0.71, 1.37)	47	0.88 (0.71, 1.10)
Q13. If I believe that I need an antibiotic and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	48	1.64 (1.39, 1.90)	23	1.49 (1.19, 1.88)	11	1.64 (1.21, 2.25)	24	1.51 (1.21, 1.88)	47	1.54 (1.32, 1.82)
Q14. Doctors often explain clearly to the patient the reasons for prescribing or not prescribing antibiotics	47	0.63 (0.43, 0.92)	23	0.66 (0.39, 1.13)	11	0.60 (0.27, 1.26)	23	1.22 (0.69, 2.22)	46	0.89 (0.60, 1.36)
Q15. Doctors often explain clearly to the patient the instructions for the use of antibiotics	47	0.59 (0.37, 0.90)	23	0.59 (0.31, 1.16)	11	0.44 (0.17, 1.10)	23	0.77 (0.39, 1.54)	46	0.62 (0.39, 1.00)
Q16. When you buy antibiotics, the pharmacist tells you about the importance of correct therapeutic compliance/adherence	48	2.44 (1.27, 4.61)	23	1.50 (0.65, 3.46)	11	3.81 (0.89, 16.16)	24	1.27 (0.57, 2.84)	47	1.42 (0.78, 2.57)

№: number of events; aIqOR: adjusted interquartile Odds Ratio; *: adjusted for gender and age

5.4.2. Comparision study of cross-sectional and longitudinal approaches in studies about *Knowledge, Attitude* and *antibiotic* misuse *Practices* in Galicia

Participants' socio-demographic characteristics

Eight hundred forty-seven out of 890 individuals completed the baseline KAP questionnaire on antibiotics, of whom 115 showed signs of antibiotic misuse Practices. Forty-three approached individuals refused to participate in the study because of lack of time. One hundred (11.81%) of the 847 participants dropout from the study; 76 did not have time to answer the follow-up questions because of work or family duties and 24 had given incorrect phone number. Therefore, data collected from the remaining 747 individuals who answered the baseline questionnaire and at least one follow-up questionnaire were included in the analysis.

Table *14* represents the general demographic characteristics of the 747 individuals. Most of them were females (N= 560, 75.0%), university graduates (N= 462, 61.8%), employed (N= 561, 75.1%), and living in a household with ≤ 4 members (N= 609, 81.5%). Around half of the participants (N= 381, 51.0%) reported not always visiting the doctor in case of sickness and 40.0% (N= 299) declared ever receiving a medical prescription over the phone.

Regarding those 100 individuals who dropped out from the study, their level of agreement on Knowledge and Attitude statements was not notably different from that of those who were followed-up. Besides, the two groups did not differ with respect to antibiotic misuse practices.

5.4.2.1. Cross-Sectional data analysis

Seventy-eight individuals showed signs of antibiotic misuse *Practices*. In this study, antibiotic misuse was defined as the occurrence of one or more of the following *Practices*: use without prescription, shortened treatment, modified dose, doubling a skipped dose, or taking it when remembered. As shown in **Table *15***, low level of *Knowledge* and medically inappropriate *Attitudes* were substantially associated with antibiotic *misuse Practices*.

Association of Knowledge about antibiotics with the misuse Practices of these drugs

Individuals who highly agreed on using antibiotics to alleviate common cold symptoms had three-fold higher odds of antibiotic misuse than those who totally rejected using antibiotics for these purposes [**Q2** aOR: 2.48 (95%CI: 1.48, 4.15)] (**Table *15***).

Individuals who showed agreement on storing antibiotics at home for a potential need in the future had almost six times higher odds of antibiotic misuse than those who refused keeping antibiotics at home [**Q11** aOR: 5.66 (95%CI: 3.14, 10.22)] (**Table *15***).

Association of Attitudes towards antibiotics with the misuse Practices of these drugs

Individuals with a high level of agreement on the statement about quitting antibiotic treatment earlier than prescribed had considerable higher odds of antibiotic misuse than those who completely disagreed on abandoning antibiotic treatment before completing the recommended duration [**Q3** aOR: 4.44 (95%CI: 2.69, 7.32)] (**Table *15***).

Individuals who did not show a complete disagreement with the statement about tendency to get antibiotics from relatives or friends without consulting a doctor had five times higher odds of misusing antibiotics [**Q5** aOR:5.12 (95%CI: 2.83, 9.26)] than those who fully rejected this statement (**Table *15***).

Individuals who preferred using antibiotics to treat sore throat infections had substantial higher odds of antibiotic misuse than those who did not prefer to use antibiotic for these conditions [**Q6** aOR:2.68 (95%CI: 1.60, 4.49)] (**Table *15***).

High odds of antibiotic misuse were observed for those who mentioned that they do not usually adhere to the prescribed treatment regimen [**Q9** aOR: 2.88 (95%CI 1.09, 7.60)] (**Table *15***). Likewise, individuals who do not know that excessive intake of antibiotics renders them ineffective were more likely to misuse antibiotics than their counterparts [**Q10** aOR:1.94 (95%CI: 1.19, 3.18)] (**Table *15***).

Association of Attitudes towards healthcare-provider with the misuse Practices of these drugs

Higher odds of antibiotic misuse were observed for individuals who would accept buying unprescribed antibiotics even when the doctor does not prescribe them [**Q13** aOR: 2.47 (95%CI: 1.45, 4.20)] (**Table *15***).

5.4.2.2. Cohort data analysis

Person-time approach using Poisson regression: *Practices* of antibiotic misuse was reported by 46 individuals during the follow-up assessment. Unlike the findings of cross-sectional approach, Poisson regression analysis showed associations with antibiotic misuse *Practices* for only three of the 16 *Knowledge* and *Attitude* statements: **1)** agreement on the statement about the willingness to store antibiotics for a potential need in the future [**Q11** $aIRR_{6\text{-}10:}$ 2.33 (95%CI: 1.20, 4.54)], **2)** agreement on the statement about using antibiotics in case of cold symptoms [**Q2** $aIRR_{3\text{-}10}$: 2.28 (95%CI: 1.24, 4.21)] and **3)** incomplete agreement on adhering to the prescribed treatment guidelines [**Q9** aIRR: 3.02 (95%CI: 1.04, 8.70) (**Table *15***).

Longitudinal approach using GLMM: The follow-up data yielded fifty events of antibiotic misuse that were included in GLMM analysis. There was no association between the *Knowledge* and *Attitude* statements and antibiotic misuse *Practices*, except for the statement about the willingness to store antibiotics for a potential need in the future [**Q11** $aOR_{6\text{-}10}$: 2.64 (1.39, 5.02)] (**Table *15***).

Robustness analysis of the cohort approach

Table *16* about MICE (missing data) analysis demonstrates that there was no substantial difference between aIRRs computed from data collected in this study and those calculated from imputed data. In addition, MICE confirmed that *Knowledge* and *Attitudes* were not associated with *Practices* of misuse of antibiotics. The two sensitivity analyses under extreme assumptions, i.e., **1)** all individuals who dropped out had misused antibiotics and **2)** all individuals who dropped out had not misused antibiotics, yielded similar findings to that of MICE analysis (**Table *17***).

Table 14 General characteristic of individuals who participated in the study about the association of *Knowledge* and *Attitudes* with *Practices* of antibiotic misuse in Galicia

Characteristic	Total (№= 747)	Cross sectional Study (№= 747) Misuse		Cohort Study (№= 747) Misuse	
		No (№= 669)	Yes (№= 78)	No (№= 701)	Yes (№= 46)
Gender					
Male	187 (25%)	164 (24.5%)	23 (29.5%)	173 (24.7%)	14 (30.4%)
Female	560 (75%)	505 (75.5%)	55 (70.5%)	528 (75.3)	32 (69.6%)
Missing	0	0	0	0	0
Age					
<35 years	131 (17.5%)	114 (17%)	17 (21.8%)	122 (17.4%)	9 (19.6%)
36 - 45 years	373 (49.9%)	345 (51.6%)	28 (35.9%)	347 (49.5%)	26 (56.5%)
>= 46 years	243 (32.5%)	210 (31.4%)	33 (42.3%)	232 (33.1%)	11 (23.9%)
Missing	0	0	0	0	0
Educational level					
Until high school	258 (34.5%)	228 (34.1%)	30 (38.5%)	433 (61.8%)	17 (37%)
University	462 (61.8%)	418 (62.5%)	44 (56.4%)	241 (34.4%)	29 (63%)
Missing	27 (3.6%)	23 (3.4%)	4 (5.1%)	27 (3.9%)	0
Family size					
≤4	609 (81.5%)	543 (81.2%)	66 (84.6%)	569 (81.2%)	40 (87%)
>4	111 (14.9%)	102 (15.2%)	9 (11.5%)	105 (15%)	6 (13%)
Missing	27 (3.6%)	24 (3.6%)	3 (3.8%)	27 (3.9%)	0
Consulting a doctor					
Not always	381 (51%)	337 (50.4%)	44 (56.4%)	353 (50.4%)	28 (60.9%)
Always	338 (45.2%)	307 (45.9%)	31 (39.7%)	320 (45.6%)	18 (39.1%)
Missing	28 (3.7%)	25 (3.7%)	3 (3.8%)	28 (4%)	0
Phone medical consultation					
No	419 (56.1%)	378 (56.5%)	41 (52.6%)	388 (55.3%)	31 (67.4%)
Yes	299 (40%)	265 (39.6%)	34 (43.6%)	284 (40.5%)	15 (32.6%)
Missing	29 (3.4%)	26 (3.9%)	3 (3.8%)	29 (4.1%)	0
Employment status					
Employed	561 (75.1%)	502 (75%)	16 (20.5)	524 (74.8%)	9 (19.6%)
Unemployed	160 (21.4%)	144 (21.5%)	59 (75.6%)	151 (21.5%)	37 (80.4%)
Missing	26 (3.5%)	23 (3.4%)	3 (3.8%)	26 (3.7%)	0

№: Number of participants

Table 15 Associations of *Knowledge* and *Attitudes* with *Practices* of *antibiotic* misuse in Galicia assessed by cohort and cross-sectional approaches

Item	Level of agreement	Cohort Study (№=747) Poisson Analysis			Cohort Study (№=1442) GLMM Analysis			Cross-sectional Study (№=747)		
		Misuse		aIRR (95% CI)	Misuse		aOR (95% CI)	Misuse		aOR (95% CI)
		No	Yes		No	Yes		No	Yes	
Q1. Antibiotics are effective against viruses										
	0	319	17	1.00	634	18	1.00	305	31	1.00
	1-2	32	1	0.55 (0.72, 4.15)	69	1	0.50 (0.06, 3.82)	29	4	1.20 (0.39, 3.67)
	3-8	230	17	1.44 (0.73, 2.83)	438	17	1.34 (0.68, 2.63)	221	26	1.16 (0.66, 2.02)
	9-10	111	11	1.69 (0.79, 3.64)	230	14	1.99 (0.96, 4.09)	106	16	1.56 (0.81, 2.98)
Q2. When I get a cold, I take antibiotics to help me feel better faster										
	0	492	25	1.00	962	28	1.00	475	42	1.00
	1-2	55	3	0.96 (0.29, 3.18)	114	3	0.86 (0.57, 2.49)	53	5	1.11 (0.42, 2.94)
	3-10	151	18	2.28 (1.24, 4.21)	306	19	2.04 (0.27, 1.60)	139	30	2.48 (1.48, 4.15)
Q3. If I feel better after a few days, I sometimes stop taking my antibiotics before completing the course of treatment										
	0	504	30	1.00	989	32	1.00	501	33	1.00
	1	22	0	NA	44	0	NA	20	2	1.45 (0.32, 6.53)
	2-10	169	16	1.52 (0.82, 2.81)	345	18	1.55 (0.85, 2.83)	143	42	4.44 (2.69, 7.32)
Q4. I expect my doctor to prescribe antibiotics if I suffer from common cold or flu symptoms										
	0	329	18	1.00	630	21	1.00	315	32	1.00
	1-2	41	2	0.84 (0.19, 3.62)	86	2	0.66 (0.15, 2.89)	41	2	0.46 (0.11, 2.02)
	3-10	327	26	1.39 (0.76, 2.54)	665	27	1.21 (0.68, 2.16)	310	43	1.39 (0.85, 2.26)
Q5. It is good to be able to get antibiotics from relatives or friends without having to see a medical doctor										
	0	636	42	1.00	1267	46	1.00	622	56	1.00
	1-10	62	4	1.03 (0.37, 2.88)	116	4	0.93 (0.33, 2.64)	45	21	5.12 (2.83, 9.26)
Q6. When I have a sore throat, I prefer to use an antibiotic										
	0	480	35	1.00	971	37	1.00	476	39	1.00
	1-2	58	0	NA	105	0	NA	52	6	1.34 (0.54, 3.35)
	3-10	158	11	0.97 (0.48, 1.93)	308	13	1.07 (0.55, 2.06)	138	31	2.68 (1.60, 4.49)
Q7. Each type of infection needs a different antibiotic										
	0-5	191	12	0.87 (0.44, 1.75)	379	14	0.98 (0.38, 1.7)	181	22	1.17 (0.66, 2.08)
	6-8	168	9	0.76 (0.35, 1.64)	330	10	0.80 (0.38, 1.7)	155	22	1.34 (0.75, 2.39)
	9-10	335	24	1.00	663	25	1.00	326	33	1.00

Item	Level of agreement	Cohort Study (№=747) Poisson Analysis			Cohort Study (№=1442) GLMM Analysis			Cross-sectional Study (№=747)		
		Misuse		aIRR (95% CI)	Misuse		aOR (95% CI)	Misuse		aOR (95% CI)
		No	Yes		No	Yes		No	Yes	
Q8. If I feel side effects during a course of treatment of antibiotics, I should stop taking them as soon as possible										
	0-4	179	12	1.00	331	13	1.00	168	23	1.00
	5	174	9	0.69 (0.19, 1.65)	351	11	0.75 (0.33, 1.71)	170	13	0.58 (0.28, 1.19)
	6-10	342	25	0.99 (0.49, 1.98)	697	26	0.91 (0.46, 1.81)	326	41	0.90 (0.52, 1.56)
Q9. I take the antibiotics according to the doctor's instructions										
	0-6	21	4	3.02 (1.04, 8.70)	47	4	2.65 (0.89, 7.93)	19	6	2.88 (1.09, 7.60)
	7-9	129	6	0.69 (0.29, 1.65)	248	6	0.62 (0.26, 1.49)	115	20	1.70 (0.97, 2.99)
	10	542	36	1.00	1077	40	1.00	527	51	1.00
Q10. If antibiotics are consumed in excess, they will not work when they are really needed										
	1-9	217	15	0.96 (0.51, 1.80)	406	15	0.92 (0.49, 1.73)	197	35	1.94 (1.19, 3.18)
	10	471	31	1.00	916	35	1.00	462	40	1.00
Q11. I prefer to keep antibiotics at home in case there is a need for them later										
	0	423	23	1.00	828	24	1.00	423	23	1.00
	1-5	156	9	1.01 (0.47, 2.19)	319	9	0.94 (0.43, 2.04)	141	24	2.99 (1.63, 5.49)
	6-10	112	14	2.33 (1.20, 4.54)	224	17	2.64 (1.39, 5.02)	96	30	5.66 (3.14, 10.22)
Q12. I trust the doctor's decision if s/he decides to prescribe or not prescribe antibiotics										
	0-8	176	14	1.18 (0.63, 2.24)	333	14	1.19 (0.63, 2.25)	167	23	1.33 (0.79, 2.26)
	9-10	504	31	1.00	987	33	1.00	483	52	1.00
Q13. If I believe that I need an antibiotic and the doctor did not prescribe it, I will get it at the pharmacy without a prescription										
	0	574	37	1.00	1139	38	1.00	558	53	1.00
	1-10	116	9	1.27 (0.61, 2.64)	232	12	1.57 (0.81, 3.07)	101	24	2.47 (1.45, 4.20)
Q14. Doctors often explain clearly to the patient the reasons for prescribing or not prescribing antibiotics										
	0-5	310	15	0.74 (0.33, 1.65)	619	15	0.64 (0.3, 1.39)	291	34	1.12 (0.59, 2.13)
	6	58	4	1.15 (0.36, 3.67)	103	3	0.76 (0.21, 2.75)	54	8	1.46 (0.58, 3.66)
	7-9	167	16	1.50 (0.68, 3.31)	335	19	1.57 (0.21, 2.75)	163	20	1.18 (0.58, 2.41)
	10	153	10	1.00	308	12	1.00	148	15	1.00

Item	Level of agreement	Cohort Study (№=747) Poisson Analysis			Cohort Study (№=1442) GLMM Analysis			Cross-sectional Study (№=747)		
		Misuse		aIRR (95% CI)	Misuse		aOR (95% CI)	Misuse		aOR (95% CI)
		No	Yes		No	Yes		No	Yes	
Q15. Doctors often explain clearly to the patient the instructions for the use of antibiotics										
	0-5	200	12	0.73 (0.36, 1.48)	399	13	0.74 (0.37, 1.48)	185	27	1.27 (0.72, 2.23)
	6-8	226	12	0.70 (0.34, 1.41)	426	13	0.72 (0.36, 1.43)	217	21	0.87 (0.48, 1.57)
	9-10	260	22	1.00	528	24	1.00	254	28	1.00
Q16. When you buy antibiotics, the pharmacist tells you about the importance of correct therapeutic compliance/adherence										
	0-3	199	11	0.76 (0.33, 1.75)	395	12	0.66 (0.3, 1.46)	186	24	1.02 (0.53, 1.99)
	4-6	153	12	1.03 (0.45, 2.36)	305	13	0.9 (0.41, 1.98)	147	18	0.99 (0.49, 2.03)
	7-9	186	12	0.915 (0.40, 2.08)	367	11	0.68 (0.3, 1.52)	180	18	0.79 (0.39, 1.60)
	10	153	11	1.00	302	14	1.00	147	17	1.00

aIRR: Incidence Rate Ratio adjusted for age and gender; CI: Confidence Interval; GLMM: generalized linear mixed models; №: Number of participants; NA: Not applicable; aOR: Odds Ratio adjusted for age and gender. Misuse is defined as the occurrence of any of the following practices: use without prescription, shortened treatment, modified dose, doubling a skipped dose or taking it when remembered.

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Table 16 IRRs and 95%CI of misuse *Practices* of antibiotics in Galicia after imputation of missing data (MICE procedure)

Item	Imputed aIRR (95% CI)
Q1. Antibiotics are effective against viruses	
0	1.00
1-2	0.93 (0.63, 1.36)
3-8	1.06 (0.84, 1.33)
9-10	0.97 (0.74, 1.28)
Q2. When I get a cold, I take antibiotics to help me feel better faster	
0	1.00
1-2	1.07 (0.78, 1.48)
3-10	0.96 (0.69, 1.32)
Q3. If I feel better after a few days, I sometimes stop taking my antibiotics before completing the course of treatment	
0	1.00
1	0.92 (0.59, 1.43)
2-10	0.93 (0.66, 1.30)
Q4. I expect my doctor to prescribe antibiotics if I suffer from common cold or flu symptoms	
0	1.00
1-2	0.96 (0.62, 1.51)
3-10	0.96 (0.80, 1.17)
Q5. It is good to be able to get antibiotics from relatives or friends without having to see a medical doctor	
0	1.00
1-10	0.91 (0.39, 2.15)
Q6. When I have a sore throat, I prefer to use an antibiotic	
0	1.00
1-2	1.05 (0.75, 1.46)
3-10	0.99 (0.77, 1.26)
Q7. Each type of infection needs a different antibiotic	
0-5	1.11 (0.89, 1.39)
6-8	1.02 (0.83, 1.25)
9-10	1.00
Q8. If I feel side effects during a course of treatment of antibiotics, I should stop taking them as soon as possible	
0-4	1.00
5	0.92 (0.73, 1.17)
6-10	1.01 (0.80, 1.27)
Q9. I take the antibiotics according to the doctor's instructions	
0-6	0.77 (0.42, 1.42)
7-9	1.03 (0.84, 1.26)
10	1.00
Q10. If antibiotics are consumed in excess, they will not work when they are really needed	
1-9	0.94 (0.76, 1.17)
10	1.00
Q11. I prefer to keep antibiotics at home in case there is a need for them later	
0	1.00
1-5	0.98 (0.78, 1.23)
6-10	0.93 (0.70, 1.24)
Q12. I trust the doctor's decision if s/he decides to prescribe or not prescribe antibiotics	
0-8	0.90 (0.72, 1.12)
9-10	1.00
Q13. If I believe that I need an antibiotic and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	
0	1.00
1-10	1.01 (0.69, 1.48)
Q14. Doctors often explain clearly to the patient the reasons for prescribing or not prescribing antibiotics	
0-5	0.99 (0.77, 1.27)
8	1.05 (0.76, 1.45)
7-9	1.04 (0.82, 1.31)
10	1.00

Item	Imputed aIRR (95% CI)
Q15. Doctors often explain clearly to the patient the instructions for the use of antibiotics	
1-5	1.05 (0.82, 1.35)
6-8	1.04 (0.84, 1.29)
9-10	1.00
Q16. When you buy antibiotics, the pharmacist tells you about the importance of correct therapeutic compliance/adherence	
0-3	0.99 (0.77, 1.30)
4-6	1.10 (0.86, 1.40)
7-9	1.10 (0.88, 1.38)
10	1.00

aIRR: Incidence Rate Ratio adjusted for age and gender; CI: Confidence Interval. Misuse is defined as the occurrence of any of the following Practices: use without prescription, shortened treatment, modified dose, doubling a skipped dose, or taking it when remembered.

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Table 17 IRRs and 95%CI from the two sensitivity analyses of the longitudinal data collected in Galicia about misuse *Practices* of *antibiotics*

Item	Lost individuals considered as non cases (№= 847)			Lost individuals considered as cases (№= 847)		
	Misuse		aIRR (95% CI)	Misuse		aIRR (95% CI)
	No	Yes		No	Yes	
Q1. Antibiotics are effective against viruses						
0	354	17	1.00	15	356	1.00
1-2	46	3	1.45 (0.42, 5.00)	3	46	1.02 (0.74, 1.39)
3-8	256	15	1.25 (0.62, 2.51)	9	262	1.10 (0.93, 1.29)
9-10	135	11	1.70 (0.79, 3.65)	7	139	1.08 (0.88, 1.32)
Q2. When I get a cold, I take antibiotics to help me feel better faster						
0	553	25	1.00	24	554	1.00
1-2	66	3	0.95 (0.29, 3.15)	1	68	1.02 (0.79, 1.32)
3-10	179	18	2.19 (1.19, 4.04)	9	188	1.12 (0.94, 1.33)
Q3. If I feel better after a few days, I sometimes stop taking my antibiotics before completing the course of treatment						
0	570	30	1.00	23	577	1.00
1	40	1	0.45 (0.62, 3.33)	2	39	0.97 (0.70, 1.35)
2-10	185	15	1.64 (0.87, 3.09)	9	191	1.08 (0.91, 1.28)
Q4. I expect my doctor to prescribe antibiotics if I suffer from common cold or flu symptoms						
0	375	18	1.00	15	378	1.00
1-2	47	2	0.86 (0.20, 3.72)	2	47	1.00 (0.73, 1.35)
3-10	374	26	1.43 (0.78, 2.62)	17	383	1.00 (0.96, 1.15)
Q5. It is good to be able to get antibiotics from relatives or friends without having to see a medical doctor						
0	725	42	1.00	33	734	1.00
1-10	73	4	0.94 (0.34, 2.63)	1	76	1.14 (0.90, 1.46)
Q6. When I have a sore throat, I prefer to use an antibiotic						
0	540	35	1.00	24	551	1.00
1-2	67	0	N.A.	2	65	1.07 (0.82, 1.40)
3-10	188	11	0.90 (0.46, 1.80)	8	191	1.12 (0.94, 1.33)
Q7. Each type of infection needs a different antibiotic						
0-5	220	12	0.86 (0.43, 1.72)	6	226	1.04 (0.88, 1.23)
6-8	190	9	0.76 (0.35, 1.64)	10	189	0.99 (0.83, 1.19)
9-10	383	24	1.00	18	389	1.00
Q8. If I feel side effects during a course of treatment of antibiotics, I should stop taking them as soon as possible						
0-4	311	16	1.00	16	311	1.00
5	96	8	1.58 (0.68, 3.69)	5	99	0.90 (0.72, 1.14)
6-10	376	21	1.06 (0.55, 2.04)	13	384	0.99 (0.85, 1.15)

Item	Lost individuals considered as non cases (№= 847)			Lost individuals considered as cases (№= 847)		
	Misuse		aIRR (95% CI)	Misuse		aIRR (95% CI)
	No	Yes		No	Yes	
Q9. I take the antibiotics according to the doctor's instructions						
0-6	24	4	3.07 (1.08, 8.72)	3	25	0.99 (0.66, 1.48)
7-9	149	6	0.66 (0.28, 1.57)	6	149	1.03 (0.86, 1.24)
10	615	36	1.00	25	626	1.00
Q10. If antibiotics are consumed in excess, they will not work when they are really needed						
1-9	254	15	1.00 (0.53, 1.86)	14	255	0.99 (0.85, 1.15)
10	530	31	1.00	20	541	1.00
Q11. I prefer to keep antibiotics at home in case there is a need for them later						
0	479	23	1.00	19	483	1.00
1-5	177	9	1.02 (0.47, 2.21)	7	179	1.01 (0.85, 1.21)
6-10	131	14	2.39 (1.25, 4.65)	8	137	1.09 (0.90, 1.33)
Q12. I trust the doctor's decision if s/he decides to prescribe or not prescribe antibiotics						
0-8	207	14	1.27 (0.67, 2.40)	13	208	0.97 (0.83, 1.15)
9-10	569	31	1.00	21	579	1.00
Q13. If I believe that I need an antibiotic and the doctor did not prescribe it, I will get it at the pharmacy without a prescription						
0	652	37	1.00	30	659	1.00
1-10	134	9	1.23 (0.59, 2.56)	4	139	1.10 (0.92, 1.33)
Q14. Doctors often explain clearly to the patient the reasons for prescribing or not prescribing antibiotics						
0-5	356	15	0.70 (0.32, 1.57)	17	354	0.99 (0.83, 1.20)
6	63	4	1.09 (0.34, 3.50)	2	65	1.06 (0.79, 1.42)
7-9	192	16	1.47 (0.66, 3.24)	6	202	1.03 (0.84, 1.27)
10	172	10	1.00	9	173	1.00
Q15. Doctors often explain clearly to the patient the instructions for the use of antibiotics						
0-5	226	12	0.73 (0.36, 1.48)	8	230	0.96 (0.81, 1.14)
6-8	248	12	0.68 (0.34, 1.37)	8	252	0.97 (0.82, 1.15)
9-10	307	22	1.00	16	313	1.00
Q16. When you buy antibiotics, the pharmacist tells you about the importance of correct therapeutic compliance/adherence						
0-3	220	11	0.77 (0.33, 1.78)	13	218	0.96 (0.83, 1.24)
4-6	182	12	0.99 (0.43, 2.62)	6	188	1.03 (0.84, 1.28)
7-9	212	12	0.88 (0.39, 2.01)	6	218	1.01 (0.83, 1.24)
10	173	11	1.00	9	175	1.00

aIRR: Incidence Rate Ratio adjusted for age and gender; CI: Confidence Interval; №: Number of participants. Misuse is defined as the occurrence of any of the following Practices: use without prescription, shortened treatment, modified dose, doubling a skipped dose, or taking it when remembered.

5.5. Association of *Knowledge* and *Attitudes* with *Practices* of tranquilizer misuse

The two KAP studies about tranquilizers in Galicia and Lebanon have been published [Psychology and Health 2021 (in print) & Drug and Alcohol Dependence 2021 (in print)]. The corresponding publication of Drug and alcohol dependence is available in Annex II page 234. The article of Psychology and Health is not reproduced. Another manuscript about the comparison of cross-sectional and longitudinal approaches is currently under review by Journal of Clinical Medicine.

5.5.1. Cross-sectional study in Lebanon

Participants' socio-demographic characteristics

One thousand three-hundred ninety-six individuals completed the questionnaire. The socio-demographic characteristics of the study population is represented in **Table *18***.

Ninety-one (6.5%) participants reported using tranquilizers in the month preceding the study, and 63 (62.2%) of them presented one or more patterns of misuse. Most individuals who misused tranquilizers were females (N=51, 81%), married (N= 57, 90.5%) and had a professionally active spouse (N=55, 87.3%). Three quarters of tranquilizer misusers reported not always visiting a doctor in case of illness (N=47, 74.6%), two thirds were university graduates (N=52, 66.7%), a similar fraction declared ever receiving a phone medical prescription (N=40, 63.5%) and never consuming alcohol (N=39, 61.9%). Almost half of the misusers had upper-intermediate household income (N= 30, 47.6%).

Patterns of tranquilizer misuse

The major pattern of misuse was storing or sharing tranquilizer leftover (N=46, 73%), followed by use of tranquilizers without prescription (N=28, 44.4%), curtailing tranquilizer treatment course (N=26, 41.3%), changing the dose of tranquilizer without medical advice (N=18, 28.6%), and doubling the dose or taking it when remembered in case of forgetting to take a previous dose (N=12, 19.0%).

Association of knowledge about tranquilizers with the misuse Practices of these drugs

Awareness about the consequences of tranquilizers was associated with lower odds of misuse of these drugs (**Table *19***).

Substantial lower odds of tranquilizer misuse were observed for individuals who knew that tranquilizers: reduce people's control over their actions had [**Q5** aIqOR: 0.50 (95%CI: 0.33, 0.77)], could increase the risk of traffic accidents [**Q6** aIqOR: 0.62 (95%CI: 0.37, 1.00)] or affect children's learning abilities [**Q7** aIqOR: 0.69 (95%CI: 0.45, 1.00)] (**Table *19***).

Association of attitudes towards tranquilizers with the misuse Practices of these drugs

Substantial associations were observed between medically in appropriate and misuse of tranquilizers.

There were five-fold higher odds of misusing tranquilizers by individuals who concur on storing tranquilizers for potential need in the future as compared to those who don´t keep these medicines [**Q11** aIqOR: 5.00 (95%CI: 3.30, 7.59)] (**Table *19***). Higher odds were also observed for these specific misuse patterns: curtailing tranquilizers treatment course [**Q11** aIqOR: 8.66 (95%CI: 3.71, 19.97)], unprescribed use of tranquilizers [**Q11** aIqOR: 5.77 (95%CI: 3.18, 10.49)], and storing or sharing tranquilizer leftovers [**Q11** aIqOR: 5.77 (95%CI: 3.57, 9.24)] (**Table 20**).

Higher odds of any misuse pattern of tranquilizers were also obtained for individuals who would agree on taking tranquilizers to improve sleeping, work better or enjoy themselves [**Q1** $aIqOR_{sleep}$: 2.35 (95%CI: 1.82, 2.99), **Q4** $aIqOR_{work}$: 1.99 (95%CI: 1.69, 2.31) and **Q3** $aIqOR_{enjoy}$: 1.30 (95%CI: 1.20, 1.41)] (**Table *19***). As for the specific patterns of misuse, these attitudes were associated with higher odds of using unprescribed tranquilizers ($1.26 \leq aIqOR \leq 2.10$), truncating the tranquilizer treatment course ($1.34 \leq aIqOR \leq 2.00$), and storing or sharing tranquilizer leftover ($1.31 \leq aIqOR \leq 2.41$) (**Table 20**).

Individuals who would accept prolonging the course of treatment with tranquilizers beyond the prescribed duration were more likely to misuse tranquilizers in general [**Q2** aIqOR: 1.26 (95%CI: 1.16, 1.36)], and to store the leftover tranquilizers [**Q2** aIqOR: 1.25 (95%CI: 1.15, 1.37)] in specific (**Table *19*** and **Table 20**). Similar findings were observed for individuals who expressed their willingness to get tranquilizers without a prescription if they believe that they need these drugs, but the doctor did not prescribe them (**Table *19*** and **Table 20**).

On the contrary, lower odds of tranquilizer misuse were found for individuals who declared their willingness to follow the physician's instructions (**Q9**). They were less likely to take tranquilizers without prescription [**Q9** aIqOR: 0.72 (95%CI: 0.59, 0.90)], or to cut-down the course of treatment [**Q9** aIqOR: 0.69 (95%CI: 0.53, 0.86)] (**Table 20**).

Association of attitudes toward healthcare provider with the misuse Practices of tranquilizers

Individuals who thought the physician clearly explains the reasons of tranquilizers prescription or non-prescription were more likely to shorten the course of treatment [**Q14** aIqOR: 3.46 (95%CI: 1.19, 9.69)] (**Table 20**).

Table 18 Demographic characteristics of individuals participated in the cross-sectional study about the association of *Knowledge* and *Attitudes* with *Practices* of tranquilizer misuse in Lebanon

Characteristic	Total (№= 1396)	Any misuse in the last month (№= 63)
Gender		
Male	271 (19.4%)	8 (12.7%)
Female	1075 (77.0%)	51 (81.0%)
Missing	50 (3.6)	4 (6.3%)
Age		
<38 years	348 (24.9%)	20 (31.7%)
39 -42 years	225 (16.1%)	8 (12.7%)
43 - 47 years	304 (21.8%)	10 (15.9%)
>= 48 years	257 (18.4%)	12 (19.0)
Missing	262 (18.8%)	13 (20.6%)
Marital status		
Married	1307 (93.6%)	57 (90.5%)
Others	72 (5.2%)	6 (9.5%)
Missing	17 (1.2%)	0
Educational level		
Until high school	242 (17.3%)	21 (38.1%)
University	1144 (81.9%)	42 (66.7%)
Missing	10 (0.7%)	0
Spouse educational level		
Until high school	301 (21.6%)	24 (38.1%)
University	1020 (73.1%)	35 (55.6%)
Missing	75 (5.4%)	4 (6.3%)
Family size		
2-4	543 (38.9%)	28 (44.4%)
5-6	706 (50.6%)	27 (42.9%)
>6	127 (9.1%)	8 (12.7%)
Missing	20 (1.4%)	0
Monthly Family income		
<500 US$	19 (1.4%)	0
500 US$ - 1499 US$	253 (18.1%)	17 (27.0%)
1500 US$ - 2500 US$	218 (15.6%)	15 (23.8%)
>2500 US$	802 (57.4%)	30 (47.6%)
Missing	104 (7.4%)	1 (1.6%)
Consulting a doctor		
Rarely or never	151 (10.8%)	5 (7.9%)
Sometimes	743 (53.2%)	42 (66.7%)
Always	490 (35.1%)	16 (25.4%)
Missing	12 (0.9%)	0
Reasons for not consulting a doctor		
No need	386 (27.7)	17 (27.0%)
Fear	28 (2.0%)	1 (1.6%)
No money	123 (8.8%)	9 (14.3%)
No time	317 (22.7%)	24 (38.1%)
Long waiting time	164 (11.7%)	12 (19.0%)
No near clinic	52 (3.7%)	5 (7.9%)
Medical consultation over the phone		
No	478 (34.2%)	22 (34.9%)
Yes	887 (63.5%)	40 (63.5%)
Missing	21 (2.2%)	1 (1.6%)
Employment status		
Employed	1039 (74.4%)	36 (57.1%)
Unemployed	336 (24.1%)	27 (42.9%)
Missing	21 (1.5%)	0
Spouse Employment Status		
Employed	1164 (83.4%)	55 (87.3%)
Unemployed	150 (10.7%)	3 (4.8%)
Missing	82 (5.9%)	5 (7.9%)
Alcohol Intake		
Never	625 (44.8%)	39 (61.9%)
In special occasions	421 (30.2%)	14 (22.2%)
Others	319 (22.9%)	10 (15.9%)
Missing	31 (2.2%)	0

№: Number of participants

Table 19 Association of *Knowledge* and *Attitudes* with any pattern of misuse *Practices* of tranquilizers by parents of schoolchildren in Lebanon

Knowledge and Attitude Statements	Q1	Q2	Q3	No misuse №	Misuse №	aOR* (95%CI)	aIqOR (95%CI)
Q1. I would agree to take tranquilizers in order to sleep better	0	0	3	1147	49	1.33 (1.22, 1.44)	2.35 (1.82, 2.99)
Q2. If I feel better after a few days, I sometimes keep taking my tranquilizers even after completing the prescribed course of treatment	0	0	1	1137	49	1.26 (1.16, 1.36)	1.26 (1.16, 1.36)
Q3. I would take tranquilizers in order to enjoy myself with my family	0	0	1	1137	49	1.30 (1.20, 1.41)	1.30 (1.20, 1.41)
Q4. I would agree to take tranquilizers when I feel down and sad in order to work better	0	0	2	1140	50	1.41 (1.30, 1.52)	1.99 (1.69, 2.31)
Q5. Tranquilizers reduce people's control over what they do	5	8	10	1131	50	0.87 (0.80, 0.95)	0.50 (0.33, 0.77)
Q6. People taking tranquilizers are at increased risk of traffic accidents	5	8	10	1131	49	0.91 (0.82, 1.00)	0.62 (0.37, 1.00)
Q7. Psychotropic drugs (such as tranquilizers) may affect children's learning abilities when prescribed to them	6	8	10	1121	50	0.91 (0.82, 1.00)	0.69 (0.45, 1.00)
Q8. If I feel side effects during a course of treatment of tranquilizers, I should stop taking it as soon as possible	6	9	10	1123	49	1.02 (0.93, 1.13)	1.08 (0.75, 1.63)
Q9. I take the tranquilizers according to the doctor's instructions	8	10	10	1116	48	0.93 (0.84, 1.02)	0.86 (0.71, 1.04)
Q10. If tranquilizers are consumed in excess, they won't work when they are really needed	8	10	10	1115	48	0.96 (0.87, 1.07)	0.92 (0.76, 1.14)
Q11. I prefer to keep tranquilizers at home in case there is a need for them later	0	0	5	1131	48	1.38 (1.27, 1.50)	5.00 (3.30, 7.59)
Q12. I trust the doctor's decision if s/he decides to prescribe or not prescribe tranquilizers	5	8	10	1124	49	1.07 (0.96, 1.18)	1.40 (0.82, 2.29)
Q13. If I believe that I need a tranquilizer and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	0	0	1	1131	49	1.30 (1.20, 1.41)	1.30 (1.20, 1.41)
Q14. Doctors often explain clearly to the patient the reasons for prescribing or not prescribing tranquilizers	2	6	8	1123	48	1.04 (0.95, 1.13)	1.27 (0.74, 2.08)
Q15. Doctors often explain clearly to the patient the instructions for the use of tranquilizers	5	7	9	1116	48	0.98 (0.89, 1.08)	0.92 (0.63, 1.36)
Q16. When you buy tranquilizers, the pharmacist tells you about the importance of correct therapeutic compliance/adherence	4	6	9	1116	49	1.06 (0.96, 1.17)	1.34 (0.82, 2.19)

*aOR: adjusted odds ratio; aIqOR: adjusted interquartile OR; Q1: 1st quartile; Q2: 2nd quartile; Q3: 3rd quartile; №: Number of participants; *: OR adjusted for age, gender and spouse employment status*

Table 20 Association of *Knowledge* and *Attitudes* with specific patterns of misuse *Practices* of tranquilizers by parents of schoolchildren in Lebanon

Knowledge and Attitude Statements	Unprescribed use				Shortening treatment				Storing leftover			
	Misuse №		aOR* (95%CI)	aIqOR (95%CI)	Misuse №		aOR* (95%CI)	aIqOR (95%CI)	Misuse №		aOR* (95%CI)	aIqOR (95%CI)
	No	Yes			No	Yes			No	Yes		
Q1. I would agree to take tranquilizers in order to sleep better	1158	24	1.28 (1.14, 1.43)	2.10 (1.48, 2.92)	1167	17	1.26 (1.11, 1.44)	2.00 (1.37, 2.99)	1130	41	1.34 (1.22, 1.46)	2.41 (1.82, 3.11)
Q2. If I feel better after a few days, I sometimes keep taking my tranquilizers even after completing the prescribed course of treatment	1148	24	1.1 (0.96, 1.25)	1.10 (0.96, 1.25)	1157	17	1.15 (0.99, 1.33)	1.15 (0.99, 1.33)	1120	41	1.25 (1.15, 1.37)	1.25 (1.15, 1.37)
Q3. I would take tranquilizers in order to enjoy myself with my family	1148	24	1.26 (1.13, 1.41)	1.26 (1.13, 1.41)	1157	17	1.34 (1.18, 1.53)	1.34 (1.18, 1.53)	1121	41	1.31 (1.20, 1.43)	1.31 (1.20, 1.43)
Q4. I would agree to take tranquilizers when I feel down and sad in order to work better	1152	24	1.34 (1.2, 1.49)	1.80 (1.44, 2.22)	1160	17	1.40 (1.23, 1.6)	1.96 (1.51, 2.56)	1126	42	1.41 (1.29, 1.55)	1.99 (1.66, 2.40)
Q5. Tranquilizers reduce people's control over what they do	1143	24	0.87 (0.77, 0.98)	0.50 (0.27, 0.90)	1151	17	0.90 (0.78, 1.03)	0.59 (0.29, 1.16)	1116	42	0.88 (0.81, 0.96)	0.53 (0.35, 0.82)
Q6. People taking tranquilizers are at increased risk of traffic accidents	1142	24	0.88 (0.77, 1.00)	0.53 (0.27, 1.00)	1150	17	0.98 (0.82, 1.17)	0.90 (0.37, 2.19)	1116	41	0.91 (0.82,1.01)	0.62 (0.37, 1.05)
Q7. Psychotropic drugs (such as tranquilizers) may affect children's learning abilities when prescribed to them	1133	24	0.91 (0.79, 1.05)	0.69 (0.39, 1.22)	1141	17	1.10 (0.88, 1.37)	1.46 (0.60, 3.52)	1106	42	0.91 (0.82, 1.02)	0.69 (0.45, 1.08)
Q8. If I feel side effects during a course of treatment of tranquilizers, I should stop taking it as soon as possible	1134	24	1.09 (0.93, 1.28)	1.41 (0.75, 2.68)	1142	17	1.21 (0.94, 1.55)	2.14 (0.78, 5.77)	1107	41	1.03 (0.92, 1.15)	1.13 (0.72, 1.75)
Q9. I take the tranquilizers according to the doctor's instructions	1126	24	0.85 (0.77, 0.95)	0.72 (0.59, 0.90)	1134	17	0.83 (0.73, 0.93)	0.69 (0.53, 0.86)	1100	40	0.95 (0.85, 1.06)	0.90 (0.72, 1.12)
Q10. If tranquilizers are consumed in excess, they won't work when they are really needed	1125	24	0.97 (0.84, 1.12)	0.94 (0.71, 1.25)	1133	17	1.28 (0.92, 1.77)	1.64 (0.85, 3.13)	1099	40	0.97 (0.87, 1.10)	0.94 (0.76, 1.21)
Q11. I prefer to keep tranquilizers at home in case there is a need for them later	1141	24	1.42 (1.26, 1.6)	5.77 (3.18, 10.49)	1149	17	1.54 (1.30, 1.82)	8.66 (3.71, 19.97)	1115	40	1.42 (1.29, 1.56)	5.77 (3.57, 9.24)
Q12. I trust the doctor's decision if s/he decides to prescribe or not prescribe tranquilizers	1135	24	0.96 (0.85, 1.09)	0.82 (0.44, 1.54)	1143	17	1.04 (0.88, 1.22)	1.22 (0.53, 2.70)	1109	41	1.12 (0.99, 1.26)	1.76 (0.95, 3.18)
Q13. If I believe that I need a tranquilizer and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	1142	24	1.41 (1.27, 1.56)	1.41 (1.27, 1.56)	1150	17	1.53 (1.35, 1.74)	1.53 (1.35, 1.74)	1115	41	1.26 (1.15, 1.38)	1.26 (1.15, 1.38)
Q14. Doctors often explain clearly to the patient the reasons for prescribing or not prescribing tranquilizers	1134	23	1.09 (0.97, 1.24)	1.68 (0.83, 3.64)	1142	16	1.23 (1.03, 1.46)	3.46 (1.19, 9.69)	1107	40	1.04 (0.94, 1.14)	1.27 (0.69, 2.19)
Q15. Doctors often explain clearly to the patient the instructions for the use of tranquilizers	1127	23	0.95 (0.83, 1.09)	0.81 (0.47, 1.41)	1135	16	1.05 (0.88, 1.26)	1.22 (0.60, 2.52)	1100	40	1.00 (0.89, 1.11)	1.00 (0.63, 1.52)
Q16. When you buy tranquilizers, the pharmacist tells you about the importance of correct therapeutic compliance/adherence	1127	24	1.11 (0.96, 1.28)	1.69 (0.82, 3.44)	1135	17	1.11 (0.94, 1.32)	1.69 (0.73, 4.01)	1100	41	1.05 (0.93, 1.16)	1.28 (0.70, 2.10)

*aOR: adjusted odds ratio; aIqOR: adjusted interquartile OR; №: Number of participants; *: OR adjusted for age, gender and spouse employment*

5.5.2. Cohort study in Spain

Participants' socio-demographic characteristics

Seven hundred forty-seven (88.19%) out of 847 recruited participants were included in the main analysis.

Table *21* represents the demographic characteristics of the participants. Most of the participants were females (N=506, 74.97%), employed (N = 561, 75.10%) and living in a household of a maximum of four members (N= 609, 81.53%). More than half of them were university graduates (N= 462, 61.85%), and had never consumed alcohol (N= 421, 56.36%). Around half of the participants had between 36 and 45 years (N=373, 49.93%) and a similar fraction declared not always consulting the doctor in case of illness (N=381, 51.00%). Two hundred ninety-nine (40.02%) participants reported ever receiving a phone medical prescription over the phone.

Fifty-eight tranquilizer misuse events were identified during the follow-up producing an overall incidence rate of 0.17 $year^{-1}$.

Association of knowledge about tranquilizers with the misuse Practices of these drugs

The level of knowledge about the consequences of tranquilizer was not associated with the misuse Practices of these drugs (**Table *22***).

Individuals who were not aware that tranquilizers decrease people's control over their actions [**Q5** 1st tertile aIRR: 1.29 (95%CI: 0.65, 2.59)], influence the learning capacity of children [**Q7** 1st tertile: aIRR: 1.17 (95%CI: 0.58, 2.33)] or become ineffective when taken in excess [**Q10** aIRR: 1.31 (95%CI: 0.74, 2.32)] were not at a higher risk of misusing tranquilizers as compared to those who had a better level of knowledge (**Table *22***).

Association of attitudes towards tranquilizers with the misuse Practices of these drugs

There were strong associations between medically inappropriate attitudes towards tranquilizers with the misuse Practices of these drugs (**Table *22***).

Individuals who showed agreement on statements about using tranquilizers to sleep or work better are at considerable higher risk of tranquilizer misuse than those who disagreed on taking tranquilizers for these purposes [**Q1** 3rd tertile: aIRR: 5.10 (95%CI: 2.74, 9.48) and **Q4** aIRR: 2.04 (95%CI: 1.05, 3.99)] (**Table *22***).

Individuals who did not totally disagree on extending tranquilizers treatment course without medical advice had two-fold higher risk of misusing these drugs than those who totally disagreed on this statement [**Q2** aIRR: 2.45 (95%CI: 1.46, 4.13)] (**Table *22***).

Individuals who do not completely refuse the intake of tranquilizers for recreational purposes are at increased risk of misusing these drugs as compared to those who totally disagreed on using tranquilizers for this motive [**Q3** 2nd tertile: aIRR: 1.85 (95%CI: 1.04, 3.32)] (**Table *22***).

Individuals who showed a preference to storing tranquilizers at home for a future need had five folds higher risk than those who totally disagree on storing tranquilizers [**Q11** aIRR: 5.07 (95%CI: 2.73, 9.40)] (**Table *22***).

Association of attitudes toward healthcare provider with the misuse Practices of tranquilizers
There was an association between negative patient-healthcare provider relationship and misuse of tranquilizers.

Individuals who declared incompletely trusting the physician's decision about tranquilizers prescription had double the risk of misusing these drugs than those who fully trust their physician [**Q12** aIRR: 1.92 (95%CI: 1.12, 3.30)] (**Table *22***).

Individuals who thought that the physician do not always explain to the patient the reasons of prescribing/non-prescribing tranquilizers with enough clarity are at increased risk of tranquilizer misuse [**Q14** 2nd tertile: aIRR: 1.98 (95%CI: 0.97, 4.06)] (**Table *22***).

Robustness Analysis

We re-estimated the aIRR under two extreme assumptions; 1) when supposing that all individuals who dropped had not experienced the event (tranquilizer misuse) similar results to those of the main analysis were obtained, but 2) when assuming that all individuals who dropped out had misused tranquilizers, the magnitude of the association was meaningfully smaller.

As shown in **Table *22***, MICE analysis confirmed the association of Knowledge and Attitudes with Practices of tranquilizer misuse, but the magnitude of association was smaller. The greatest differences were seen for aIRR estimates of **Q1** (from 5.10, 95%CI: 2.74-9.48 to 2.16, 95%CI: 1.46-3.19), **Q2** (from 2.45, 95%CI: 1.46-4.13 to 1.58, 95%CI: 1.11-2.26) and **Q11** (from 5.07, 95%CI: 2.73-9.40 to 1.70, 95%CI: 1.13-2.56).

Following the correction for non-differential exposure misclassification using the sensitivity and specificity estimates, a higher magnitude of ORs was observed, particularly high for **Q2, Q3, Q6, Q13, Q14** and **Q16** (data not shown). The results we observed were then conservative.

Table 21 General characteristic of individuals who participated in the study about the association of *Knowledge* and *Attitudes* with *Practices* of tranquilizer misuse in Galicia

Characteristic	Total (№= 747)	Tranquilizer Misusers (№= 58)
Sex		
Male	187 (25.03%)	8 (13.79%)
Female	560 (74.97%)	50 (86.21%)
Missing	0	0
Age		
<35 years	131 (17.54%)	8 (13.79%)
36 - 45 years	373 (49.93%)	27 (46.55%)
>= 46 years	243 (32.53%)	23 (39.66%)
Missing	0	0
Educational level		
Until high school	258 (34.54%)	22 (37.93%)
University	462 (61.85%)	36 (62.07%)
Missing	27 (3.61%)	0
Family size		
≤4	609 (81.53%)	52 (89.66%)
>4	111 (14.86%)	6 (10.34%)
Missing	27 (3.61%)	0
Consulting a doctor		
Not always	381 (51.00%)	37 (63.79%)
Always	338 (45.25%)	21 (36.21%)
Missing	28 (3.75%)	0
Medical consultation over the phone		
No	419 (56.09%)	29 (50.00%)
Yes	299 (40.03%)	28 (48.28%)
Missing	29 (3.88%)	1 (1.72%)
Employment status		
Employed	561 (75.10%)	39 (67.24%)
Unemployed	160 (21.42%)	19 (32.76)
Missing	26 (3.48%)	0
Alcohol Intake		
Never/less than once per month	421 (56.36%)	35 (60.34%)
Others	298 (39.89%)	23 (39.66%)
Missing	28 (3.75%)	0

№: Number of participants

Table 22 Incidence Rate Ratio (IRR) of *tranquilizer* misuse *Practices* according to quantiles of levels of agreement of the Galician population on *Knowledge* and *Attitudes* statements

***Knowledge* or *Attitude* Statement** Quantile of level of agreement	**Level of agreement***	**Person-weeks of observations**	**Misuse №**	**Crude IRR (95%CI)**	**Adjusted IRR (95%CI)****	
					Without imputation	**After imputation**
Q1. I would agree to take tranquilizers in order to sleep better						
1st tertile	0-5	9988	18	1.00	1.00	1.00
2nd tertile	6-7	1893	13	3.81 (1.87, 7.78)	3.19 (1.54 – 6.61)	1.69 (1.16, 2.45)
3rd tertile	8-10	2380	26	6.06 (3.32, 11.06)	5.10 (2.74 – 9.48)	2.16 (1.46, 3.19)
Q2. If I feel better after a few days, I sometimes keep taking my tranquilizers even after completing the prescribed course of treatment						
Totally disagree	0	9776	28	1.00	1.00	1.00
Not totally disagree	1-10	4027	29	2.51 (1.50, 4.22)	2.45 (1.46 – 4.13)	1.58 (1.11, 2.26)
Q3. I would take tranquilizers in order to enjoy myself with my family						
1st tertile	0	8108	24	1.00	1.00	1.00
2nd tertile	1-5	4146	22	1.79 (1.01, 3.20)	1.85 (1.04 - 3.32)	1.26 (0.85, 1.86)
3rd tertile	6-10	1921	11	1.93 (0.95, 3.95)	1.87 (0.91 - 3.85)	1.64 (0.99, 2.70)
Q4. I would agree to take tranquilizers when I feel down and sad in order to work better						
1st tertile	0-1	7779	23	1.00	1.00	1.00
2nd tertile	2-5	4156	20	1.63 (0.89, 2.96)	1.63 (0.89 - 2.97)	1.11 (0.79, 1.57)
3rd tertile	6-10	2190	14	2.16 (1.11, 4.20)	2.04 (1.05 – 3.99)	1.47 (0.98, 2.21)
Q5. Tranquilizers reduce people's control over what they do						
1st tertile	0-5	6305	30	1.41 (0.71, 2.81)	1.29 (0.65 - 2.59)	1.37 (0.76, 2.47)
2nd tertile	6-9	4324	15	1.03 (0.47, 2.23)	1.07 (0.49 – 2.32)	1.29 (0.86, 1.94)
3rd tertile	10	3261	11	1.00	1.00	1.00
Q6. People taking tranquilizers are at increased risk of traffic accidents						
1st tertile	0-5	4121	19	1.17 (0.64, 2.14)	1.08 (0.59 - 1.97)	1.26 (0.83, 1.90)
2nd tertile	6-8	3868	12	0.80 (0.39, 1.58)	0.79 (0.40 - 1.59)	1.12 (0.81, 1.55)
3rd tertile	9-10	6105	24	1.00	1.00	1.00

***Knowledge* or *Attitude* Statement** Quantile of level of agreement	**Level of agreement***	**Person-weeks of observations**	**Misuse №**	**Crude IRR (95%CI)**	**Adjusted IRR (95%CI)****	
					Without imputation	**After imputation**
Q7. Psychotropic drugs (such as tranquilizers) may affect children's learning abilities when prescribed to them						
1st tertile	0-5	5717	25	1.23 (0.62, 2.44)	1.17 (0.58 - 2.33)	1.13 (0.61, 2.07)
2nd tertile	6-9	5013	18	1.01 (0.49, 2.09)	1.05 (0.51 - 2.18)	1.09 (0.71, 1.67)
3rd tertile	10	3369	12	1.00	1.00	1.00
Q8. If I feel side effects during a course of treatment of tranquilizers, I should stop taking it as soon as possible						
Disagree	0-5	6498	25	1.00	1.00	1.00
Agree	6-10	7589	32	1.10 (0.65, 1.85)	1.19 (0.70 – 2.01)	0.80 (0.57, 1.12)
Q9. I take the tranquilizers according to the doctor's instructions						
Totally agree	10	9148	31	1.00	1.00	1.00
No totally agree or disagree	0-9	4827	26	1.59 (0.94, 2.68)	1.66 (0.98 - 2.80)	1.13 (0.78, 1.64)
Q10. If tranquilizers are consumed in excess, they won't work when they are really needed						
Disagree	0-5	3512	17	1.30 (0.73, 2.29)	1.31 (0.74 - 2.32)	1.08 (0.74, 1.57)
Agree	6-10	10452	39	1.00	1.00	1.00
Q11. I prefer to keep tranquilizers at home in case there is a need for them later						
1st tertile	0	7521	15	1.00	1.00	1.00
2nd tertile	1-5	3488	10	1.44 (0.65, 3.20)	1.46 (0.66 - 3.25)	1.32 (0.88, 1.97)
3rd tertile	6-10	2975	32	5.39 (2.92, 9.96)	5.07 (2.73 - 9.40)	1.70 (1.13, 2.56)
Q12. I trust the doctor's decision if s/he decides to prescribe or not prescribe tranquilizers						
Totally agree	10	7318	22	1.00	1.00	1.00
No totally agree or disagree	0-9	6867	35	1.70 (0.99, 2.89)	1.92 (1.13 - 3.30)	1.29 (0.91, 1.83)
Q13. If I believe that I need a tranquilizer and the doctor did not prescribe it, I will get it at the pharmacy without a prescription						
Totally disagree	0	10882	38	1.00	1.00	1.00
No totally disagree or agree	1-10	3253	18	1.58 (0.90, 2.78)	1.55 (0.88 - 2.73)	1.19 (0.77, 1.84)

***Knowledge* or *Attitude* Statement** Quantile of level of agreement	**Level of agreement***	**Person-weeks of observations**	**Misuse №**	**Crude IRR (95%CI)**	**Adjusted IRR (95%CI)****	
					Without imputation	**After imputation**
Q14. Doctors often explain clearly to the patient the reasons for prescribing or not prescribing tranquilizers						
1st tertile	0-5	6234	22	1.16 (0.56, 3.84)	1.30 (0.63 - 2.68)	1.35 (0.73, 2.49)
2nd tertile	6-9	4211	24	1.88 (0.92, 3.84)	1.98 (0.97 – 4.06)	1.31 (0.87, 1.95)
3rd tertile	10	3630	11	1.00	1.00	1.00
Q15. Doctors often explain clearly to the patient the instructions for the use of tranquilizers						
Not tally agree or disagree	0-7	7247	27	0.85 (0.50, 1.42)	0.91 (0.54 - 1.52)	1.10 (0.71, 1.72)
Totally agree	8-10	6810	30	1.00	1.00	1.00
Q16. When you buy tranquilizers, the pharmacist tells you about the importance of correct therapeutic compliance/ adherence						
1st tertile	0-4	3670	20	1.10 (0.58, 2.10)	1.16 (0.61 - 2.23)	1.39 (0.79, 2.44)
2nd tertile	5-8	6890	20	0.59 (0.31, 1.12)	0.62 (0.32 – 1.20)	1.12 (0.70, 1.79)
3rd tertile	9-10	3440	17	1.00	1.00	1.00

*CI: Confidence Interval; №: Number of participants; IRR: Incidence Rate Ratio; *: participants level of agreement on the corresponding statement expressed in a 0-10 Likert scale; **: IRR adjusted for sex, age and occupational status*

5.5.3. Comparison study of cross-sectional and longitudinal approaches in studies about *Knowledge, Attitude* and *tranquilizer* misuse Practices in Galicia

Association of Knowledge with Practices of tranquilizer misuse

The cross-sectional and longitudinal approaches on tranquilizer misuse revealed that globally, there is no association between the level of *Knowledge* (Q5-Q8 and Q10) and the outcome *"any misuse" Practices* of tranquilizers (**Table *23***). However, the analysis of the individual types of misuse *Practices* using the longitudinal approach indicated substantial higher odds of the *Practice* "sharing or storing tranquilizer leftover" by individuals who do not know that *tranquilizers can affect people's control over what they do* **(Q5)** [$aOR_{1st\ tertile}$= 3.24 (95% CI: 1.12 - 9.38)], and by those who are not aware of *an excessive consumption of tranquilizers might reduce their effect in the future* **(Q10)** [$aOR_{1st\ tertile}$= 4.12 (95% CI: 1.5 - 11.33)]. These associations were not observed in the cross-sectional approach (**Table *24***).

Association of personal Attitude towards tranquilizers with misuse Practices

Both approaches showed a strong association between personal *Attitudes* towards tranquilizers and the misuse *Practices* of these drugs, nevertheless the magnitude of association was different between the cross-sectional and the longitudinal approaches.

In reference to people with the lowest level of agreement, there are considerable higher odds of the outcome "any misuse" *Practice* by individuals who would *agree to take tranquilizers to improve sleep* [**Q1**, cross-sectional: $aOR_{3rd\ tertile}$: 4.90 (95% CI: 2.66 – 9.02); longitudinal $aOR_{3rd\ tertile}$: 5.72 (95% CI: 2.43 - 13.44)], *enjoy themselves* [**Q3**, cross-sectional: $aOR_{3rd\ tertile}$: 2.55 (95% CI: 1.35 - 4.83); longitudinal $aOR_{3rd\ tertile}$: 2.07 (95% CI: 0.88 - 4.82)] or *work better* [**Q4**, cross-sectional: $aOR_{3rd\ tertile}$: 3.18 (95% CI: 1.69 - 5.26); longitudinal $aOR_{3rd\ tertile}$: 2.35 (1.04 - 5.28)] (**Table *23***).

The odds of the outcome "any misuse" *Practice* are also high for individuals who would accept *continue taking tranquilizers even after completing the prescribed course of treatment* [**Q2**, cross-sectional: $aOR_{3rd\ tertile}$= 4.79 (95% CI: 2.39 - 9.60); longitudinal: $aOR_{3rd\ tertile}$= 6.33 (95% CI: 2.45 - 16.34)]; are willing to *keep tranquilizers at home in case of future need* [**Q11**, cross-sectional $aOR_{3rd\ tertile}$= 6.75 (95% CI: 3.49 - 13.08); longitudinal: $aOR_{3rd\ tertile}$= 9.49 (4.05 - 22.25)]; or who would *agree on getting tranquilizers without a prescription* [**Q13**, cross-sectional $aOR_{3rd\ tertile}$ 4.20 (95% CI: 1.99 - 8.87); longitudinal: $aOR_{3rd\ tertile}$= 5.5 (95% CI: 2.03 - 14.87)] (**Table *23***).

Individuals with those medically disapproved attitudes are at substantial higher odds of "shortening the course of treatment", "storing tranquilizer leftover" and "modifying the prescribed dose" (**Table *24***).

Association of patients' *Attitudes* towards healthcare provider and tranquilizer misuse *Practices*

The longitudinal approach showed that an incomplete *trust with the doctors' decision to prescribe tranquilizers or not* (**Q12**) is associated with higher odds of the outcome "any misuse" *Practices* of tranquilizers [**Q12** $aOR_{2nd\ tertile}$= 2.23 (95% CI: 1.08 - 4.6)] (**Table *23***). In the cross-sectional analysis, the association was not observed between **Q12** and the outcome "any

misuse" *Practices.* Nevertheless, the cross-sectional approach showed higher odds of the outcomes "shortening the course of treatment" [**Q12** $aOR_{1st\ tertile}$= 3.11 (95% CI: 1.20 - 8.07)] and "modifying the prescribed dose" [**Q12** $aOR_{1st\ tertile}$= 2.45 (95% CI: 1.12 - 5.39)] (**Table *23*** and **Table *24***). No association was observed between Q12 and "modifying the prescribed dose" [**Q12** $aOR_{1st\ tertile}$= 0.66(95% CI: 0.16 - 2.75)] in the longitudinal approach (**Table *24***).

There was not enough observations to analyze the outcome "shortening the course of treatment" using the longitudinal approach. The cross-sectional approach revealed that strongly *believing that pharmacists do not properly explain the importance of correct therapeutic compliance* (**Q16**) is associated with higher odds of "shortening the course of treatment" [**Q16** $aOR_{1st\ tertile}$= 2.96 (95% CI: 1.00 - 8.74)] (**Table *24***).

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Table 23 Estimates of the association of *Knowledge* and *Attitudes* of the Galician population with any misuse *Practice* of tranquilizers using cross-sectional and longitudinal approaches

Knowledge or Attitude Statement, level of agreement	**Cross-sectional approach (№= 847)**			**Longitudinal approach (№= 1343)**		
	No misuse (№)	**Misuse (№)**	**aOR (95%CI)***	**No misuse (№)**	**Misuse (№)**	**aOR (95%CI)****
Q1. I would agree to take tranquilizers in order to sleep better						
0-5	528	27	1.00	857	40	1.00
6-8	150	21	2.64 (1.43 – 4.88)	217	44	4.63 (2.17 - 9.88)
9-10	81	26	4.90 (2.66 – 9.02)	129	37	5.72 (2.43 - 13.44)
Q2. If I feel better after a few days, I will keep taking my tranquilizers even after completing the prescribed course of treatment						
0	529	35	1.00	835	62	1.00
1-5	163	23	2.22 (1.26 – 3.91)	265	31	1.66 (0.79 - 3.47)
6-10	44	16	4.79 (2.39 – 9.60)	63	28	6.33 (2.45 - 16.34)
Q3. I would take tranquilizers in order to enjoy myself with my family						
0	439	31	1.00	696	57	1.00
1-5	215	24	1.69 (0.96 – 2.99)	343	37	1.58 (0.78 - 3.19)
6-10	99	19	2.55 (1.35 – 4.83)	156	27	2.07 (0.88 - 4.82)
Q4. I would agree to take tranquilizers when I feel down and sad in order to work better						
0	380	23	1.00	597	51	1.00
1-5	254	26	1.77 (0.98 - 3,20)	417	35	1.16 (0.57 - 2.37)
6-10	116	24	3.18 (1.69 - 5.96)	177	35	2.35 (1.04 - 5.28)
Q5. Tranquilizers reduce people's control over what they do						
0-4	150	21	1.33 (0.72 - 2.44)	245	44	1.91 (0.87 - 4.2)
5-7	297	24	0.79 (0.44 – 1.42)	461	39	0.89 (0.42 - 1.89)
8-10	290	29	1.00	465	37	1.00
Q6. People taking tranquilizers are at increased risk of traffic accidents						
0-5	216	25	1.11 (0.60 – 2.03)	343	36	1.06 (0.48 - 2.33)
6-9	289	24	0.86 (0.47 – 1.56)	447	43	0.99 (0.46 - 2.1)
10	245	24	1.00	400	38	1.00
Q7. Psychotropic drugs (such as tranquilizers) may affect children's learning abilities when prescribed to them						
0-5	313	34	1.09 (0.62 – 1.90)	477	56	0.97 (0.48 - 1.97)
6-8	196	14	0.78 (0.39 – 1.56)	319	21	0.57 (0.24 - 1.38)
9-10	241	25	1.00	393	40	1.00
Q8. If I feel side effects during a course of treatment of tranquilizers, I should stop taking it as soon as possible						
0-5	346	19	0.72 (0.41 – 1.26)	542	49	0.89 (0.43 - 1.85)
6-9	165	19	1.11 (0.58 – 2.12)	256	34	1.57 (0.68 - 3.62)
10	238	26	1.00	388	38	1.00
Q9. I would take the *tranquilizers* according to the doctor's instructions						
0-7	163	14	1.00 (0.53 – 1.88)	259	22	0.88 (0.38 – 2.00)
8-9	100	12	1.42 (0.71 – 2.82)	150	28	2.59 (1.15 - 5.88)
10	480	47	1.00	768	71	1.00

Knowledge or Attitude Statement, level of agreement	**Cross-sectional approach (№= 847)** **No misuse (№)**	**Misuse (№)**	**aOR (95%CI)***	**Longitudinal approach (№= 1343)** **No misuse (№)**	**Misuse (№)**	**aOR (95%CI)****
Q10. If *tranquilizers* are consumed in excess, they won't work when they are really needed						
0-6	216	15	0.66 (0.35 – 1.25)	328	40	1.49 (0.73 - 3.03)
7-9	147	17	1.21 (0.66 – 2.23)	224	27	1.51 (0.66 - 3.44)
10	380	41	1.00	627	51	1.00
Q11. I prefer to keep *tranquilizers* at home in case there was a need for them later						
0-3	485	23	1.00	780	36	1.00
4-8	202	27	3.00 (1.66 – 5.43)	296	44	2.7 (1.28 - 5.70)
9-10	62	23	6.75 (3.49–13.08)	102	41	9.49 (4.05 - 22.25)
Q12. I will trust the doctor's decision if s/he decided to prescribe or not prescribe *tranquilizers*						
0-6	166	19	1.35 (0.75 – 2.46)	268	30	1.35 (0.61 - 3.01)
7-9	202	18	1.05 (0.57 – 1.93)	302	43	2.23 (1.08 - 4.6)
10	387	37	1.00	626	48	1.00
Q13. If I believe that I need a *tranquilizer* and the doctor did not prescribe it, I will get it at the pharmacy without a prescription						
0	579	47	1.00	828	84	1.00
1-5	138	14	1.31 (0.68 – 2.52)	207	13	0.65 (0.25 - 1.66)
6-10	36	12	4.20 (1.99 – 8.87)	57	23	5.5 (2.03 - 14.87)
Q14. I think that doctors often explain clearly to the patients the reasons for prescribing or not prescribing *tranquilizers*						
0-5	334	28	0.93 (0.52 – 1.67)	516	50	1.04 (0.5 - 2.16)
6-8	175	22	1.45 (0.78 – 2.71)	254	34	1.57 (0.7 - 3.54)
9-10	242	24	1.00	418	37	1.00
Q15. I think that doctors often explain clearly to the patients the instructions for the use of *tranquilizers*						
0-5	291	27	1.19 (0.66 – 2.14)	453	42	0.95 (0.46 - 1.96)
6-8	181	21	1.50 (0.80 – 2.81)	261	34	1.49 (0.68 - 3.25)
9- 10	280	24	1.00	473	45	1.00
Q16. I think that, when dispensing *tranquilizers*, the pharmacists tell the customers about the importance of correct therapeutic compliance/adherence						
0-4	182	24	0.89 (0.48 – 1.65)	298	43	1.24 (0.55 - 2.77)
5-8	388	24	0.46 (0.25 – 0.83)	578	42	0.59 (0.27 - 1.28)
9-10	178	26	1.00	298	36	1.00

CI: Confidence interval; №: Number of Participants; OR: Odds Ratio; ***:** *OR adjusted for age, gender, alcohol intake and medical consultation over the phone;* ****:** *OR adjusted for age, gender, employment status and frequency of doctor consultation in case of illness. Misuse is defined as the occurrence of any of the following Practices: use without prescription, shortened treatment, modified dose, doubling a skipped dose, or taking it when remembered.*

Table 24 Estimates of the association of *Knowledge* and *Attitudes* of the Galician population with specific aspects of misuse *Practices* of tranquilizers using cross-sectional and longitudinal approaches

Knowledge or Attitude	Cross-sectional approach (№= 847)						Longitudinal approach (№= 1343)			
Statement	**Shortened treatment**		**Stored leftover**		**Changed dose**		**Stored leftover**		**Changed dose**	
Level of agreement	**№**	**aOR (95%CI)***	**№**	**aOR (95%CI)***	**№**	**aOR (95%CI)***	**№**	**aOR (95%CI)****	**№**	**aOR (95%CI)****
Q1. I would agree to take tranquilizers in order to sleep better										
0-5	7	1.00	15	1.00	14	1.00	20	1.00	7	1.00
6-8	9	3.93 (1.41, 10.95)	15	3.29 (1.55, 6.97)	7	1.52 (0.59, 3.90)	19	3.36 (1.24, 9.13)	7	4.31 (1.03, 17.93)
9-10	8	5.93 (2.04, 17.19)	17	5.84 (2.76, 12.36)	13	4.13 (1.81, 9.45)	18	4.55 (1.51, 13.74)	25	16.98 (4.67, 61.77)
Q2. If I feel better after a few days, I will keep taking my tranquilizers even after completing the prescribed course of treatment										
0	10	1.00	22	1.00	13	1.00	27	1.00	19	1.00
1-5	8	2.42 (0.94, 6.28)	15	2.19 (1.10, 4.36)	14	3.47 (1.59, 7.59)	20	2.66 (1.04, 6.78)	9	1.3 (0.39, 4.32)
6-10	6	5.78 (2.01, 16.69)	10	4.54 (2.02, 10.22)	7	4.33 (1.57, 11.95)	10	3.59 (0.98, 13.22)	11	4.93 (1.35, 17.94)
Q3. I would take tranquilizers in order to enjoy myself with my family										
0	11	1.00	19	1.00	13	1.00	30	1.00	18	1.00
1-5	6	1.97 (0.71, 5.47)	17	1.92 (0.97, 3.80)	10	1.59 (0.68, 3.70)	10	0.88 (0.31, 2.5)	11	1.1 (0.35, 3.44)
6-10	7	1.34 (0.51, 3.55)	11	2.48 (1.13, 5.44)	11	3.27 (1.37, 7.76)	17	2.63 (0.93, 7.45)	10	1.8 (0.52, 6.16)
Q4. I would agree to take tranquilizers when I feel down and sad in order to work better										
0	9	1.00	15	1.00	11	1.00	21	1.00	22	1.00
1-5	8	2.25 (0.85, 5.96)	14	1.37 (0.65, 2.91)	12	1.62 (0.70, 3.74)	13	1.16 (0.42, 3.21)	7	0.52 (0.16, 1.74)
6-10	6	1.02 (0.36, 2.91)	17	3.45 (1.65, 7.21)	10	2.33 (0.93, 5.82)	23	3.54 (1.27, 9.85)	10	1.22 (0.36, 4.09)
Q5. Tranquilizers reduce people's control over what they do										
0-4	5	0.84 (0.28, 2.52)	12	1.11 (0.52, 2.37)	11	1.85 (0.78, 4.42)	26	3.24 (1.12, 9.38)	16	2.4 (0.71, 8.05)
5-7	9	0.84 (0.33, 2.11)	16	0.81 (0.41, 1.62)	12	1.00 (0.42, 2.36)	16	0.97 (0.33, 2.89)	14	1.24 (0.37, 4.17)
8-10	10	1.00	19	1.00	11	1.00	14	1.00	9	1.00
Q6. People taking tranquilizers are at increased risk of traffic accidents										
0-5	6	0.77 (0.26, 2.28)	18	1.39 (0.67, 2.89)	12	0.98 (0.42, 2.29)	20	1.43 (0.5, 4.12)	9	0.98 (0.28, 3.4)
6-9	10	1.03 (0.40, 2.68)	15	0.90 (0.42, 1.91)	9	0.62 (0.26, 1.51)	20	1.13 (0.39, 3.24)	17	1.32 (0.42, 4.15)
10	8	1.00	14	1.00	12	1.00	16	1.00	13	1.00
Q7. Psychotropic drugs (such as tranquilizers) may affect children's learning abilities when prescribed to them										
0-5	4	2.38 (0.71, 7.92)	8	2.00 (0.85, 4.72)	13	0.90 (0.39, 2.04)	30	1.17 (0.47, 2.92)	18	1.14 (0.35, 3.66)
6-8	10	1.78 (0.73, 4.36)	17	1.41 (0.73, 2.73)	8	0.96 (0.38, 2.45)	4	0.26 (0.06, 1.21)	12	1.51 (0.43, 5.31)
9-10	10	1.00	22	1.00	12	1.00	20	1.00	9	1.00
Q8. If I feel side effects during a course of treatment of tranquilizers, I should stop taking it as soon as possible										
0-5	9	0.46 (0.18, 1.16)	16	0.55 (0.27, 1.12)	14	0.83 (0.37, 1.87)	18	0.53 (0.2, 1.42)	13	0.69 (0.23, 2.11)
6-9	5	0.61 (0.20, 1.80)	13	1.09 (0.51, 2.32)	9	1.09 (0.42, 2.80)	18	1.27 (0.44, 3.65)	10	1.25 (0.35, 4.4)
10	11	1.00	18	1.00	11	1.00	21	1.00	16	1.00
Q9. I would take the tranquilizers according to the doctor's instructions										
0-7	6	2.31 (0.90, 5.91)	10	1.11 (0.52, 2.35)	9	1.57 (0.69, 3.57)	17	2.03 (0.74, 5.55)	4	0.56 (0.13, 2.42)
8-9	7	2.22 (0.74, 6.60)	8	1.45 (0.64, 3.32)	6	1.34 (0.48, 3.73)	15	3.45 (1.17, 10.15)	9	2.17 (0.66, 7.14)
10	11	1.00	29	1.00	19	1.00	25	1.00	26	1.00

Knowledge or Attitude	Cross-sectional approach (№= 847)						Longitudinal approach (№= 1343)			
Statement	**Shortened treatment**		**Stored leftover**		**Changed dose**		**Stored leftover**		**Changed dose**	
Level of agreement	**№**	**aOR (95%CI)***	**№**	**aOR (95%CI)***	**№**	**aOR (95%CI)***	**№**	**aOR (95%CI)****	**№**	**aOR (95%CI)****
Q10. If tranquilizers are consumed in excess, they won't work when they are really needed										
0-6	5	0.58 (0.21, 1.65)	11	0.85 (0.41, 1.78)	10	1.18 (0.50, 2.75)	26	4.12 (1.5, 11.33)	12	1.72 (0.52, 5.66)
7-9	5	1.21 (0.42, 3.47)	11	1.22 (0.58, 2.57)	7	1.48 (0.61, 3.59)	16	3.09 (0.96, 9.93)	16	3.72 (1.16, 11.94)
10	14	1.00	25	1.00	15	1.00	12	1.00	11	1.00
Q11. I prefer to keep tranquilizers at home in case there was a need for them later										
0-3	7	1.00	14	1.00	11	1.00	20	1.00	8	1.00
4-8	9	2.71 (0.98, 7.48)	14	6.86 (3.11, 15.11)	10	2.05 (0.85, 4.95)	15	1.38 (0.47, 4.01)	13	3.91 (1.11, 13.83)
9-10	8	6.86 (2.37, 19.86)	19	11.78(5.54, 25.02)	12	6.08 (2.50, 14.83)	22	6.72 (2.34, 19.3)	18	13.94 (3.82, 50.85)
Q12. I will trust the doctor's decision if s/he decided to prescribe or not prescribe tranquilizers										
0-6	10	3.11 (1.20, 8.07)	11	1.25 (0.59, 2.65)	13	2.45 (1.12, 5.39)	19	2.33 (0.81, 6.69)	7	0.66(0.16, 2.75)
7-9	6	1.55 (0.53, 4.57)	14	1.46 (0.72, 2.95)	7	0.93 (0.35, 2.48)	23	2.97 (1.1, 8.03)	13	1.78(0.6, 5.24)
10	8	1.00	22	1.00	14	1.00	15	1.00	19	1.00
Q13. If I believe that I need a tranquilizer and the doctor did not prescribe it, I will get it at the pharmacy without a prescription										
0	15	1.00	27	1.00	17	1.00	38	1.00	28	1.00
1-5	4	1.05 (0.34, 3.25)	10	1.66 (0.78, 3.57)	9	2.15 (0.90, 5.14)	9	1.1 (0.34, 3.51)	4	0.66(0.15, 2.9)
6-10	5	4.40 (1.50, 12.93)	9	5.05 (2.17, 11.74)	7	6.15 (2.35, 16.05)	9	3.1 (0.81, 11.84)	7	3.2(0.76, 13.52)
Q14. I think that doctors often explain clearly to the patients the reasons for prescribing or not prescribing tranquilizers										
0-5	8	2.41 (0.85, 6.84)	17	1.06 (0.50, 2.25)	15	1.14 (0.49, 2.62)	28	4.11 (1.11, 15.24)	15	0.88(0.29, 2.64)
6-8	9	0.81 (0.30, 2.24)	17	2.07 (0.97, 4.41)	9	1.33 (0.53, 3.37)	25	7.87 (2.04, 30.36)	8	1.04(0.3, 3.67)
9-10	7	1.00	13	1.00	10	1.00	4	1.00	16	1.00
Q15. I think that doctors often explain clearly to the patients the instructions for the use of tranquilizers										
0-5	6	2.78 (0.91, 8.56)	16	1.24 (0.59, 2.60)	15	1.53 (0.66, 3.52)	23	2.26 (0.75, 6.83)	11	0.74(0.22, 2.45)
6-8	11	1.24 (0.47, 3.27)	16	2.01 (0.95, 4.26)	8	1.32 (0.51, 3.44)	25	4.65 (1.52, 14.23)	12	1.78(0.57, 5.59)
9- 10	7	1.00	14	1.00	10	1.00	9	1.00	16	1.00
Q16. I think that, when dispensing tranquilizers, the pharmacists tell the customers about the importance of correct therapeutic compliance/adherence										
0-4	11	2.96 (1.00, 8.74)	13	0.72 (0.34, 1.53)	12	1.95 (0.82, 4.66)	19	1.4 (0.47, 4.2)	14	0.83(0.27, 2.59)
5-8	8	1.23 (0.39, 3.84)	16	0.43 (0.21, 088)	11	0.69 (0.29, 1.63)	23	0.8 (0.28, 2.25)	7	0.33(0.1, 1.09)
9-10	5	1.00	18	1.00	11	1.00	15	1.00	18	1.00

CI: Confidence interval; №: Number of participants; OR: Odds Ratio; ****:*** *OR adjusted for age, gender, alcohol intake and medical consultation over the phone* *****:*** *OR adjusted for age, gender, employment status and frequency of doctor consultation in case of illness.*

5.6. Dose-response meta-analysis of the association of income with antibiotic misuse *Practices*

The manuscript of the meta-analysis of income and antibiotic misuse was submitted for publication and is currently under review by European Journal of Health Economics.

Literature Search and Study Selection

The selection process of studies about the association of income with antibiotic misuse *Practices* is represented in **Figure *7***. Out of 1,453 identified studies, 314 were selected for full text review. Fifty-one studies involving 51,008 individuals and 18,094 antibiotic misuse events were included in the meta-analysis (**Table *25***). These studies originated from 22 countries and were published between 2001 and 2021. All studies were of cross-sectional design and published in English, except for one in Spanish [165] and another in Croatian [166].

Continuous approach of dose-response meta-analysis

The data the 51 studies included in the meta-analysis were compatible with a flat linear association between income standardized to GDP per capita based on PPP and antibiotic misuse (OR= 1.00; p-value= 0.954, *p*-value non-linearity= 0.452). **Figure *8*** represents the dose-response trend of summary ORs of antibiotic misuse conferred by income standardized to GDP per capita based on PPP. Likewise, the association of income standardized to adjusted net national income per capita and antibiotic misuse followed a flat linear trend (OR= 1.00; p-value= 0.940).

Categorical approach of dose-response meta-analysis

In the analysis of income standardized to GDP per capita based on PPP, overall, in reference to low income (1st tertile), there is no association between income and general antibiotic misuse [medium income$_{2nd\ tertile}$: OR= 1.04 (95%CI: 0.89, 1.20), and high income$_{3rd\ tertile}$: OR= 1.03 (95%CI: 0.82, 1.29)] (**Table *26***). However, in the subgroup analysis, certain associations between income and antibiotic misuse were observed. As compared with low income individuals, those with medium income are at 19% higher odds of the misuse *Practice* "*storage of antibiotic leftover"* [OR=1.19 (95%CI: 1.07, 1.32)]; but high income individuals have 51% lower odds of the misuse *Practice* "*non-adherence"* to antibiotic treatment [OR= 0.49, (95%CI: 0.34, 0.70)] (**Table *26***). In upper-middle wealth countries, high income people have 11% higher odds of any *Practice* of antibiotic misuse than those with low income (OR= 1.11; 95%CI: 1.00, 1.22) (**Table *26***). An association of medium income level with antibiotic misuse was also suggested in African countries (OR= 1.18; 95%CI: 1.00, 1.39) (**Table *26***).

Comparing to studies undertaken until 2015, there were higher odds of antibiotic misuse in medium income [OR $_{until\ 2015}$= 0.95 (95%CI: 0.75, 1.20) and OR $_{after\ 2015}$= 1.12 (95%CI: 0.99, 1.26)] and high income individuals [OR$_{until\ 2015}$= 0.91 (95%CI: 0.62, 1.35) and OR$_{after\ 2015}$= 1.15 (95%CI: 0.93, 1.41)] after 2015 (**Table *26***). There was no meaningful difference in the odds of antibiotic misuse by income level (medium and high) when countries were classified according to the literacy rate of their population (**Table *26***).

Similar findings were obtained for the categorical approach of income standardized to net national income per capita to that of income standardized to GDP per capita based on PPP (data not shown).

Methodological characteristics of studies included in the dose-response meta-analysis of income and antibiotic misuse *Practices*

Studies were sub-grouped based on their use of a pretested or validated questionnaire. No meaningful change in the pooled OR estimates were observed for medium and high income when the analysis was restricted to those studies that used pretested or validated questionnaires [OR_{medium}= 1.06 (95%CI: 0.91, 1.24) and OR_{high}= 1.04 (95%CI: 0.85, 1.27) (**Table *26***).

Stratifying the studies according to their comparability for age, gender, education and family size, showed that studies that incompletely controlled for those variables generated higher ORs than those with complete control for the four variables. This observation applies for both medium income [$OR_{incomplete}$= 1.09; (95%CI: 0.95, 1.24) and $OR_{complete}$= 0.90 (95%CI: 0.71, 1.15)] and high income categories [$OR_{incomplete}$= 1.05 (95%CI: 0.84, 1.31) and $OR_{complete}$= 0.60 (95%CI: 0.30, 1.23)] (**Table *26***).

There was no notable difference in the summary estimates upon stratifying the analysis according to the quality score of studies (**Table *26***).

The shape of the funnel plot (**Figure *9***) and the results of Egger's test (p-value = 0.39) and that of the trim-and-fill analysis which did not suggest the addition of any study, confirmed the absence of publication bias.

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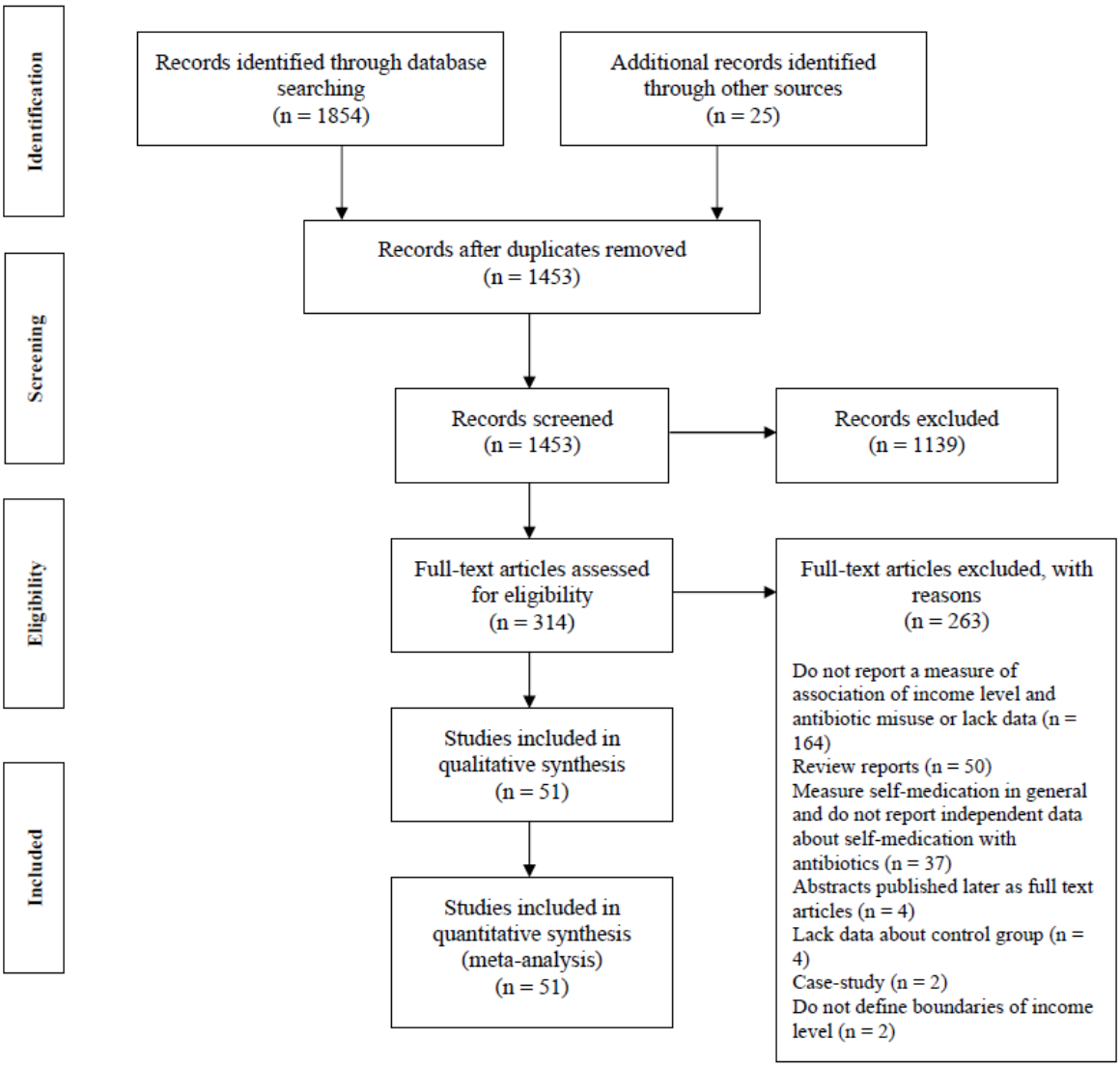

Figure 7 Flow diagram of the selection of studies about income level and misuse of antibiotics

Table 25 General characteristics of studies included the meta-analysis of income level and antibiotic misuse

Author, Year	Country	Setting	Age (Years)	Sex	Outcome	Mean Income (USD)	Total N/level	Outcome/ level	Odds Ratio (95%CI)	Adjustment, restriction or matching variables
Moktan 2021 [167]	India	Attendants of public hospital	18-90	M: 309 F: 195	Use without prescription	37.50 112.51 225.01 375.01	137 185 129 53	41 59 52 19	Reference category 1.10 (0.68 - 1.77) 1.58 (0.95 - 2.63) 1.31 (0.67 - 2.56)	age, gender, educational level, marital status, public and private clinics, frequency of doctors' consultation, family/friend influence (other family members self-medicating with antibiotics), symptoms (minor illness)
Chen 2020 [168]	Mali	Medical university students	Mean (SD) 21.3 (2.4)	M:310 F:136	Storage of antibiotics	82.95 506.50 1181.60	290 114 42	168 77 27	Reference category 1.51 (0.96 - 2.38) 1.31 (0.67 - 2.56)	age
					Use without prescription	82.95 506.50 1181.60	290 114 42	73 29 19	Reference category 1.01 (0.62 - 1.67) 2.46 (1.27 - 4.77)	
Elmahi 2020 [169]	Sudan	General population	≥18	M: 130 F: 116	Use without prescription	49.50 149.50	182 64	110 38	1.05 (0.59 - 1.87) Reference category	age, pregnancy, current antibiotic use
Mallah 2020 [170]	Lebanon	Children´s caregivers	≥18	M:276 F:1092	Any misuse practice	249.50 999.50 2000.00 3000.50	21 260 223 808	2 34 17 36	Reference category 1.43 (0.32 - 6.41) 0.78 (0.17 - 3.65) 0.44 (0.10 - 1.98)	age, sex, educational level, area of residence, alcohol consumption, access to medical care facilities, and frequency of telephone medical consultation.,
Nusair 2020 [171]	Jordan	General population	0 to >65	M: 674 F: 1169	Use without prescription	88.75 266.61 444.11	175 659 1042	61 253 458	Reference category 1.16 (0.82 - 1.65) 1.47 (1.05 - 2.05)	past month antibiotic use
Rathish 2020 [48]	Sri Lanka	General population	Mean (SD): 36 (21)	M: 181 F: 203	Use without prescription	150.00 450.00	267 117	263 111	Reference category 2.15 (0.37 - 12.54)	NA
Xu 2020 [172]	China	Children´s caregivers	Parents with children <13 years old	M: 1344 F: 4935	Use without prescription	377.50 1132.58 1887.58	--- --- ---	--- --- ---	Reference category 0.76 (0.57 - 1.03) 0.81 (0.54 - 1.21)	age, gender, educational level, medical background, residential location
					Storage of antibiotics	377.50 1132.58 1887.58	--- --- ---	--- --- ---	Reference category 1.03 (0.91 - 1.17) 1.16 (0.99 - 1.36)	
Ateshim 2019 [173]	Eritrea	General population	Median (IQR): 37 (24)	M: 238 F: 339	Use without prescription	0.00 32.53 113.78 211.28	291 92 136 58	--- --- --- ---	Reference category 0.92 (0.54 - 1.56) 1.22 (0.78 - 1.19) 1.43 (0.75 - 2.73)	age, gender, educational level, marital status, occupational status, knowledge about antibiotics, attitudes towards antibiotics

Author, Year	Country	Setting	Age (Years)	Sex	Outcome	Mean Income (USD)	Total N/level	Outcome/ level	Odds Ratio (95%CI)	Adjustment, restriction or matching variables
Benameur 2019 [174]	Saudi Arabia	University students	Mean (SD): 20.96 (0.148)	M:166 F:69	Use without prescription	133.37 667.50 1468.63	164 50 18	95 26 14	Reference category 0.79 (0.42 - 1.49) 2.54 (0.80 - 8.06)	age, gender, educational level, marital status, speciality (medical vs non-medical), residential location, health insurance
Bogale 2019 [49]	Ethiopia	General population	18 to > 60	M: 246 F: 349	Use without prescription	10.75 32.27 64.52 107.52	--- --- --- ---	46 74 42 92	Reference category 2.55 (1.18 - 5.50) 1.08 (0.47 - 2.46) 1.42 (0.62 - 3.25)	age, gender, educational level, marital status, residential location, occupational status, healthcare profession
Bulabula 2019 [47]	South Africa	Pregnant women attending public hospital	Mean (SD): 29 (6.1)	F: 301	Use without prescription	49.50 174.50 375.00 625.00	--- --- --- ---	--- --- --- ---	Reference category 5.40 (0.90 - 29.90) 4.10 (0.80 - 19.40) 6.40 (1.20 - 35.20)	age, gender, educational level, residential location, knowledge about antibiotics, attitudes towards antibiotics
Mate 2019 [175]	Mozambique	General population	Median (IQR): 33 (25-47)	M:294 F:797	Use without prescription	21.24 63.75 127.51 212.51	528 224 183 117	108 45 40 26	Reference category 0.98 (0.66 - 1.44) 1.09 (0.72 - 1.64) 1.11 (0.68 - 1.80)	age
					Incomplete course of treatment	21.24 63.75 127.51 212.51	506 215 175 114	150 68 60 21	Reference category 1.10 (0.78 - 1.55) 1.24 (0.86 - 1.79) 0.54 (0.32 - 0.89)	
Mukattash 2019 [176]	Jordan	Children´s caregivers	20 to ≥ 50	M: 134 F: 712	Use without prescription	352.50 1058.21 1763.21	94 325 427	41 141 150	Reference category 0.99 (0.62 - 1.57) 0.70 (0.44 - 1.10)	age
Sun 2019 [59]	China	Children´s caregivers	Parents with children <13 years old	M: 2243 F: 7283	Storage of antibiotics	230.50 615.50 1154.00 1923.00	2102 2889 2749 1786	874 1434 1355 917	Reference category 1.22 (1.08 - 1.38) 1.17 (1.02 - 1.33) 1.36 (1.16 - 1.60)	age, gender of the parents, gender of the child, educational level, socioeconomic characteristics (residential location and GDP per capita), health insurance, specialty (medical vs non-medical)
Hu 2018 [177]	China	Medical university students	Mean (SD): 22 (1.5)	M: 661 F: 1158	Use without prescription	768.50 2306.50	1565 254	59 18	Reference category 1.95 (1.13 - 3.36)	age, gender, educational level, parents' educational level, parents medical background, residential location, knowledge - attitudes - and practice score, center of recruitment

Author, Year	Country	Setting	Age (Years)	Sex	Outcome	Mean Income (USD)	Total N/level	Outcome/ level	Odds Ratio (95%CI)	Adjustment, restriction or matching variables
Tong 2018 [52]	China	Attendants of primary care clinics	<45 to >60	M:340 F:374	Non-adherence	153.20	162	150	Reference category	age, gender, educational level, residential location, occupation, employment status, knowledge about antibiotics
						344.78	180	163	0.72 (0.33 - 1.57)	
						651.18	187	158	0.40 (0.20 - 0.82)	
						880.98	185	150	0.33 (0.16 - 0.66)	
Peng 2018 [50]	China	University students	*Guizhou* Mean (SD): 21.3 (2.1) *Zhejiang* Mean (SD): 19.7 (2.6)	M: 2035 F: 1960	Use without prescription	230.92	---	---	Reference category	age, socioeconomic characteristics (GDP per capita and residential location)
						1001.00	---	---	0.65 (0.39 - 1.09)	
						2079.08	---	---	0.66 (0.33 - 1.31)	
					Storage of antibiotics	230.92	---	---	Reference category	
						1001.00	---	---	1.30 (1.10 - 1.53)	
						2079.08	---	---	1.14 (0.90 - 1.43)	
					Buying without prescription	230.92	---	---	Reference category	
						1001.00	---	---	1.14 (0.90 - 1.44)	
						2079.08	---	---	1.05 (0.76 - 1.46)	
Redzick 2018 [166]	Croatia	Attendants of primary care clinics	---	M: 142 F: 402	Use without prescription	84.62	88	5	Reference category	age
						226.12	55	13	5.14 (1.72 - 15.38)	
						339.32	97	4	0.71 (0.19 - 2.75)	
						452.52	100	15	2.93 (1.02 - 8.42)	
						594.02	199	25	2.39 (0.88 - 6.45)	
Wang 2018 [178]	China	University students	Mean (SD): 20.7 (2.7)	M: 5515 F: 5677	Storage of antibiotics	230.92	3417	---	Reference category	age, gender, educational level, parents' educational level, parents medical background, residential location, speciality (medical vs non-medical)
						1001.00	5823	---	1.15 (1.04 - 1.27)	
						2310.08	1435	---	1.02 (0.88 - 1.19)	
						3850.08	517	---	1.00 (0.81 - 1.23)	
					Use without prescription	230.92	3417	---	Reference category	
						1001.00	5823	---	0.89 (0.67 - 1.19)	
						2310.08	1435	---	1.13 (0.75 - 1.71)	
						3850.08	517	---	0.93 (0.53 - 1.63)	
Abdelrahman 2017 [179]	Saudi Arabia	General population	<18 to >65	M: 735 F: 293	Use without prescription	200.12	368	112	Reference category	age
						867.62	146	60	1.59 (1.07 - 2.37)	
						2002.50	198	72	1.31 (0.91 - 1.88)	
						3337.63	316	146	1.96 (1.43 - 2.69)	
Albawani 2017 [180]	Yemen	Attendants of pharmacies	Mean (SD): 28.6 (7.7)	M: 204 F: 159	Use without prescription	116.80	268	229	Reference category	age
						352.80	51	46	1.57 (0.59 - 4.19)	
						581.90	44	41	2.33 (0.69 - 7.89)	

Author, Year	Country	Setting	Age (Years)	Sex	Outcome	Mean Income (USD)	Total N/level	Outcome/ level	Odds Ratio (95%CI)	Adjustment, restriction or matching variables
Erku 2017 [54]	Ethiopia	General population	Mean (SD): 33.19 (10.82)	M: 163 F: 487	Any misuse practice	50.00 125.50 175.50	331 201 118	282 170 83	Reference category 0.95 (0.58 - 1.55) 0.41 (0.25 - 0.68)	age, gender, educational level, marital status, household size, employment status, frequency of visiting health care institutions, satisfaction about healthcare service
Gebrekirstos 2017 [181]	Ethiopia	Attendants of pharmacies	Median (IQR): 30 (16)	M: 473 F: 307	Use without prescription	3.26 13.00 26.00 39.02	130 92 81 477	76 41 32 218	1.67 (1.13 - 2.48) 0.96 (0.61 - 1.50) 0.78 (0.48 - 1.26) Reference category	age, gender, educational status, marital status, employment status, household size, residential location, type of illness, healthcare insurance, previous experience with antibiotics, access to healthcare
Gillani 2017 [182]	Pakistan	Non-medical university students	Mean (SD): 23.0 (3.4)	M:352 F:375	Use without prescription	75.00 225.00 400.00 600.01	245 180 136 166	110 80 54 82	Reference category 0.98 (0.67 - 1.45) 0.81 (0.53 - 1.24) 1.20 (0.81 - 1.78)	age, specialty (non-medical)
Hassali 2017 [183]	Malaysia	General population	Mean (SD): 28.7 (7.4)	M: 171 F: 229	Any misuse practice	124.88 499.88 1000.00 1500.13	231 94 47 28	82 29 13 7	Reference category 0.51 (0.27 - 0.98) 0.40 (0.16 - 0.78) 0.42 (0.13 - 1.34)	age, gender, educational level, marital status, race, healthcare related occupation, employment status, health insurance
Jamhour 2017 [85]	Lebanon	General population	>18	M: 182 F: 218	Use without prescription	499.50 1500.00	88 97	36 54	Reference category 1.81 (1.01 - 3.25)	age, gender, educational level, specialty (unrelated to health care)
Kajeguka 2017 [61]	Tanzania	General population	Mean (SD): 35.4 (13.4)	M:144 F:156	Use without prescription	49.50 300.50 700.50	162 102 36	70 74 23	2.82 (0.47 - 16.68) 1.02 (0.22 - 4.76) Reference category	age, gender, educational level, marital status, employment status, self-treated condition
Kurniawan 2017 [184]	Indonesia	Attendants of primary care clinics	Median (IQR): 45 (18-49)	M: 137 F: 263	Use without prescription	87.50 262.50	186 54	146 34	Reference category 0.52 (0.24, 1.12)	age, gender, educational level, marital status, employment status, health insurance
Nuñez 2017 [185]	Perú	University students	Mean: 19.82	M: 492 F: 508	Use without prescription	462.00 1386.62 2772.62 4620.62	321 322 178 179	204 211 119 120	Reference category 1.09 (0.79 - 1.51) 1.16 (0.79 - 1.70) 1.17 (0.79 - 1.72)	age
Senadheera 2017 [53]	Sri Lanka	General population	≥18	M: 190 F: 174	Use without prescription	87.50 262.51	292 288	15 26	Reference category 1.83 (0.95 - 3.54)	age, gender, educational level, employment status, health insurance, household size, receiving medical treatment in the last three months, knowledge of antibiotic name

Author, Year	Country	Setting	Age (Years)	Sex	Outcome	Mean Income (USD)	Total N/level	Outcome/ level	Odds Ratio (95%CI)	Adjustment, restriction or matching variables
Torres 2017 [165]	Ecuador	General population	18 - 64	M:97 F:110	Use without prescription	349.50 1100.00 1775.00 2250.50	200 132 36 8	98 68 14 2	Reference category 1.11 (0.71 - 1.72) 0.66 (0.32 - 1.37) 0.35 (0.07 - 1.76)	age
Aleem 2016 [186]	Saudi Arabia	Children´s caregivers	<25 to ≥55	M: 249 F: 382	Use without prescription	667.50 2002.63	91 519	17 54	Reference category 0.50 (0.26, 0.95)	age, gender, educational level, household size
Bilal 2016 [187]	Pakistan	Attendants of public hospital	Mean (SD): 48.6 (4.4)	M: 263 F: 137	Use without prescription	35.00 105.00 210.00 415.00 685.01	180 73 49 36 62	172 62 36 29 26	Reference category 0.26 (0.10 - 0.68) 0.13 (0.05 - 0.33) 0.19 (0.06 - 0.57) 0.03 (0.01 - 0.08)	age, residential location, specialty (non-medical related participants)
Zhu 2016 [188]	China	University students	18-45 (IQR: 21-22)	M: 369 F: 291	Use without prescription	40.00 120.08 240.08 400.08	45 423 173 19	28 192 83 13	Reference category 0.50 (0.27 - 0.95) 0.56 (0.29 - 1.10) 1.32 (0.42 - 4.11)	age, gender, educational level, major, healthcare insurance, residential location
Ding 2015 [189]	China	Children´s caregivers	≤ 29 to ≥ 50	M: 70 F: 652	Non-adherence	67.08 268.33 536.66	78 384 260	15 111 76	Reference category 1.71 (0.93 - 3.13) 1.73 (0.93 - 3.24)	age, access to healthcare (number of clinics)
Gebeyehu 2015 [190]	Ethiopia	General population	Mean (SD): *Urban* 34.1 (12.9) *Rural* 34.5 (11.5)	M:263 F:819	Any misuse practice	25.47 76.50 127.53 178.53 229.53	108 177 77 19 7	30 59 26 3 2	Reference category 1.30 (0.77 - 2.20) 1.33 (0.70 - 2.50) 0.49 (0.13 - 1.79) 1.04 (0.19 - 5.65)	age, gender, educational level, marital status, employment status, residential location, household size level of healthcare service satisfaction, knowledge on antibiotics use
Yousif 2015 [191]	Saudi Arabia	General population	≥18	M: 228 F: 172	Use without prescription	1335.00 4005.13	219 172	173 142	Reference category 0.80 (0.50 - 1.30)	age, gender, educational level, marital status, employment status, residential location
Cheaito 2014 [84]	Lebanon	Attendants of pharmacies	Mean (SD): 38.24 (13.7)	M: 143 F: 176	Use without prescription	1000.00 3000.00	278 40	117 17	Reference category 1.02 (0.52 - 1.99)	age, gender, educational level, marital status, employment status, health insurance, having a reference doctor and frequency of consultation
Eticha 2014 [192]	Ethiopia	University students	Mean (SD): 21 (2.06)	M: 267 F: 140	Use without prescription	6.28 18.92 31.56	159 160 88	42 38 32	Reference category 0.87 (0.52 - 1.44) 1.59 (0.91 - 2.79)	age, gender, university year, religion, residential location

Author, Year	Country	Setting	Age (Years)	Sex	Outcome	Mean Income (USD)	Total N/level	Outcome/ level	Odds Ratio (95%CI)	Adjustment, restriction or matching variables
Hu 2014 [193]	Australia	General population	Mean (SD): 33 (8.2) Range: 14-63	M: 170 F: 258	Storage of antibiotics	1904.13 5712.46	150 278	85 118	Reference category 0.56 (0.38 – 0.84)	age, gender, educational level, residential location, employment status, marital status, parental status, language proficiency, main language spoken at home, health insurance
Lv 2014 [194]	China	University students	NA	M:341 F:390	Any misuse practice	41.00 123.08 246.08 410.08	139 447 131 14	58 175 56 5	Reference category 1.14 (0.76 - 1.71) 1.00 (0.59 - 1.67) 1.26 (0.39 - 4.13)	gender, university year, residential location, major (medical vs non-medical), health insurance
Mihretie 2014 [195]	Ethiopia	General population	Mean (SD): 37.8 (12.2)	M: 34 F: 17	Use without prescription	13.75 38.78 67.53 102.53	14 10 10 14	9 8 8 6	Reference category 2.22 (0.33 - 14.80) 2.22 (0.33 - 14.80) 0.42 (0.09 - 1.91)	age
Shah 2014 [196]	Pakistan	University students	Mean (SD): 20.04 (1.74)	M: 253 F: 178	Use without prescription	250.00 750.00 1250.00 1750.01	115 139 70 73	51 73 38 28	Reference category 1.39 (0.85 - 2.28) 1.49 (0.82 - 2.71) 0.78 (0.43 - 1.42)	age, specialty (non-medical)
Abobotain 2013 [197]	Saudi Arabia	Children´s caregivers	<25 to ≥55	M:241 F:369	Use without prescription	667.37 2002.50	91 519	17 54	Reference category 0.50 (0.26, 0.95)	age, educational level, marital status, household size, number of children < 12 years old, healthcare related profession
Pan 2012 [46]	China	University students	Mean (SD): 22.3 (2.6)	M:745 F:555	Use without prescription	38.75 116.33 232.58 387.58	548 668 74 10	215 352 46 8	Reference category 1.73 (1.37 - 2.17) 2.54 (1.54 - 4.20) 6.20 (1.30 - 29.45)	age, gender, major, residential location, healthcare insurance
Widayati 2011 [198]	Indonesia	General population	Median (Range) *Prescribed* 40.5 (18 - 69) *Self-medicated* 43 (18 - 66)	M: 309 F: 250	Use without prescription	74.50 224.50 550.00 1050.50	41 24 5 4	19 15 1 2	Reference category 1.93 (0.69 - 5.40) 0.29 (0.03 - 2.82) 1.16 (0.15 - 9.03)	age, gender, educational level, marital status, household size, employment status, healthcare insurance

Author, Year	Country	Setting	Age (Years)	Sex	Outcome	Mean Income (USD)	Total N/level	Outcome/ level	Odds Ratio (95%CI)	Adjustment, restriction or matching variables
Ilhan 2009 [57]	Turkey	Attendants of primary care clinics	Mean (SD) 39.5 (15.2)	M:1652 F:1044	Use without prescription	157.43 472.93 788.43 1103.93 1419.43	272 1148 505 265 350	46 188 107 61 84	Reference category 0.96 (0.67 - 1.39) 1.32 (0.89 - 1.97) 1.73 (1.11 - 2.70) 1.55 (1.02 - 2.36)	age, gender, educational level, marital status, employment status, household size, healthcare insurance (social security), perceived health status, presence of chronic diseases
Hadi 2008 [199]	Indonesia	Attendants of primary care clinics	Median (range) 31 (0-87)	M: 1147 F: 1849	Use without prescription	13.50 40.50	192 274	30 42	Reference category 0.98 (0.59, 1.63)	age, gender, educational level, residential location, ethnicity, household size, healthcare insurance
Al-Azzam 2007 [200]	Jordan	General population	>65	M:1040 F:1093	Use without prescription	88.75 266.61 444.11	606 721 806	204 309 329	Reference category 1.48 (1.18 - 1.85) 1.36 (1.09 - 1.69)	NA
Sawair 2007 [201]	Jordan	Attendants of primary care clinics	≤16 to >65	M: 220 F: 257	Use without prescription	139.30 420.00 700.70	140 133 204	46 63 85	Reference category 1.94 (1.18 - 3.21) 1.35 (0.85 - 2.14)	age, gender, educational level, marital status, employment status, healthcare insurance, smoking habits, self-reported health status, chronic comorbidities
Awad 2005 [51]	Sudan	General population	≤20 to >60	M: 790 F: 960	Use without prescription	19.25 67.40 125.15	--- --- ---	--- --- ---	Reference category 0.78 (0.59 - 1.00) 0.61 (0.42 - 0.87)	age, gender, educational level

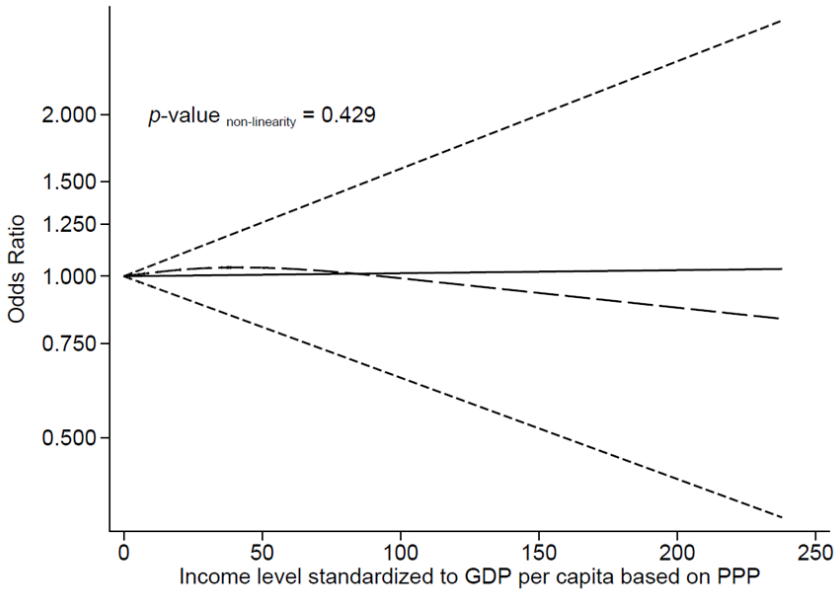

Figure 8 Trend of the association of income level standardized to GDP per capita based on PPP and antibiotic misuse.
Solid line represents the linear trend. Long-dashed line represents the non-linear restricted cubic spline approach. Short-dashed lines represents 95%CI

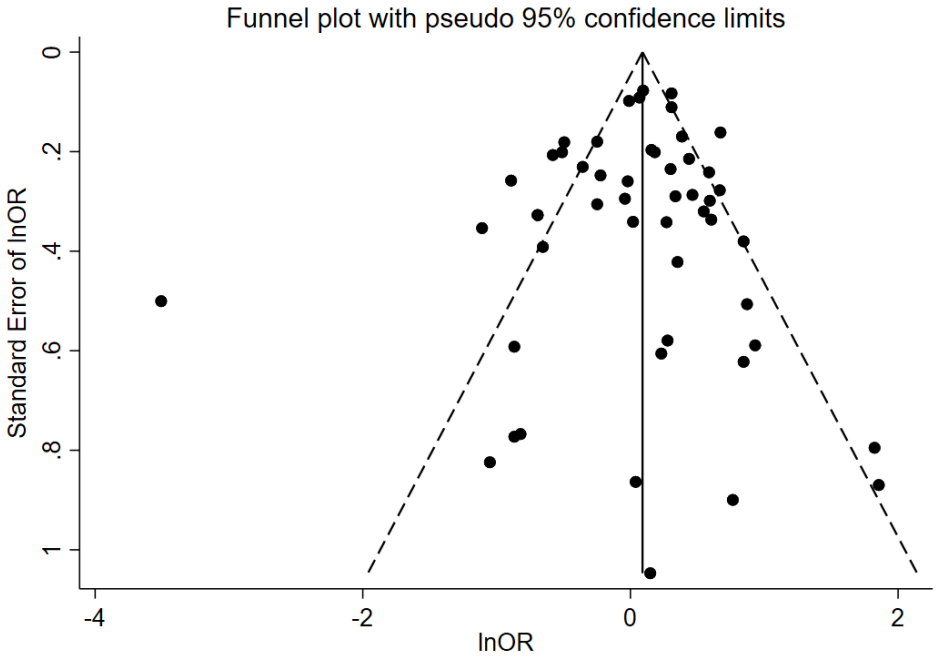

Figure 9 Funnel plot of studies included in the meta-analysis about income and antibiotic misuse

Table 26 Meta-analysis of the association of income level represented as units of growth domestic product (GDP) per capita based on purchasing power parity (PPP) with antibiotic misuse

	Number of studies	Medium income OR (95%CI)	High income OR (95%CI)
All studies	57	1.04 (0.89, 1.20)	1.03 (0.82, 1.29)
Type of misuse			
Use without prescription	43	1.06 (0.87, 1.28)	1.07 (0.84, 1.37)
Storage of antibiotics	6	1.19 (1.07, 1.32)	1.04 (0.92, 1.17)
Non-adherence	3	1.10 (0.89, 1.35)	0.49 (0.34, 0.70)
Country economy			
Low	16	1.02 (0.83, 1.24)	0.90 (0.59, 1.37)
Lower-middle	11	1.14 (0.73, 1.80)	0.92 (0.46, 1.84)
Upper-middle	25	1.17 (0.91, 1.49)	1.11 (1.00, 1.22)
High	5	0.90 (0.44, 1.85)	1.04 (0.33, 3.28)
WHO Region			
African	14	1.18 (1.00, 1.39)	0.96 (0.67, 1.38)
Eastern Mediterranean	17	0.92 (0.65, 1.32)	0.95 (0.58, 1.57)
South-East Asian	6	1.11 (0.62, 2.00)	1.53 (0.81, 2.92)
Western Pacific	16	0.99 (0.82, 1.20)	1.05 (0.92, 1.19)
Survey year			
Until 2015	29	0.95 (0.75, 1.20)	0.91 (0.62, 1.35)
After 2015	28	1.12 (0.99, 1.26)	1.15 (0.93, 1.41)
Literacy rate			
<90%	20	1.03 (0.82, 1.29)	1.02 (0.68, 1.54)
≥90%	37	1.09 (0.93, 1.28)	1.02 (0.84, 1.23)
Pre-tested or validated questionnaire			
No	10	1.02 (0.51, 2.06)	0.90 (0.34, 2.36)
Yes	47	1.06 (0.91, 1.24)	1.04 (0.85, 1.27)
Adjustment			
Incomplete	47	1.09 (0.95, 1.24)	1.05 (0.84, 1.31)
Complete	10	0.90 (0.71, 1.15)	0.60 (0.30, 1.23)
Quality Score			
Lower quality (≤ 3 points)	24	0.99 (0.75, 1.31)	1.09 (0.72, 1.66)
Higher quality (> 3 points)	33	1.04 (0.86, 1.25)	1.03 (0.81, 1.31)

CI: Confidence interval; OR: odds ratio

5.7. Dose-response meta-analysis of the association of education with antibiotic misuse *Practices*

Literature Search and Study Selection

Eighty-five studies fulfilled the inclusion criteria and were included in the meta-analysis of the association of education level and antibiotic misuse (**Figure *10***). The studies were published between 2000 and 2021. They were and carried out in 42 countries and involved a total population of N= 85789 individuals. The most common antibiotic misuse *Practices* was use without prescription (N= 15780) followed by storage of antibiotic leftover (N= 6077) and non-adherence to antibiotic treatment instructions (N= 2293). **Table *27***, **Figure *11*** and **Figure *12*** represent the general characteristics of the included studies. Two studies were of cohort design and the remaining 83 were cross-sectional. Seven studies reported data for two types of antibiotic misuse [56, 63, 172, 175, 202-204] and an eighth study provided data for three types of misuse [205]. Each misuse *Practice* reported in those eight studies was treated as a separate study, making a total of 94 studies introduced in the dose-response analysis. Five studies were published in Croatian [166], Italian [206], and Spanish [165, 207, 208] and the remaining 80 were available in English.

Overall association of education with antibiotic misuse

In reference to low education level (≤ 9 years), overall, there is no association between medium education (> 9-12 years) and antibiotic misuse [OR= 0.94 (95%CI: 0.83, 1.06)] (**Table *28***). However, individuals with high education level (>12 years) have 14% lower odds of antibiotic misuse, albeit the estimated confidence intervals are large (OR= 0.86; 95%CI: 0.72, 1.03) (**Table *28***). In the continuous approach, the data from the 94 studies included in the meta-analysis accords well with a flat linear association between education level and misuse of antibiotics [OR= 0.99 (95%CI: 0.97, 1.00)] (**Table *28*** and **Figure *13***).

Subgroup analyses

In the stratified analysis by the **type of misuse,** both the categorical and continuous approaches showed that there is no association between education level and the misuse *Practices* "*antibiotic use without prescription"* [OR of 1-year increment = 0.99 (95% CI: 0.97, 1.00)] or *"non-adherence to treatment"* [OR of 1-year increment = 0.99 (95%CI: 0.96, 1.03)]. However, there is 41% higher odds of the misuse *Practice "antibiotic storage"* for individuals with high education than for those with low education [OR= 1.41 (95%CI: 1.22, 1.64)]. Medium education level is also positively associated with *"antibiotic storage"* [OR= 1.17 (95%CI: 0.93, 1.48)] (**Table *28***). These results are consistent with that obtained from the continuous approach in which each 1-year increment in education is associated with 3% higher odds of "antibiotic storage" [OR=1.03 (95%CI: 1.01, 1.06)] (**Table *28***). The continuous approach also indicated that each 1-year increase in education is associated with 9% lower odds of *any Practice* of antibiotic misuse [OR= 0.91 (95%CI: 0.87, 0.95)] (**Table *28***).

With respect to **country economy**, in high-wealth countries, individuals with medium education level have 20% reduced odds of practicing any type of antibiotic misuse than those with low education level [OR= 0.80 (95%CI: 0.66, 0.97)]. In lower-middle economy countries, individuals with high education have 30% lower odds of antibiotic misuse than those with low

education [OR= 0.70 (95%CI; 0.44, 1.13)], and each 1-year increment in education is associated with 3% lower odds of antibiotic misuse [OR= 0.97 (95%CI: 0.93, 1.01)] (**Table *28***).

Stratifying by **WHO regions** revealed that in the Eastern Mediterranean region, individuals with high education is associated with 36% lower odds of any *Practice* of antibiotic misuse than those with low education level [OR= 0.64 (95%CI: 0.42, 1.00)]. Inversely, in the European region, individuals with high education have 25% higher odds of antibiotic misuse than those with low education [OR= 1.25 (95%CI: 1.00, 1.58)]. Likewise, in the continuous approach, every 1-year increase in education is associated with 4% lower odds of antibiotic misuse in the Eastern Mediterranean region [OR= 0.96 (95%CI: 0.93, 1.00)] and 2% higher odds of misuse in the European region [OR= 1.02 (95%CI: 1.00, 1.04)] (**Table *28***).

Summary estimates from studies published **after 2015** indicated 19% lower odds of antibiotic misuse by individuals with high education level than those with low education level [OR= 0.81; (95%CI: 0.64, 1.02)]. Each 1-year increment in education is associated with 2% reduced odds of antibiotic misuse after 2015 [$OR_{\text{after 2015}}$= 0.98 (95%CI: 0.96, 1.00)] (**Table *28***).

Methodological characteristics of included studies

Pooled estimate from the 68 studies that used a **pretested or validated questionnaire** did not notably differ from that estimated from all studies for medium education [OR= 1.01 (95%CI: 0.89, 1.15)] as well as for 1-year increment [OR= 0.99 (95%CI: 0.98, 1.01)]. Nevertheless, the association of high education with antibiotic misuse was less strong among studies that applied validated questionnaire than among all studies analyzed together (OR= 0.95; 95%CI: 0.80, 1.13) (**Table *28***).

No association between education and antibiotic misuse was observed in the subgroup of studies that controlled for age and gender or in the subgroup of studies with higher quality score (>3 points) (**Table *28***).

The funnel plot of studies reporting medium education level was slightly skewed to the left (**Figure 14**). However, the absence of publication bias was confirmed by both Eggers's test (p-value= 0.065) and trim-and-fill analysis that did not suggest the addition of any study.

The funnel plot of studies that assessed high education level was also slightly skewed to the left (**Figure 14**). Egger's test indicated the presence of publication bias (p-value= 0.001), but no additional studies were suggested by trim-and-fill analysis.

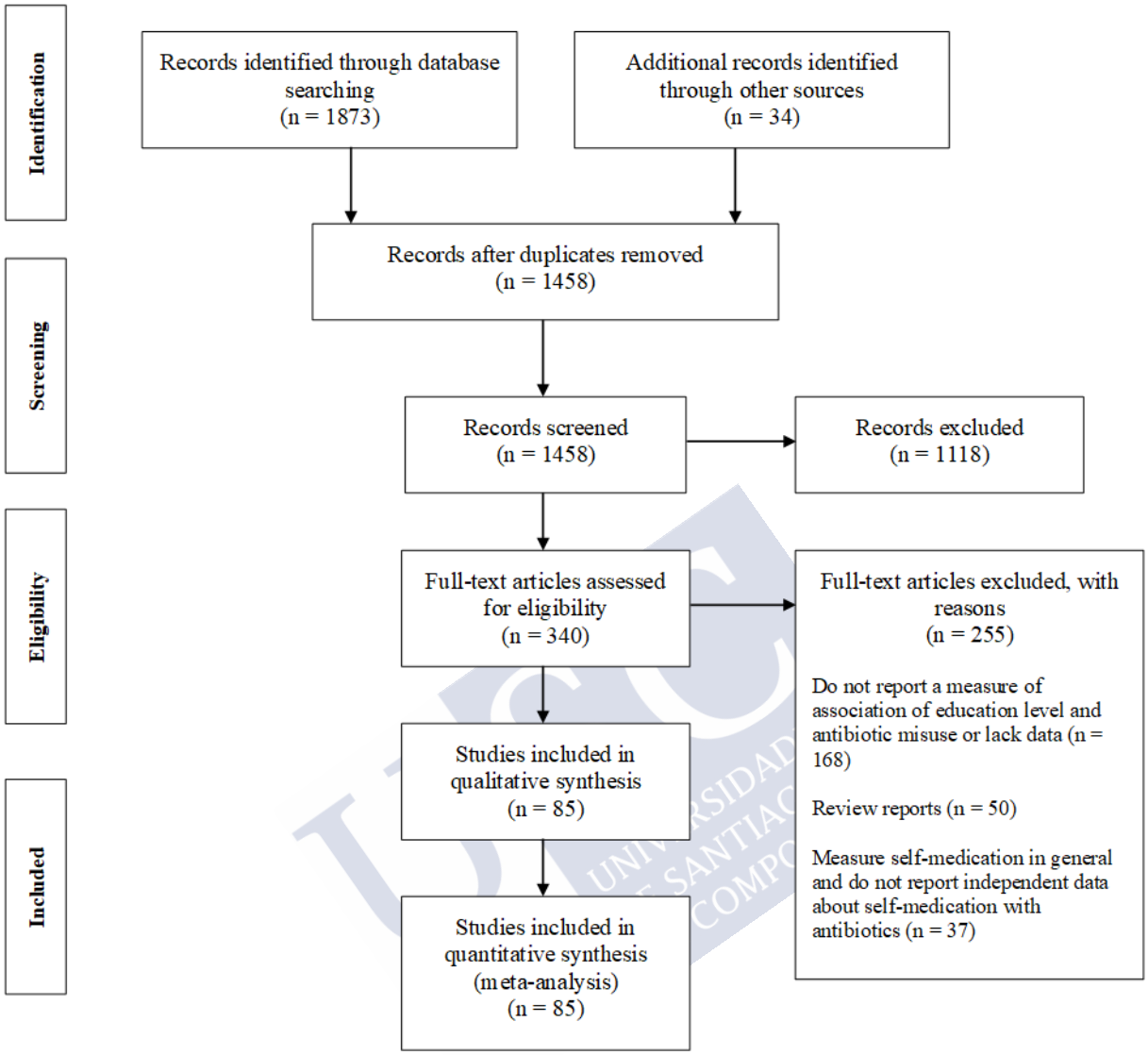

Figure 10 Flow diagram of the selection of studies about the association of education level with misuse of antibiotics

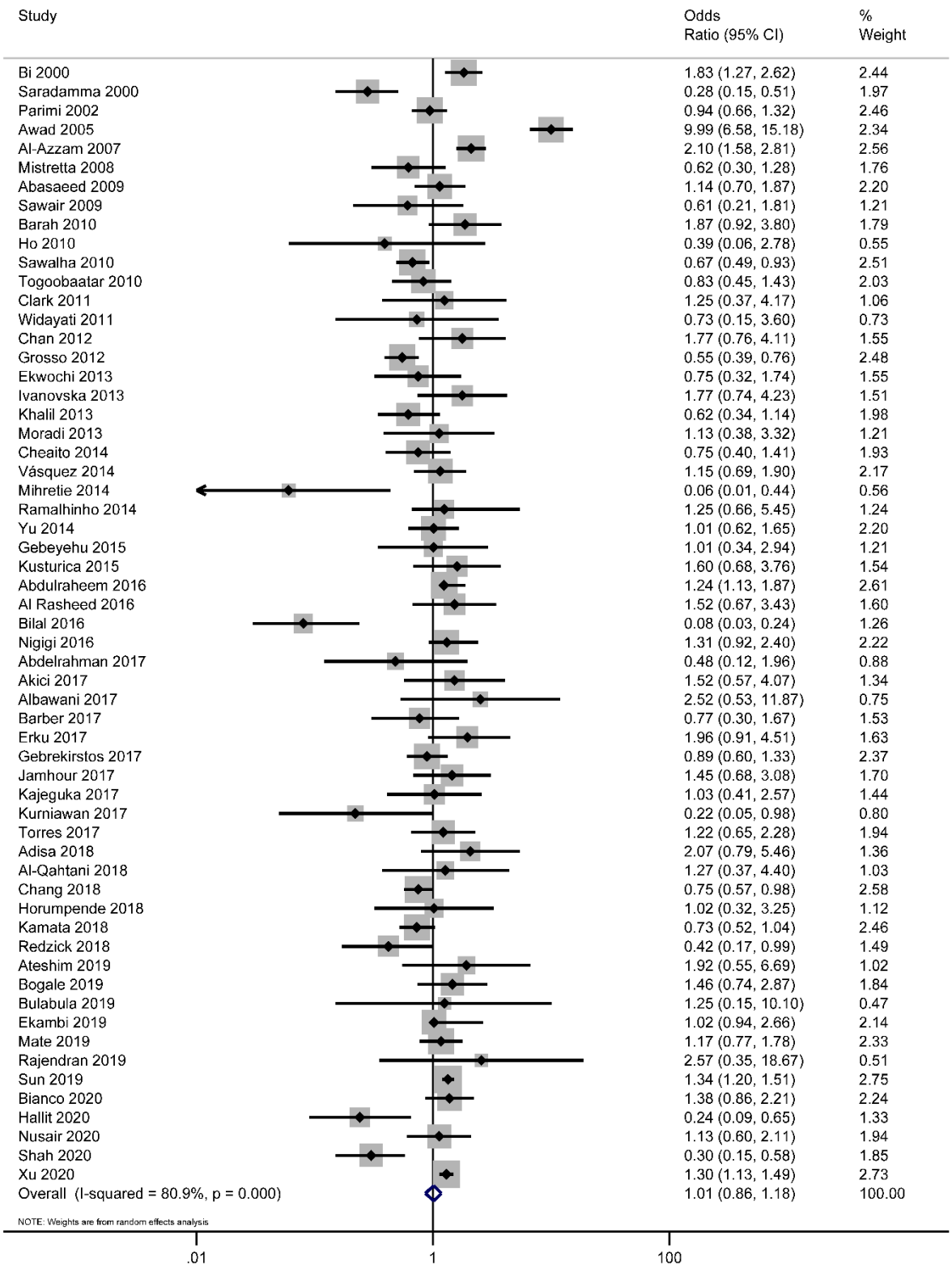

Figure 11 Forest plot of studies examining the association between medium education and antibiotic misuse

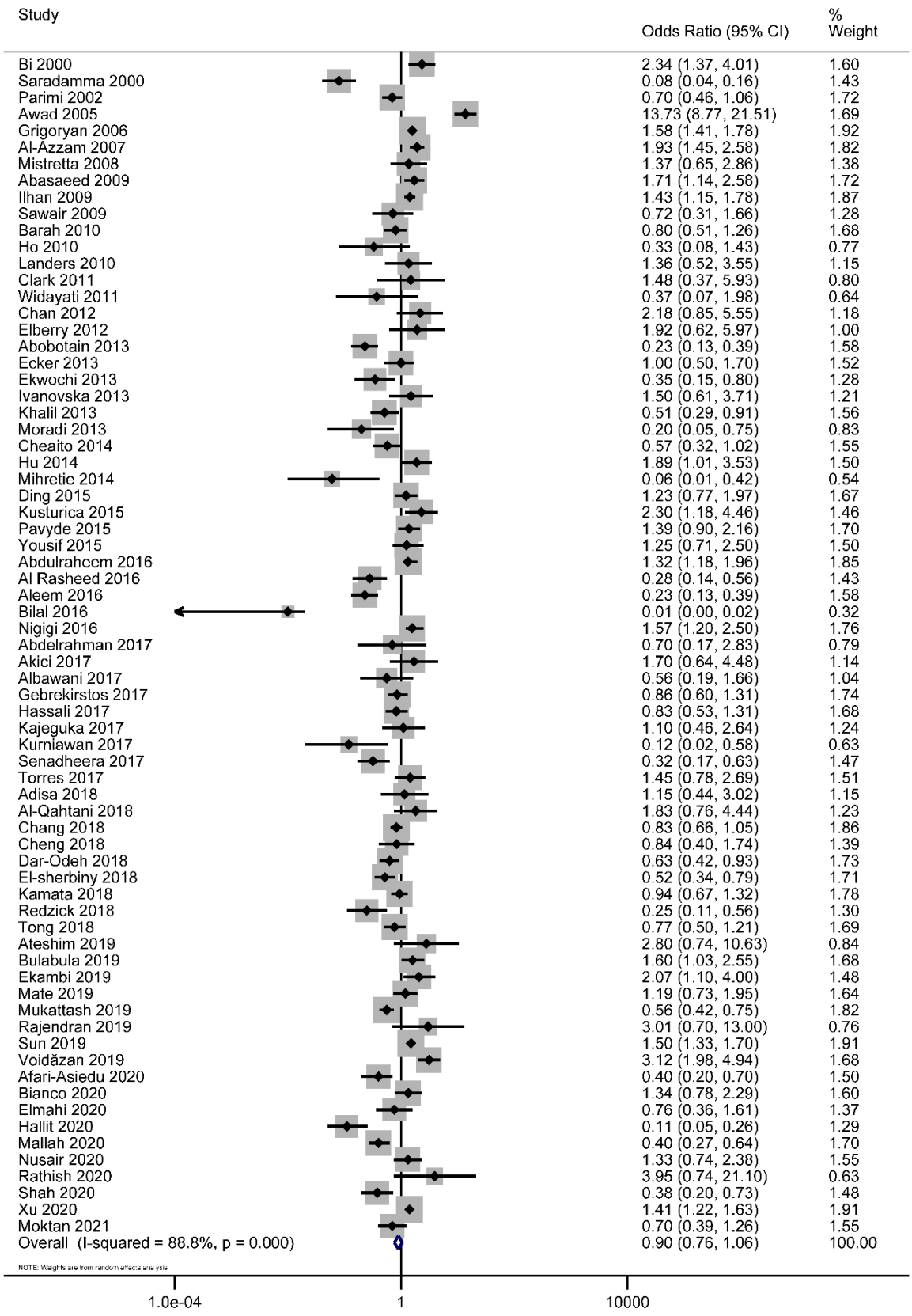

Figure 12 Forest plot of studies examining the association between high education and antibiotic misuse

Table 27 General characteristics of studies included in the dose-response meta-analysis about education level and misuse of antibiotics

Source	Country	Age (years)	Gender	Population	Type of misuse	Dose	N	n	OR (95% CI)	Adjustment, restriction or matching factors
Cohort studies										
Afari-Asiedu 2020 [209]	Ghana	Adults (<20 to >60)	M: 36.0% F: 64%	General population	Any misuse	0.0 3.5 8.0 13.0	283 176 138 164	27 19 22 34	1.00 0.90 (0.40, 1.70) 0.60 (0.30, 1.10) 0.40 (0.20, 0.70)	Age, gender, marital status, occupation, place of residence, health insurance, type of drug supplier
Ho 2010 [210]	Australia	Adults (≥ 18) ≤ 30 to > 45	M: 43% F: 57%	Emergency department attendants	Non-adherence	3.0 9.0 12.0 15.5	16 70 35 71	4 16 10 9	1.00 0.79 (0.46, 4.55) 0.39 (0.06, 2.78) 0.33 (0.08, 1.43)	Age, gender, marital status, employment status, having a regular general practitioner, number of usual medications, place of birth, use of herbal medicine
Cross-sectional studies										
Moktan 2021 [167]	India	Adults (>18)	M: 61.3% F: 38.7%	Attendants of primary care centers	Use without prescription	0.0 6.5 14.5 19.0	28 206 158 112	12 65 59 35	1.00 0.61 (0.28, 1.37) 0.79 (0.35, 1.80) 0.61 (0.26, 1.42)	Age, gender, marital status, income, public and private clinics, frequency of doctors' consultation, family/friend influence (other family members self-medicating with antibiotics), symptoms (minor illness)
Bianco 2020 [211]	Italy	Adults mean ± SD: 47.8 ± 16.7	M: 41.2% F: 58.8%	Attendants of primary care centers	Use without prescription	4.0 11.0 16.0	--- --- ---	--- --- ---	1.00 1.38 (0.86, 2.21) 1.34 (0.78, 2.29)	Age, gender, marital status, employment status, nationality, having a kid who had used antibiotics in the last year
Elmahi 2020 [169]	Sudan	Adults (>18)	M: 52.8% F: 47.2%	General population	Use without prescription	6.0 14.5	35 211	23 125	1.00 0.76 (0.36, 1.61)	Age
Hallit 2020 [212]	Lebanon	Adults mean ± SD: *bad practice* 33.33 ± 8.80 *good practice* 31.49 ± 6.68	M: 48.5% F: 51.5%	Children caregivers	Any misuse	3.0 11.0 14.5	48 40 116	40 22 41	1.00 0.24 (0.09, 0.65) 0.11 (0.05, 0.26)	Age
Mallah 2020 [170]	Lebanon	Adults (>18)	M: 19.4% F: 76.8%	Children caregivers	Any misuse	6.0 14.5	252 1157	31 62	1.00 0.40 (0.27, 0.64)	Age, gender, area of residence, access to medical care facilities, frequency of telephone medical consultation
Nusair 2020 [171]	Jordan	Unrestricted age group	M: 36.6% F: 63.4%	General population	Use without prescription	0.0 5.5 11.5 15.5	51 52 273 1505	18 20 104 632	1.00 1.15 (0.51, 2.55) 1.13 (0.60, 2.11) 1.33 (0.74, 2.38)	---

Source	Country	Age (years)	Gender	Population	Type of misuse	Dose	N	n	OR (95% CI)	Adjustment, restriction or matching factors
Rathish 2020 [48]	Sri Lanka	Unrestricted age group Mean ± SD: 36.0 ± 21.0	M: 47% F: 53%	General population	Use without prescription	11.0 13.5	252 132	247 127	1.00 3.95 (0.74, 21.10)	---
Shah 2020 [213]	Pakistan	≥ 15	M: 33% F: 67%	General population	Use without prescription	0.0 4.5 10.5 14.5	45 231 198 221	25 30 54 71	1.00 0.12 (0.06, 0.24) 0.30 (0.15, 0.58) 0.38 (0.20, 0.73)	Age
Xu 2020 [172]	China	Parents with children <13 years old	M: 21.5% F: 78.5%	Children caregivers	Use without prescription	4.5 11.0 14.5	1344 1771 3164	--- --- ---	1.00 0.85 (0.58, 1.25) 0.77 (0.53, 1.14)	Age, gender, income, medical background, residential location
					Antibiotics Storage	4.5 11.0 14.5	1344 1771 3164	--- --- ---	1.00 1.38 (1.19, 1.60) 1.55 (1.33, 1.81)	
Ateshim 2019 [173]	Eritrea	Median (IQR): 37 (24)	M: 41.2% F: 58.8%	General population	Use without prescription	0.0 3.0 6.5 9.5 14.0	32 64 95 246 140	11 22 33 111 81	1.00 1.96 (0.56, 6.88) 1.62 (0.46, 5.72) 1.92 (0.55, 6.69) 2.8 (0.74, 10.63)	Age, gender, income, marital status, occupational status, knowledge about antibiotics, attitudes towards antibiotics
Bogale 2019 [49]	Ethiopia	18 to > 60	M: 41.3% F: 58.7%	General population	Use without prescription	0.0 4.5 10.5 14.5	--- --- --- ---	26 72 75 81	6.39 (1.45, 28.19) 1.50 (0.82, 2.74) 1.46 (0.74, 2.87) 1.00	Age, gender, income, marital status, residential location, occupational status, healthcare profession
Bulabula 2019 [47]	South Africa	Mean ± SD: 29 ± 6.1	F: 100%	Pregnant women attending public hospital	Use without prescription	5.0 11.0 15.5	14 228 5	--- --- ---	1.00 1.25 (0.15, 10.10) 1.60 (1.03, 2.55)	Age, gender, income, residential location, , knowledge about antibiotics, attitudes towards antibiotics
Ekambi 2019 [214]	Cameroon	≥ 15 Mean ± SD: 35.02 ± 10.5	M: 52% F: 48%	Attendants of pharmacies	Use without prescription	3.0 10.0 15.0	25 86 66	8 28 33	1.00 1.02 (0.94, 2.66) 2.07 (1.10, 4.00)	Age, gender, marital status, occupation
Mate 2019 [175]	Mozambique	Adults (>18) Median (IQR): 33 (25-47)	M: 26.9% F: 73.1%	General population	Use without prescription	0.0 4.0 11.5 14.5	69 344 555 114	17 63 119 28	1.00 0.69 (0.37, 1.26) 0.83 (0.47, 1.50) 1.00 (0.50, 1.99)	Age
					Non-adherence	0.0 4.0 11.5 14.5	65 334 531 110	15 88 177 33	1.00 1.19 (0.64, 2.23) 1.67 (0.91, 3.05) 1.43 (0.70, 2.90)	

Source	Country	Age (years)	Gender	Population	Type of misuse	Dose	N	n	OR (95% CI)	Adjustment, restriction or matching factors
Mukattash 2019 [176]	Jordan	20 to ≥ 50	M: 15.8% F: 84.2%	Children caregivers	Use without prescription	6.0 18.0	205 1487	106 554	1.00 0.56 (0.42, 0.75)	Age
Rajendran 2019 [215]	India	Adults (>18)	M: 51% F: 49%	General population	Use without prescription	9.5 11.0 14.0	151 60 540	2 2 21	1.00 2.57 (0.35, 18.67) 3.01 (0.70, 13.00)	Age
Sun 2019 [59]	China	Parents with children <13 years old	M: 23.5% F: 76.5%	Children caregivers	Antibiotics storage	5.0 11.0 14.5	2519 2765 4242	1026 1365 2189	1.00 1.34 (1.20, 1.51) 1.50 (1.33, 1.70)	Age, gender of the parents, gender of the child, socioeconomic characteristics (residential location and GDP per capita), health insurance, specialty (medical vs non-medical)
Voidăzan 2019 [216]	Romania	Adults (20-80) Mean ± SD: 45 ± 12.5	M: 36.5% F: 63.5%	Attendants of primary care centers	Use without prescription	2.5 9.0 15.0 22.5	200 564 438 790	11 94 102 77	1.00 3.43 (1.80, 6.56) 5.22 (2.73, 9.96) 1.86 (0.97, 3.56)	---
Adisa 2018 [217]	Nigeria	Mothers of children under five	F: 100%	Mothers of children under five attending primary care centers	Use without prescription	3.0 9.5 14.5	19 148 160	8 89 73	1.00 2.07 (0.79, 5.46) 1.15 (0.44, 3.02)	Gender
Al-Qahtani 2018 [218]	Saudi Arabia	Adults (≥18)	M: 43.4% F: 56.6%	Attendants to primary care centers	Use without prescription	0.0 3.5 10.5 15.5 21.0	13 39 108 281 48	4 13 39 119 23	1.00 1.13 (0.29, 4.35) 1.27 (0.37, 4.40) 1.65 (0.50, 5.49) 2.07 (0.56, 7.65)	Age, gender
Chang 2018 [219]	China	Caregivers of children under seven	M: 33.3% F: 66.7%	Caregivers of children under seven	Use without prescription	4.5 11.0 14.5 19.0	336 1428 1407 187	--- --- --- ---	1.00 0.75 (0.57, 0.98) 0.82 (0.62, 1.08) 0.86 (0.56, 1.32)	Gender, child gender and age, number of children, health insurance, residential location
Cheng 2018 [220]	China	30 to ≥ 71	M: 41.4% F: 68.3%	General rural population	Use without prescription	0.0 3.5 8.0 13.0	135* 165* 227* 97*	83* 112* 139* 57*	1.00 1.19 (0.69, 2.05) 0.89 (0.50, 1.57) 0.84 (0.40, 1.74)	Age, gender, household size, health insurance
Dar-Odeh 2018 [221]	Saudi Arabia	15-64 Mean ± SD: 29.08 ± 9.32	M: 40.7% F: 59.3%	Attendants of primary care centers	Use without prescription	6.0 15.5 21.0	138 333 29	47 81 7	1.00 0.63 (0.41, 0.97) 0.62 (0.25, 1.56)	Age
El-Sherbiny 2018 [55]	Egypt	Adults (≥ 18)	M: 50.3% F: 49.7%	Attendants of primary care centers	Any misuse	6.0 14.5	419 181	--- ---	1.00 0.52 (0.34, 0.79)	Age, gender, income, occupation, residential location

Source	Country	Age (years)	Gender	Population	Type of misuse	Dose	N	n	OR (95% CI)	Adjustment, restriction or matching factors
Horumpende 2018 [222]	Tanzania	Median (IQR): 23 (20.5 - 36.5)	M: 53.33% F: 46.67%	General population	Use without prescription	0.0	17	9	1.00	Age, gender, income, marital status, occupation
						4.0	111	70	1.45 (0.46, 4.51)	
						10.0	172	95	1.02 (0.32, 3.25)	
Kamata 2018 [63]	Japan	20 - 69	M: 51.2% F: 48.8%	General population	Antibiotics storage	5.0	111	18	1.00	Age
						11.0	1265	115	0.52 (0.30, 0.89)	
						14.5	1932	254	0.78 (0.46, 1.32)	
					Non-adherence	5.0	111	26	1.00	
						11.0	1265	282	0.94 (0.59, 1.48)	
						14.5	1932	479	1.08 (0.69, 1.69)	
Ngu 2018 [223]	Cameroon	≥ 21 Median (IQR): 35 (27 - 49)	M: 44.8% F: 55.2%	Attendants of primary care centers	Use without prescription	0.0	29	14	1.00	Age
						6.5	279	115	0.75 (0.35, 1.62)	
Redzick 2018 [166]	Croatia	---	M: 26.1% F: 73.9%	Attendants of primary care centers	Use without prescription	4.5	32	8	1.00	Age
						10.5	312	38	0.42 (0.17, 0.99)	
						14.5	60	4	0.21 (0.06, 0.78)	
						19.0	140	12	0.28 (0.10, 0.76)	
Tong 2018 [52]	China	<45 to >60	M: 47.6% F: 52.4%	Attendants of primary care centers	Non-adherence	6.5	323	286	1.00	Age, gender, income, residential location, occupation, employment status, knowledge about antibiotics
						14.5	391	335	0.77 (0.50, 1.21)	
Abdelrahman 2017 [179]	Saudi Arabia	<18 to >65	M: 71.5% F: 28.5%	General population	Use without prescription	0.0	8	4	1.00	Age
						5.0	58	21	0.57 (0.13, 2.51)	
						11.0	360	117	0.48 (0.12, 1.96)	
						15.5	602	248	0.70 (0.17, 2.83)	
Albawani 2017 [180]	Yemen	≥ 18 Mean ± SD: 28.6 ± 7.7	M: 56.2% F: 43.8%	Attendants of pharmacies	Use without prescription	5.0	40	36	1.00	Age
						11.0	71	68	2.52 (0.53, 11.87)	
						15.0	229	191	0.56 (0.19, 1.66)	

Source	Country	Age (years)	Gender	Population	Type of misuse	Dose	N	n	OR (95% CI)	Adjustment, restriction or matching factors
Akici 2017 [205]	Turkey	≥ 15	M: 42.6% F: 57.4%	Attendants of primary care centers	Use without prescription	0.0	18	8	1.00	---
						4.5	18	6	0.63 (0.16, 2.41)	
						10.5	18	8	1.11 (0.29, 4.20)	
						14.5	18	9	1.25 (0.34, 4.64)	
					Non-adherence	0.0	9	6	1.00	
						4.5	9	6	1.00 (0.14, 7.10)	
						10.5	9	7	1.75 (0.22, 14.22)	
						14.5	9	7	1.75 (0.22, 14.22)	
					Antibiotics storage	0.0	8	3	1	
						4.5	9	4	1.67 (0.23, 12.22)	
						10.5	8	5	2.78 (0.37, 21.03)	
						14.5	9	6	3.33 (0.45, 24.44)	
Barber 2017 [62]	Philippines	Adults (≥ 18) Median (IQR): 32 (20)	M: 37.2% F: 56.7%	General population	Use without prescription	3.5	83	69	1.00	Age, gender, household size
						10.5	186	143	0.77 (0.30, 1.67)	
Erku 2017 [54]	Ethiopia	<29 to > 60 Mean ± SD: 33.19 ± 10.82	M: 25.9% F: 74.9%	General population	Use without prescription	0.0	182	125	5.01 (2.62, 9.34)	Age, gender, income, marital status, household size, employment status, frequency of visiting health care institutions, satisfaction about healthcare service
						4.5	201	180	2.81 (1.32, 6.15)	
						10.5	179	159	1.96 (0.91, 4.51)	
						14.5	88	71	1.00	
Gebrekirstos 2017 [181]	Ethiopia	Adults (≥ 18) Median (IQR): 30 (16)	M: 60.6% F: 39.4%	Attendants of pharmacies	Use without prescription	0.0	152	75	1.00	Age, gender, income, marital status, employment status, household size, residential location, type of illness, healthcare insurance, previous experience with antibiotics, access to healthcare
						4.5	149	71	0.93 (0.59, 1.47)	
						10.5	260	121	0.89 (0.60, 1.33)	
						14.5	219	100	0.86 (0.60, 1.31)	
Hassali 2017 [183]	Malaysia	Adults (≥ 18) Mean ± SD: 28.7 ± 7.4	M: 42.75% F: 57.25%	General population	Any misuse	8.5	61	20	1.00	Age, gender, income, marital status, race, healthcare related occupation, employment status, health insurance
						14.0	339	111	0.83 (0.53, 1.31)	
Jamhour 2017 [85]	Lebanon	Adults (≥ 18)	M: 45.5% F: 54.5%	General population	Use without prescription	4.5	34	14	1.00	Age, gender, educational level, specialty (unrelated to health care)
						11.0	151	76	1.45 (0.68, 3.08)	
Kajeguka 2017 [61]	Tanzania	Adults (≥ 18) Mean ± SD: 35.4 ± 13.4	M: 48.0% F: 52.0%	General population	Use without prescription	0.0	26	16	1.00	Age, gender, income, marital status, employment status, self-treated condition
						4.0	87	33	0.38 (0.12, 0.94)	
						11.0	74	46	1.03 (0.41, 2.57)	
						16.0	133	72	1.10 (0.46, 2.64)	
Kurniawan 2017 [184]	Indonesia	Adults (≥ 18) Median (IQR): 45 (18-49)	M: 34.3% F: 65.8%	Attendants of primary care centers	Use without prescription	3.5	26	24	1.00	Age, gender, income, marital status, employment status, health insurance
						8.0	44	37	0.44 (0.08, 2.30)	
						11.0	139	101	0.22 (0.05, 0.98)	
						14.5	31	18	0.12 (0.02, 0.58)	

Source	Country	Age (years)	Gender	Population	Type of misuse	Dose	N	n	OR (95% CI)	Adjustment, restriction or matching factors
Senadheera 2017 [53]	Sri Lanka	Adults (≥ 18)	M: 31.30% F: 68.70%	General population	Use without prescription	11.0 13.5	362 245	14 37	1.00 0.32 (0.17, 0.63)	Age, gender, income, employment status, health insurance, household size, receiving medical treatment in the last three months, knowledge of antibiotic name
Torres 2017 [165]	Ecuador	Adults (≥ 18) range: 18 - 64	M: 45.6% F: 54.4%	General population	Use without prescription	3.5 10.5 14.5	51 173 195	22 83 102	1.00 1.22 (0.65, 2.28) 1.45 (0.78, 2.69)	Age
Abdulraheem 2016 [224]	Nigeria	Adults (≥ 18) Median (range): 25 (19-68)	M: 61.1% F: 38.9%	Attendants of primary care centers	Use without prescription	3.5 9.5 14.5	623 390 137	--- --- ---	1.00 1.24 (1.13, 1.87) 1.32 (1.18, 1.96)	Age, gender, symptoms, occupation
Aleem 2016 [186]	Saudi Arabia	<25 to ≥55	M: 39.5% F: 60.5%	Children caregivers	Use without prescription	6.0 15.0	102 508	29 42	1.00 0.23 (0.13, 0.39)	Age, gender, income, household size
Al Rasheed 2016 [225]	Saudi Arabia	Adults (> 18)	M: 23.2% F: 76.8%	Attendants of primary care centers	Use without prescription	0.0 3.5 10.5 15.5	100 186 145 145	13 16 13 50	1.00 1.59 (0.73, 3.45) 1.52 (0.67, 3.43) 0.28 (0.14, 0.59)	Age, gender, marital status, employment status, occupation, symptoms
Bilal 2016 [187]	Pakistan	Mean ± SD: 48.6 ± 4.4	M: 65.8% F: 34.2%	Attendants of primary care centers	Use without prescription	0.0 9.5 11.5 14.5 19.5	161 86 65 50 38	159 81 49 26 10	1.00 0.20 (0.04, 1.07) 0.04 (0.01, 0.17) 0.01 (0.003, 0.06) 0.004 (0.001, 0.02)	Age, residential location, specialty (non-medical related participants)
Nigigi 2016 [226]	Kenya	Adults (≥ 18)	M: 32.0% F: 68.0%	Attendants of primary care centers	Use without prescription	0.0 4.0 9.5 13.5	48 115 179 20	12 35 61 9	1.00 1.13 (0.90, 1.97) 1.31 (0.92, 2.40) 1.57 (1.20, 2.50)	---
Ding 2015 [189]	China	Adults ≤ 29 to > 50	M: 9.7% F: 90.3%	Children caregivers	Non-adherence	3.0 8.0 13.0	198 304 120	68 87 47	1.00 0.77 (0.52, 1.13) 1.23 (0.77, 1.97)	Age, access to healthcare (number of clinics)
Gebeyehu 2015 [190]	Ethiopia	Mean ± SD: *urban:* 34.1 ± 12.9 *rural:* 34.5 ± 11.5	M: 24.3% F: 75.7%	General population	Use without prescription	0.0 4.5 10.5 14.5	137 145 89 35	56 40 14 10	4.21 (1.47, 12.07) 2.01 (0.93, 4.34) 1.01 (0.34, 2.94) 1	Age, gender, educational level, marital status, employment status, residential location, household size, level of healthcare service satisfaction, knowledge on antibiotics use
Kusturica 2015 [227]	Serbia	Adults (≥ 18)	M: 20.1% F: 79.9%	General population	Antibiotics storage	4.5 10.5 14.0 16.5	27 169 25 162	9 75 10 84	1.00 1.60 (0.68, 3.76) 2.53 (0.89, 7.23) 2.15 (0.91, 5.08)	Age

Source	Country	Age (years)	Gender	Population	Type of misuse	Dose	N	n	OR (95% CI)	Adjustment, restriction or matching factors
Pavyde 2015 [60]	Lithuania	Adults (≥ 18) Mean ± SD: 38.6 ± 13.9	M: 42.1% F: 57.9%	Attendants of pharmacies	Use without prescription	6.0 14.5	298 707	--- ---	1.00 1.39 (0.90, 2.16)	Age, gender, residential location, parenthood, knowledge of antibiotics, occupation
Yousif 2015 [191]	Saudi Arabia	Adults (≥18)	M: 57.0% F: 43.0%	General population	Use without prescription	6.0 15.5	96 295	80 235	1.00 1.25 (0.71, 2.50)	Age, gender, income, marital status, employment status, residential location
Cheaito 2014 [84]	Lebanon	Adults (≥ 18) Mean ± SD: 38.24 ± 13.7	M: 44.8% F: 55.2%	Attendants of pharmacies	Use without prescription	3.0 10.5 17.5	67 96 156	34 42 58	1.00 0.75 (0.40, 1.41) 0.57 (0.32, 1.02)	Age, gender, income, marital status, employment status, health insurance, having a reference doctor and frequency of consultation
Vásquez 2014 [208]	Ecuador	≥65	M: 45.8% F: 54.2%	General population	Use without prescription	3.0 11.5	463 205	52 26	1.00 1.15 (0.69, 1.90)	Age
Hu 2014 [193]	Australia	≥14 Mean ± SD: 33 ± 8.2	M: 45.0% F: 55.0%	General population	Use without prescription	6.0 14.5	67 402	14 134	1.00 1.89 (1.01, 3.53)	Age, gender, income, residential location, employment status, marital status, parental status, language proficiency, main language spoken at home, health insurance
Mihretie 2014 [195]	Ethiopia	≥17 Mean ± SD: 37.8 ± 12.2	M: 4.4% F: 95.6%	General population	Use without prescription	4.0 10.5 14.5	29 7 9	27 3 4	1.00 0.06 (0.01, 0.44) 0.06 (0.01, 0.42)	Age
Ramalhinho 2014 [228]	Portugal	Adults (≥ 18)	M: 48.7% F: 51.3%	General population	Use without prescription	4.5 11.0 15.5	308* 445* 293*	268* 340* 223*	0.84 (1.41, 11.78) 1.25 (0.66, 5.45) 1.00	Age, gender, marital status, employment status, residential location, access to healthcare, chronic disease, easy access to unprescribed antibiotics, occupation
Yu 2014 [229]	China	Adults ≤ 20 to > 40	M: 25.6% F: 74.4%	Children caregivers	Use without prescription	3.5 8.0 11.0 14.5	16 371 258 203	--- --- --- ---	0.19 (0.05, 0.75) 1.07 (0.64, 1.81) 1.01 (0.62, 1.65) 1.00	Age, gender, child age, number of children, medical insurance
Abobotain 2013 [197]	Saudi Arabia	<25 to ≥55	M: 39.5% F: 60.5%	Children caregivers	Use without prescription	6.0 14.5	102 508	29 42	1.00 0.23 (0.13, 0.39)	Age, income, marital status, household size, number of children, healthcare related profession
Ecker 2013 [207]	Peru	Mean ± SD: 31.4 ± 10.8	F: >94.9%	Children caregivers	Use without prescription	3.5 9.0 14.5	188 781 232	--- --- ---	1.00 1.2 (0.7, 1.9) 1.0 (0.5, 1.7)	Age, gender, caregiver-child relatedness, age of the child, access to healthcare
Ekwochi 2013 [230]	Nigeria	---	M: 59.0% F: 41.0%	Children caregivers	Use without prescription	3.0 9.5 14.5	31 83 96	19 45 34	1.00 0.75 (0.32, 1.74) 0.35 (0.15, 0.80)	---

Source	Country	Age (years)	Gender	Population	Type of misuse	Dose	N	n	OR (95% CI)	Adjustment, restriction or matching factors
Ivanovska 2013 [202]	Macedonia	Adults (≥ 18)	M: 31.3% F: 68.7%	General population	Use without prescription	0.0	11	4	1.00	Age, occupation
						5.0	41	21	1.83 (0.47, 7.25)	
						11.5	256	112	1.36 (0.39, 4.77)	
						16.0	94	37	1.14 (0.31, 4.15)	
					Antibiotics storage	0.0	11	6	1.00	
						5.0	41	28	1.79 (0.46, 6.97)	
						11.5	256	187	2.26 (0.67, 7.64)	
						16.0	94	66	1.96 (0.55, 6.97)	
Khalil 2013 [231]	Saudi Arabia	≥ 15	M: 80.8% F: 19.1%	Attendants of primary care centers	Use without prescription	4.5	107	93	1.00	---
						11.0	435	350	0.62 (0.34, 1.14)	
						15.5	233	180	0.51 (0.27, 0.97)	
						21.0	18	14	0.53 (0.15, 1.83)	
Moradi 2013 [232]	Iran	Mean ± SD: 29.2 ± 8.05	M: 33.3% F: 66.7%	Attendants of pharmacies and primary care centers	Non-adherence	2.5	23	16	1.00	---
						11.0	50	36	1.13 (0.38, 3.32)	
						15.5	19	6	0.20 (0.05, 0.75)	
Chan 2012 [58]	Hong Kong, China	Adults (≥ 18)	M: 46.0% F: 54.0%	General population	Non-adherence	3.0	47	---	1.00	Age, gender, antibiotic knowledge
						9.5	165	---	1.77 (0.76, 4.11)	
						14.5	150	---	2.18 (0.85, 5.55)	
Elberry 2012 [233]	Saudi Arabia	≥ 20	F: 100%	Mothers	Use without prescription	6.0	34	2	1.00	Gender
						15.5	116	11	1.68 (0.35, 7.96)	
						21.0	49	6	2.23 (0.42, 11.79)	
Grosso 2012 [204]	Italy	<25 to >65	M: 43.1% F: 56.9%	Attendants of primary care centers	Use without prescription	4.0	489	82	0.39 (0.26, 0.61)	Age, gender, occupation
						11.0	268	61	0.41 (0.26, 0.64)	
						16.0	176	74	1.00	
					Non-adherence	4.0	502	169	1.77 (1.13, 2.75)	
						11.0	276	45	0.79 (0.48, 1.31)	
						16.0	178	33	1.00	
Clark 2011 [234]	Azerbaijan	Adults (≥ 18)	M: 43.6% F: 56.4%	General population	Use without prescription	0.0	35	8	1.00	Age, gender, ethnicity, household size
						7.0	646	123	1.23 (0.45, 3.36)	
						10.5	74	14	1.25 (0.37, 4.17)	
						13.5	37	9	1.48 (0.37, 5.93)	
Widayati 2011 [198]	Indonesia	Adults (≥ 18)	M: 38.3% F: 61.7%	General population	Use without prescription	3.5	8	5	1.00	Age, gender, income, marital status, household size, employment status, healthcare insurance
						8.0	8	3	0.36 (0.05, 2.73)	
						11.0	31	17	0.73 (0.15, 3.60)	
						14.5	21	8	0.37 (0.07, 1.98)	

Source	Country	Age (years)	Gender	Population	Type of misuse	Dose	N	n	OR (95% CI)	Adjustment, restriction or matching factors
Barah 2010 [235]	Syria	Adults (≥ 18)	M: 52% F: 48%	General population	Use without prescription	5.0	80	54	1.00	Age
						11.0	83	66	1.87 (0.92, 3.80)	
						15.5	89	55	0.78 (0.42, 1.47)	
						21.0	90	57	0.83 (0.44, 1.57)	
Landers 2010 [236]	United States	Mean ± SD: 33.7 ± 8.7	F: 100%	General population	Use without prescription	4.5	31	11	1.00	Age, gender
						13.0	42	18	1.36 (0.52, 3.55)	
Sawalha 2010 [237]	Palestine	---	NA	General population	Antibiotics Storage	3.5	239	86	1.00	---
						10.0	591	162	0.67 (0.49, 0.93)	
Togoobaatar 2010 [238]	Mongolia	Mean ± SD: 35.4 ± 11.9	F: 100%	General population	Use without prescription	5.0	183	---	1.20 (0.70, 2.20)	Gender, occupation
						12.0	320	---	1.00	
Abasaeed 2009 [239]	United Arab Emirates	Adults ≤ 20 to > 50	M: 65.8% F: 34.2%	Attendants of a book fair	Antibiotics storage	3.5	163	37	1.00	Age
						11.0	191	48	1.14 (0.70, 1.87)	
						15.5	496	166	1.71 (1.14, 2.58)	
Ilhan 2009 [57]	Turkey	Adults (≥ 18) Mean ± SD: 39.5 ± 15.2	M: 38.7% F: 61.3%	Attendants of primary care centers	Use without prescription	4.0	906	141	1.00	Age, gender, income, marital status, employment status, household size, healthcare insurance (social security), perceived health status, presence of chronic diseases
						12.5	1787	373	1.43 (1.15, 1.78)	
Sawair 2009 [201]	Jordan	16 - 65	M: 46.1% F: 53.9%	Attendants of primary care centers	Use without prescription	0.0	14	7	1.00	Age, gender, income, marital status, employment status, healthcare insurance, smoking habits, self-reported health status, chronic comorbidities
						5.5	37	15	0.68 (0.20, 2.35)	
						11.5	203	77	0.61 (0.21, 1.81)	
						15.5	198	85	0.75 (0.25, 2.23)	
						21.0	25	10	0.67 (0.18, 2.49)	
Hadi 2008 [199]	Indonesia	Adults (≥ 18)	M: 37.4% F: 62.6%	Attendants of primary care centers	Use without prescription	2.5	63	26	1.00	Age, gender, income, residential location, ethnicity, household size, healthcare insurance
						6.0	402	192	1.30 (0.76, 2.22)	
Mistretta 2008 [206]	Italy	≥ 10 Mean ± SD: 53.7 ± 17.7	M: 41.3% F: 58.7%	Attendants of primary care centers	Use without prescription	2.5	144	124	1.00	Age, gender, occupation, family size
						7.0	165	142	0.73 (0.36, 1.46)	
						11.0	195	160	0.62 (0.30, 1.28)	
						16.0	132	86	1.37 (0.65, 2.86)	
Al-Azzam 2007 [200]	Jordan	Unrestricted age category >17 to <60	M: 48.8% F: 51.2%	General population	Use without prescription	0.0	315	86	1.00	---
						5.5	396	143	1.51 (1.09, 2.08)	
						11.5	709	313	2.10 (1.58, 2.81)	
						15.5	713	300	1.93 (1.45, 2.58)	
Grigoryan 2006 [56]	19 European countries	Adults (≥ 18)	M: 46.8% F: 53.2%	General population	Use without prescription	6.0	---	---	1.00	Age, gender, country, chronic diseases
						14.0	---	---	1.36 (1.10, 1.68)	
					Antibiotics storage	6.0	---	---	1.00	
						14.0	---	---	1.69 (1.47, 1.94)	

Source	Country	Age (years)	Gender	Population	Type of misuse	Dose	N	n	OR (95% CI)	Adjustment, restriction or matching factors
Awad 2005 [51]	Sudan	≤20 to >60	M: 45.1% F: 54.9%	General population	Use without prescription	0.0	156	63	1.00	Age, gender, income
						3.5	285	155	1.76 (1.18, 2.61)	
						7.5	392	262	2.98 (2.03, 4.36)	
						10.0	474	413	9.99 (6.58, 15.18)	
						14.5	443	400	13.73 (8.77, 21.51)	
Parimi 2002 [203]	Trinidad and Tobago	Adults (≥ 18)	M: 33.3% F: 66.7%	General population	Use without prescription	3.5	126	34	1.00	Age
						9.5	323	71	0.76 (0.47, 1.22)	
						14.5	147	25	0.55 (0.31, 0.99)	
					Antibiotics storage	3.5	124	26	1.00	
						9.5	308	74	1.19 (0.72, 1.98)	
						14.5	147	28	0.89 (0.49, 1.61)	
Bi 2000 [240]	China	---	F: 100%	Children caregivers	Use without prescription	3.5	140	65	1.00	Gender
						8.0	442	259	1.63 (1.11, 2.39)	
						11.0	780	478	1.83 (1.27, 2.62)	
						14.5	97	65	2.34 (1.37, 4.01)	
Saradamma 2000 [241]	India	> 6	M: 48.5% F: 51.5%	General population	Use without prescription	4.0	87	38	1.00	---
						10.5	136	24	0.28 (0.15, 0.51)	
						14.5	137	8	0.08 (0.04, 0.18)	
						19.0	45	3	0.09 (0.03, 0.32)	

CI: Confidence Interval; N: total number of participants per education level; n: number of participants who misused antibiotics; OR: Odds Ratio; *: data provided by author

Table 28 Summary odds ratios (OR) and their 95% confidence interval (CI) estimated by categorical and continuous approaches of dose-response meta-analysis on education and antibiotic misuse

Group of studies	№ of studies	Medium versus low education level OR (95%CI)	High versus low education level OR (95%CI)	1-year increase in education OR (95%CI)
All studies	94	0.94 (0.83, 1.06)	0.86 (0.72, 1.03)	0.99 (0.97, 1.00)
Study design				
Cohort	2	---	---	0.93 (0.89, 0.97)
Cross-sectional	92	0.95 (0.84, 1.07)	0.88 (0.73, 1.05)	0.99 (0.97, 1.00)
Type of antibiotic misuse				
Use without prescription	70	0.94 (0.82, 1.08)	0.85 (0.68, 1.06)	0.99 (0.97, 1.00)
Storage of antibiotics	10	1.17 (0.93, 1.48)	1.41 (1.22, 1.64)	1.03 (1.01, 1.06)
Non-adherence	9	0.98 (0.65, 1.49)	0.98 (0.71, 1.35)	0.99 (0.96, 1.03)
Several concomitant types of misuse	5	---	---	0.91 (0.87, 0.95)
Country economy				
Low	14	0.84 (0.54, 1.32)	0.69 (0.37, 1.28)	0.97 (0.92, 1.02)
Lower-middle	24	0.94 (0.74, 1.19)	0.70 (0.44, 1.13)	0.97 (0.93, 1.01)
Upper-middle	30	1.02 (0.89, 1.17)	0.95 (0.78, 1.16)	1.00 (0.98, 1.02)
High	25	0.80 (0.66, 0.97)	0.97 (0.74, 1.27)	1.00 (0.97, 1.03)
WHO Region				
Africa	18	0.93 (0.75, 1.16)	0.84 (0.59, 1.21)	0.98 (0.95, 1.01)
Eastern Mediterranean	27	0.91 (0.68, 1.22)	0.64 (0.42, 1.00)	0.96 (0.93, 1.00)
European	18	1.02 (0.81, 1.28)	1.25 (1.00, 1.58)	1.02 (1.00, 1.04)
Region of the Americas	6	1.06 (0.82, 1.38)	0.98 (0.69, 1.38)	1.00 (0.97, 1.03)
South-East Asia	8	0.61 (0.30, 1.23)	0.45 (0.14, 1.41)	0.93 (0.81, 1.06)
Western Pacific	17	0.94 (0.77, 1.14)	1.11 (0.94, 1.31)	1.01 (0.99, 1.03)
Publication year				
Until 2015	42	0.99 (0.81, 1.21)	0.95 (0.74, 1.22)	1.00 (0.97, 1.02)
After 2015	52	0.92 (0.81, 1.05)	0.81 (0.64, 1.02)	0.98 (0.96, 1.00)
Pre-tested or validated questionnaire				
No	26	0.75 (0.59, 0.95)	0.65 (0.41, 1.02)	0.97 (0.94, 1.01)
Yes	68	1.01 (0.89, 1.15)	0.95 (0.80, 1.13)	0.99 (0.98, 1.01)
Restriction, matching or adjustment for age and gender				
No	47	0.86 (0.72, 1.02)	0.70 (0.53, 0.94)	0.97 (0.93, 1.01)
Yes	47	1.00 (0.85, 1.19)	1.05 (0.87, 1.28)	1.00 (0.99, 1.02)
Quality Score				
Lower quality (≤ 3 points)	34	0.84 (0.67, 1.04)	0.76 (0.52, 1.10)	0.98 (0.95, 1.01)
Higher quality (> 3 points)	60	1.00 (0.87, 1.15)	0.93 (0.77, 1.11)	0.99 (0.98, 1.01)

OR: Odds Ratio; CI: Confidence Interval

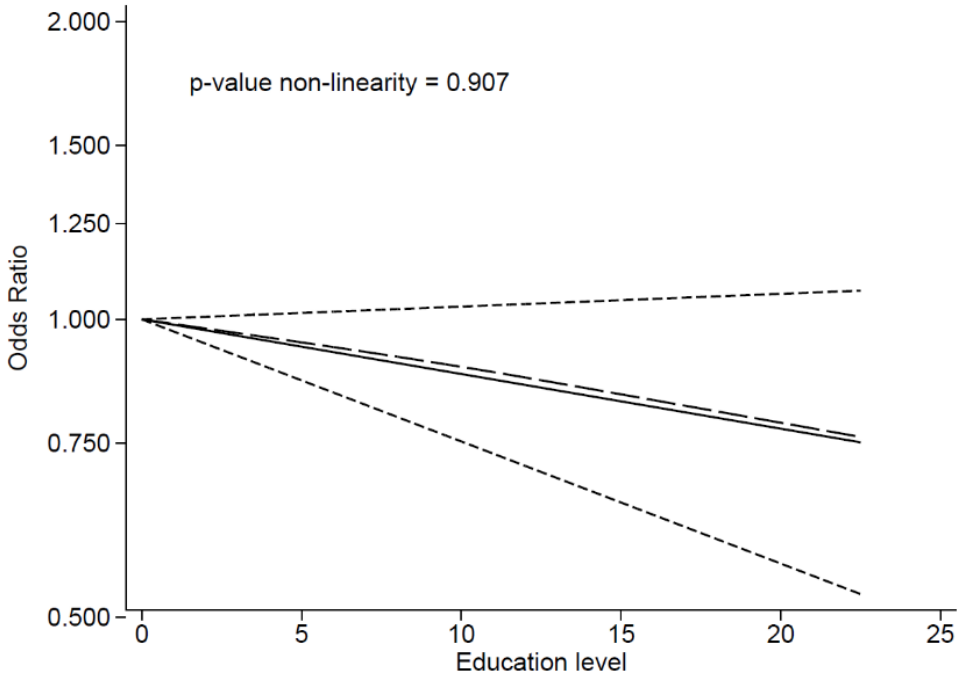

Figure 13 Trend of the association of education level with antibiotic misuse
Solid line represents the linear trend. Short-dashed lines represents 95% confidence intervals. Long-dashed line represents the non-linear restricted cubic spline approach.

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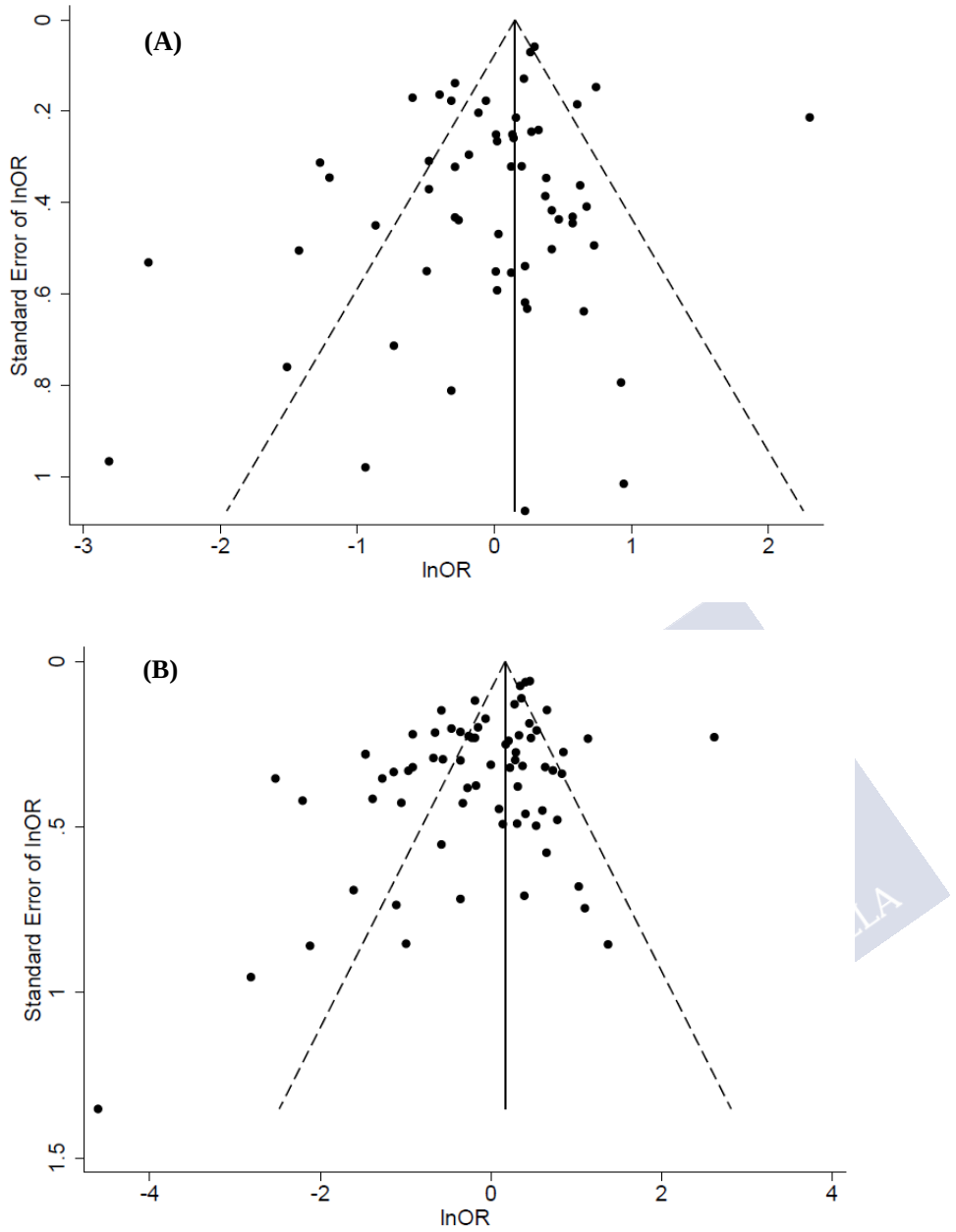

Figure 14 Funnel plot of the studies about education and antibiotic misuse.
A) represents the subgroup of studies that assessed the association of medium education with antibiotic misuse.
B) represents the subgroup of studies that assessed the association of high education with antibiotic misuse.

5.8. Meta-analysis of the association of macrolides with congenital malformation

The meta-analysis of macrolides and congenital malformation has been published (Drug Safety 2020, 43(3), 211-221) and the corresponding publication is available in Annex II page 235.

Literature Search and Study Selection

Figure *15* represents the process of the selection of studies included in the meta-analysis of the association of prenatal exposure to macrolides with congenital malformation. Twenty-one studies published between 1998 and 2017 fulfilled the inclusion criteria (**Table *29***, **Table *30*** and **Figure *16***). The studies were mainly conducted in Europe and North America. They included 17 cohort and four population-based case control studies with an average of 10,483 cases and 12,937 controls. Two studies examined the effect of two different macrolides but involved the same population were pooled and analyzed as one study [242, 243].

The included studies applied as comparator fetuses who were not exposed to any drug before birth (comparison group 1: 14 studies) and/or fetuses who were prenatally exposed to drugs that are not macrolide antibiotics or non-teratogens (comparison group 2: 13 studies).

Three analytical approached that involved comparison group 1, comparison group 2 and a mixture of the two comparison groups (comparison group 3) were carried out and yielded similar results (**Table *31***, **Table *32*** and **Table *33***). In comparison with fetuses who were not exposed to any drug (comparison group 1), overall, there is no association between prenatal exposure to macrolides and congenital malformation [OR: 1.05 (95%CI: 0.99, 1.12)] (**Table *31***). Studies that applied comparison group 2 and those studies that used mixed controls of groups 1 and 2 (comparison group 3), revealed a borderline positive association between macrolides prenatal exposure and congenital malformation [OR: 1.06 (95%CI: 1.00, 1.12) and 1.06 (95%CI: 1.01, 1.10), respectively] (**Table *32*** and **Table *33***).

The association between macrolides and congenital malformation was not observed in any of the subgroups when compared to fetuses unexposed to any drug before birth (comparison group 1). The heterogeneity between studies was absent-to-marginal (**Table *31***).

In the analysis that involved comparison groups 2 and 3, a substantial amount of heterogeneity across studies of several subgroups was present (**Table *32*** and **Table *33***). A slightly higher odds ratio of congenital malformation was observed for studies carried out in Europe [OR_{group2}: 1.15 (95%CI: 1.01, 1.31) and OR_{group3}: 1.12 (1.03, 1.22)] than that undertaken in North America [$OR_{group\ 2}$: 1.04 (95%CI: 0.98, 1.11) and OR_{group3}:1.03 (95%CI: 0.98, 1.09)] (**Table *32*** and **Table *33***). Higher odds were also observed for musculoskeletal system [OR_{group2}: 1.21 (95%CI: 1.08, 1.35) and OR_{group3}: 1.15 (95%CI: 1.05, 1.26)] and digestive system malformations [OR_{group3}: 1.14 (95%CI: 1.02, 1.26)] (**Table *32*** and **Table *33***).

No association was found between macrolides prenatal exposure and cardiovascular congenital malformations when compared with fetuses unexposed to any drug (comparison group 1) (Table 31) and to the mixed comparison group (comparison group 3) (Table 33). However, a negative association existed when compared to fetuses prenatally exposed to other antibiotics [OR group 2: 0.87 (95%CI: 0.81, 0.95)] (Table 32). When group 3 was used a comparator, a marginal association was also observed for the subgroups: cohort studies [OR_{group3}: 1.07 (95%CI: 1.02, 1.13)], and macrolides exposure during the first trimester of pregnancy [OR_{group3}: 1.06 (95%CI: 1.01, 1.12)] (**Table *33***).

Studies included in the meta-analysis provided data about several classes of macrolides. The classes were mainly: erythromycin, azithromycin, clarithromycin and roxithromycin. Analyzing the effect of each type of macrolides separately revealed a substantial but statistically non-significant association of roxithromycin prenatal exposure with congenital malformation in the three approaches: [OR_{group1}: 2.03 (95%CI: 0.75, 5.48), OR_{group2}: 1.50 (95%CI: 0.81, 2.77), and OR_{group3}: 1.63 (95%CI: 0.96, 2.75)] (**Table *31***, **Table *32*** and **Table *33***).

Methodological assessment

A median quality score of 4 points was obtained from the quality assessment. In the studies that used fetuses unexposed to any medicine as a reference (comparison group 1), no difference was found between higher (≥ 4 points) and lower quality (< 4 points) studies [OR_{group1}: 1.04 (95%CI: 0.95, 1.14) versus OR_{group1}: 1.06 (95%CI: 0.98, 1.16), respectively] (**Table *31***). However, when comparison groups 2 and 3 were used, higher quality studies yielded a statistically significant association that was similar to the one estimated from all studies [$OR_{group\ 2}$: 1.08 (95%CI: 1.01, 1.15) and OR_{group3}: 1.07 (95%CI: 1.01, 1.13)] (**Table *32*** and **Table *33***). The association was not statistically significant in the group of lower quality studies [OR_{group2}: 1.02 (95%CI: 0.92, 1.13) and OR_{group3}: 1.04 (95%CI: 0.97, 1.12)] (**Table *32*** and **Table *33***). There was no meaningful difference between studies with full adjustment and those with incomplete adjustment in the three approaches (**Table *31***, **Table *32*** and **Table *33***).

The sensitivity analysis under the extreme assumptions showed no increase in the odds of congenital malformations from prenatal exposure to macrolides [OR: 1.00 (95%CI: 0.98, 1.03)].

Publication bias

The funnel plot showed some degree of asymmetry with a larger number of studies favouring the presence of association between macrolides prenatal exposure and congenital malformation (right hand side of the figure, OR>1) (**Figure 17**), yet the negative result of Egger's regression test did not confirm this asymmetry (p-value= 0.074). The trim-and-fill analysis suggested the imputation of six additional studies and a corrected OR of 1.02 (95%CI: 1.00, 1.04).

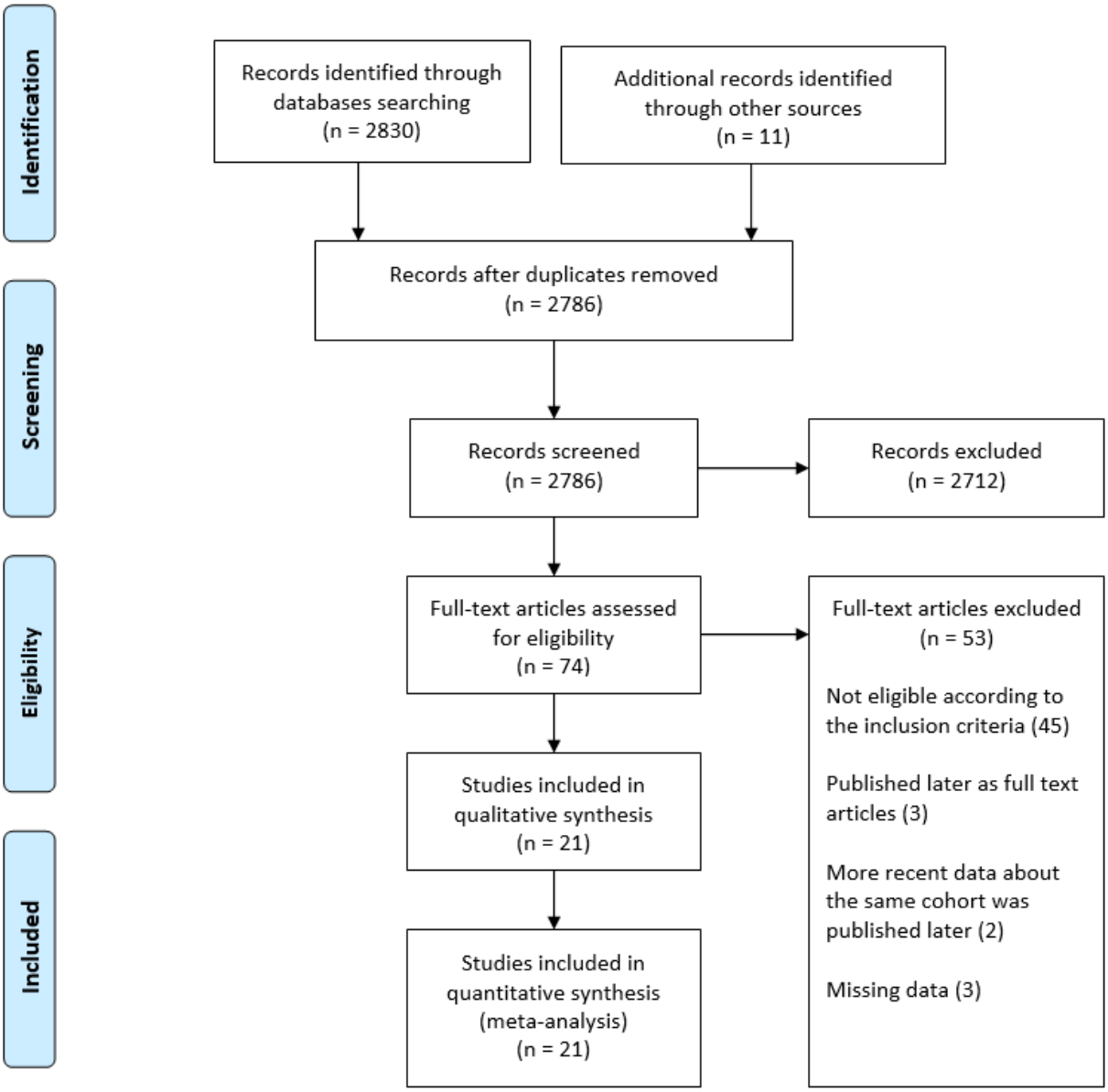

Figure 15 Flow diagram of the selection of studies about macrolides prenatal exposure and congenital malformation

Table 29 Characteristics of cohort studies of macrolides prenatal exposure and congenital malformations

Source	Type of Macrolide	Country	Type of malformation	Exposure Period (months of pregnancy)	Comparison Type and OR (95% CI)	Cases/ Cohort Size	General OR (95% CI)	Adjustment, Matching, and Restriction Factors
Muanda 2017 [244]	azithromycin, erythromycin, clarithromycin	Quebec	Cardiac, digestive, head and neck, musculoskeletal, nervous, respiratory, urogenital	1 – 3	Unexposed to any antibiotic: 1.08 (0.95, 1.23) Exposed to non-macrolide antibiotics: 1.04 (0.95, 1.14)	13, 852/139,938 1627/15469	1.05 (0.98, 1.14)	Maternal age, urinary tract infections, socio-demographic variables, chronic maternal illness, endometriosis and other maternal infections, healthcare utilization, year of delivery, infant's gender
Lê Nguyên 2017 [245]	macrolides	France	Congenital malformations	1 – 3	Unexposed to any antibiotic: 1.02 (0.71, 1.46) Treated with penicillin: 0.93 (0.63, 1.37)	47/62,846 47/12,193	0.98 (0.75, 1.27)	Maternal age, long-term maternal illness, gestity, parity, multiple pregnancy
Källén. 2014 [246]	erythromycin	Sweden	Any, cardiac	1 – 3	Unexposed to any antibiotic: 1.14 (0.96, 1.36)	70339/1575847	1.14 (0.96, 1.36)	Maternal age, year of delivery, parity, smoking, obesity
Lund 2014 [72]	azithromycin, clarithromycin, erythromycin, roxithromycin, spiramycin,	Denmark	Infantile hypertrophic pyloric stenosis	• 1 – 6 • 6 – 9	Unexposed to any antibiotic: 1.23 (0.85, 1.76) Exposed to non-macrolide antibiotics: 1.23 (0.83, 1.83)	30/315569 159/60732	1.23 (0.94, 1.60)	Birth order, infant's sex, calendar period, current age of the infant
Andersen 2013 [74]	clarithromycin	Denmark	Cardiac, musculoskeletal, urogenital	1 – 3	Unexposed to any antibiotic: 1.03 (0.53, 2.00)	24817/705837	1.03 (0.53, 2.00)	Maternal age, education, number of previous births, economic status
Dinur 2013 [247]	azithromycin, clarithromycin, erythromycin, roxithromycin	Israel	Cardiac, digestive	1 – 3	Unexposed to any antibiotic: 1.07 (0.84, 1.38)	---/105492	1.07 (0.84, 1.38)	Maternal age, year of delivery, parity, ethnicity, chronic maternal illness

Source	Type of Macrolide	Country	Type of malformation	Exposure Period (months of pregnancy)	Comparison Type and OR (95% CI)	Cases/ Cohort Size	General OR (95% CI)	Adjustment, Matching, and Restriction Factors
Bar-Oz 2012 [248]	azithromycin, roxythromycin, clarithromycin	• Czech Republic • Germany • Israel • Italy • Netherlands	Cardiac	1 – 3	Exposed to non-teratogenic agents: 1.42 (0.70, 2.88)	32/1146	1.42 (0.70, 2.88)	Maternal age, smoking, alcohol consumption, previous abortions, previous child with structural anomaly, macrolide exposure
Romøren 2012 [249]	erythromycin, azithromycin, clarithromycin, spiramycin	Norway	Any, Cardiac	1 – 3	Unexposed to any antibiotic: 1.02 (0.86, 1.23) Exposed to non-macrolide antibiotics: 1.15 (0.96, 1.38)	8865/178142 413/9069	1.08 (0.95, 1.24)	Maternal age, urinary tract infections, chronic maternal illness, parity, marital status, smoking, pregnancy supplement, previous abortions
Cooper 2009 [250]	azithromycin, erythromycin	United States	Any, digestive, head and neck, nervous, musculoskeletal, urogenital	• 1 – 3 • 1 – 9	Unexposed to any antibiotic: 0.92 (0.73, 1.16) Exposed to non-macrolide antibiotics: 1.03 (0.88, 1.21)	869/30,049 589/7471	0.99 (0.87, 1.13)	Maternal age, year of delivery, race, rural residence, economic status, chronic maternal illness, filling of prescriptions of other known teratogens
Bar-Oz 2008 [251]	azithromycin, roxythromycin, clarithromycin	• Croatia • Israel	Cardiac	1 – 3	Exposed to non-macrolide antibiotics: 1.62 (0.68, 3.86)	32/1066	1.62 (0.68, 3.86)	Unadjusted
Chun 2006 [252]	roxythromycin	South Korea	Major	1 – 3	Unexposed to any teratogenic agent: 1.37 (0.07, 27.57)	3/187	1.37 (0.07, 27.57)	Maternal age, gravity
Sarkar 2006 [253]	azithromycin	Canada	Major	1 – 3	Exposed to any non-teratogen: 1.01 (0.20, 5.11)	6/227	1.01 (0.20, 5.11)	Maternal age, gestational age at call, smoking, alcohol consumption
Wolfgang 2005 [254]	roxithromycin	Hungary	Congenital anomalies	1 – 3	Unexposed to any antibiotic: 2.13 (0.75, 6.1)	15/275	2.13 (0.75, 6.1)	Maternal age, gestational age at call

Source	**Type of Macrolide**	**Country**	**Type of malformation**	**Exposure Period** (months of pregnancy)	**Comparison Type and OR (95% CI)**	**Cases/ Cohort Size**	**General OR (95% CI)**	**Adjustment, Matching, and Restriction Factors**
Cooper 2002 [255]	erythromycin, non-erythromycin, lincomycin, clindamycin, clarithromycin, azithromycin, dirithromycin	United States	Digestive	• 6 – 9 • 1 – 9	Exposed to non-macrolide antibiotics: 1.28 (0.96, 1.70)	679/260,799	1.28 (0.96, 1.70)	Maternal age, education, geographic residence, use of other antibiotics, infant´s gender, infant´s race, birth order, year of delivery, infant´s postnatal prescriptions for erythromycin
Mahon 2001 [256]	macrolides	United States	Digestive	1 – 9	Unexposed to any antibiotic: 1.19 (0.6, 2.3)	43/14,876	1.19 (0.6, 2.3)	Birth weights, gestational age
Einarson 1998 [257]	clarithromycin	Canada	Major	1 – 3	Exposed to non-teratogenic antibiotics: 1.1 (0.44, 2.78)	19/266	1.1 (0.44, 2.78)	Maternal age, smoking, alcohol consumption
Wilton 1998 [258]	azithromycin	United Kingdom	Congenital anomalies	1 – 3	Exposed to non-macrolide antibiotics: 1.75 (0.01, 31.23)	14/556	1.75 (0.01, 31.23)	Unadjusted

Table 30 Characteristics of case-control studies of macrolides prenatal exposure and congenital malformations

Source	Type of Macrolide	Country	Type of malformation	Exposure Period (months of pregnancy)	Comparison Type and OR (95% CI)	№ Cases/Controls	General OR (95% CI)	Adjustment, Matching, and Restriction Factors
Lin KJ, et al. 2013 [259]	Any macrolide, erythromycin, non-erythromycin	• Canada • United States	Cardiac, digestive, head and neck, musculoskeletal, nervous, respiratory, urogenital	• 1 – 3 • 3 – 6 • 6 – 9	Unexposed to any antibiotic: 0.99 (0.85, 1.16)	4867/6,952	0.99 (0.85, 1.16)	Maternal age, calendar year when they were ascertained, race, education, geographic residence, obesity, family history of congenital malformations or diabetes mellitus, smoking, pregnancy supplement, multiple pregnancy, urinary tract infections, maternal chronic illness
Crider KS, et al. 2009 [70]	erythromycin	United States	Cardiac, digestive, head and neck, musculoskeletal, nervous, urogenital	1 – 3	Unexposed to any antibiotic: 1.12 (0.96, 1.32) Exposed to non-macrolide antibiotics: 1.01 (0.91, 1.13)	13155/4941 1384/516	1.04 (0.95, 1.15)	Maternal age, race, education, obesity, gestational age at call, pregnancy supplements, smoking, alcohol consumption
Louik C, et al. 2002	erythromycin	• Canada • United States	Digestive	• 1 – 6 • 6 – 9	Unexposed to any antibiotic: 0.81 (0.57, 1.14)	1,044/1704	0.81 (0.57, 1.14)	Maternal age, geographic region, study period, parity, infant´s gender, gestational age
Czeizel AE, et al. 2000 [&] Czeizel AE, et al. 1999 [242, 243]	erythromycin, spiramyicn, roxithromycin, oleandomycin, josamycin,	Hungary	Cardiac, head and neck, musculoskeletal, urogenital, nervous, others	• 1 – 3 • 1 – 9	Exposed to other agents (not macrolides): 1.19 (0.92, 1.54)	22,865/38,151	1.19 (0.92, 1.54)	Maternal age, urogenital disorders, birth order, maternal chronic illness, other drug uses

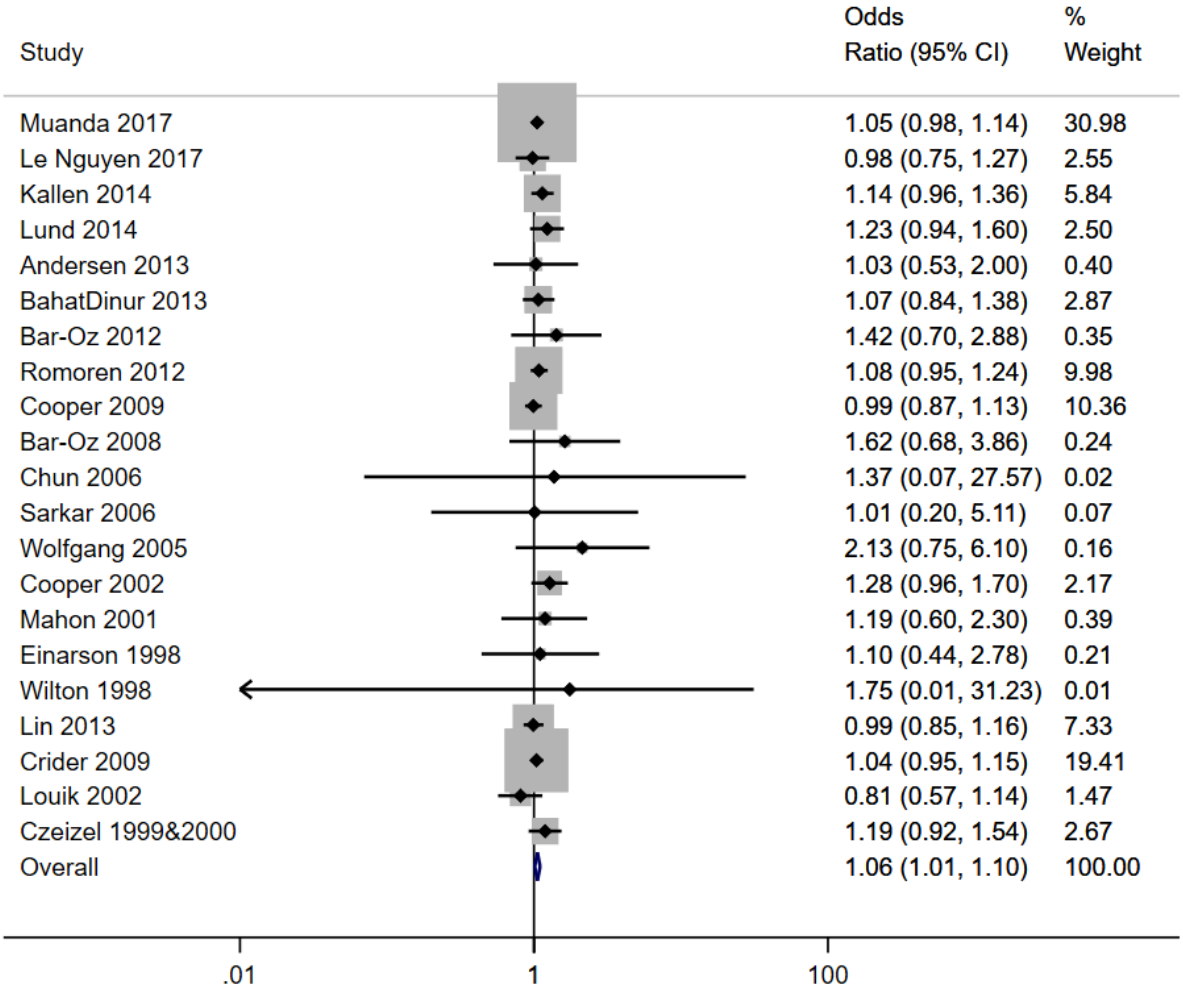

Figure 16 Forest plot of studies included in the meta-analysis about macrolides prenatal exposure and congenital malformations

Table 31 Pooled Odds Ratios (ORs) and 95% Confidence Intervals (CIs) of macrolides prenatal exposure and congenital malformations (comparison group 1: fetuses not exposed to any drug)

	№ of studies	OR (95% CI) Fixed effects	OR (95% CI) Random effects	Ri*	Q test (p value)
Any congenital malformation					
All studies	14	1.05 (0.99, 1.12)	1.05 (0.99, 1.12)	0.00	0.81
Study Design					
Cohort	11	1.07 (0.99, 1.15)	1.07 (0.99, 1.15)	0.00	0.90
Case-control studies	3	1.02 (0.92, 1.14)	1.01 (0.88, 1.17)	0.39	0.21
Anatomic location					
Cardiovascular	8	1.03 (0.93, 1.14)	1.05 (0.90, 1.22)	0.48	0.07
Head and Neck	4	1.27 (0.94, 1.72)	1.27 (0.94, 1.72)	0.00	1.00
Musculoskeletal system	5	1.06 (0.91, 1.24)	1.06 (0.85, 1.31)	0.33	0.27
Digestive system	8	1.13 (0.97, 1.31)	1.12 (0.9, 1.33)	0.18	0.30
Urogenital system	5	1.00 (0.80, 1.24)	0.98 (0.71, 1.35)	0.43	0.17
Nervous system	4	1.14 (0.86, 1.52)	1.12 (0.81, 1.55)	0.19	0.28
Adjustment					
Full	2	1.04 (0.94, 1.15)	1.04 (0.94, 1.15)	0.00	0.50
Incomplete	12	1.06 (0.98, 1.15)	1.06 (0.98, 1.15)	0.00	0.75
Quality score					
≥ 4	7	1.04 (0.95, 1.14)	1.04 (0.95, 1.14)	0.00	0.78
< 4	7	1.06 (0.98, 1.16)	1.06 (0.98, 1.16)	0.00	0.56
Macrolide exposure period					
First trimester	11	1.07 (1.00, 1.14)	1.07 (1.00, 1.14)	0.00	0.93
Third trimester	3	1.00 (0.79, 1.28)	1.08 (0.73, 1.59)	0.60	0.11
Geographic location					
Europe	6	1.10 (0.98, 1.23)	1.10 (0.98, 1.23)	0.00	0.71
North America	6	1.03 (0.96, 1.12)	1.03 (0.96, 1.12)	0.00	0.45
Type of treatment					
Erythromycin	7	1.05 (0.97, 1.15)	1.05 (0.97, 1.15)	0.00	0.46
Azithromycin	2	1.15 (0.97, 1.36)	1.15 (0.97, 1.36)	0.00	0.37
Clarithromycin	2	1.10 (0.88, 1.38)	1.10 (0.88, 1.38)	0.00	0.84
Roxithromycin	2	2.03 (0.75, 5.48)	2.03 (0.75, 5.48)	0.00	0.79

*CI: Confidence Interval; OR: Odds Ratio; *Ri: Proportion of total variance due to between-study variance*.

Table 32 Pooled Odds Ratios (ORs) and 95% Confidence Intervals (CIs) of macrolides prenatal exposure and congenital malformations. (Comparison group 2: fetuses exposed to non-teratogenic drugs/non-macrolides)

	№ of studies	OR (95% CI) Fixed effects	OR (95% CI) Random effects	Ri*	Q test (p value)
Any congenital malformation					
All studies	13	1.06 (1.00, 1.12)	1.06 (1.00, 1.12)	0.00	0.88
Study Design					
Cohort	11	1.07 (1.00, 1.15)	1.07 (1.00, 1.15)	0.00	0.86
Case-control studies	2	1.03 (0.93, 1.14)	1.03 (0.93, 1.14)	0.00	0.36
Anatomic location					
Cardiovascular	7	0.87 (0.81, 0.95)	0.93 (0.80, 1.07)	0.50	0.10
Head and Neck	4	1.08 (0.90, 1.29)	1.05 (0.78, 1.42)	0.54	0.12
Musculoskeletal system	4	1.21 (1.08, 1.35)	1.21 (1.08, 1.35)	0.00	0.85
Digestive system	5	1.14 (0.98, 1.33)	1.11 (0.90, 1.38)	0.44	0.15
Urogenital system	4	0.89 (0.76, 1.05)	0.92 (0.60, 1.39)	0.84	0.001
Nervous system	4	1.14 (0.92, 1.42)	1.05 (0.68, 1.62)	0.70	0.03
Adjustment					
Full	2	1.05 (0.96, 1.15)	1.05 (0.96, 1.15)	0.00	0.48
Incomplete	11	1.07 (0.99, 1.15)	1.07 (0.99, 1.15)	0.00	0.84
Quality score					
≥ 4	8	1.08 (1.01, 1.15)	1.08 (1.01, 1.15)	0.00	0.74
< 4	5	1.02 (0.92, 1.13)	1.02 (0.92, 1.13)	0.00	0.86
Macrolide exposure period					
First trimester	9	1.05 (0.99, 1.12)	1.05 (0.99, 1.12)	0.00	0.83
Third trimester	2	1.33 (0.99, 1.79)	1.33 (0.99, 1.79)	0.00	0.34
Geographic location					
Europe	7	1.15 (1.01, 1.31)	1.15 (1.01, 1.31)	0.00	0.90
North America	6	1.04 (0.98, 1.11)	1.04 (0.98, 1.11)	0.00	0.81
Type of treatment					
Erythromycin	6	0.92 (0.86, 0.99)	0.99 (0.83, 1.18)	0.84	0.00
Azithromycin	6	1.08 (0.98, 1.19)	1.08 (0.98, 1.19)	0.00	0.63
Clarithromycin	4	0.92 (0.82, 1.04)	0.92 (0.82, 1.04)	0.00	0.95
Roxithromycin	3	1.50 (0.81, 2.77)	1.74 (0.69, 4.37)	0.53	0.13

*CI: Confidence Interval; OR: Odds Ratio; *Ri: Proportion of total variance due to between-study variance*.

Table 33 Pooled Odds Ratios (ORs) and 95% Confidence Intervals (CIs) of macrolides prenatal exposure and congenital malformations. (Comparison group 3: mixed population of unexposed fetuses)

	Number of studies	OR (95% CI) Fixed effects	OR (95% CI) Random effects	Ri*	Q test (p value)
Any congenital malformation					
All studies	21	1.06 (1.01, 1.10)	1.06 (1.01, 1.10)	0.00	0.86
Study Design					
Cohort	17	1.07 (1.02, 1.13)	1.07 (1.02, 1.13)	0.00	0.93
Case-control studies	4	1.03 (0.95, 1.11)	1.02 (0.94, 1.12)	0.14	0.35
Anatomic location					
Cardiovascular	11	0.93 (0.87, 0.98)	1.03 (0.89, 1.18)	0.71	0.002
Head and Neck	5	1.13 (0.96, 1.32)	1.12 (0.93, 1.35)	0.19	0.31
Musculoskeletal system	6	1.15 (1.05, 1.26)	1.15 (1.05, 1.26)	0.00	0.40
Digestive system	9	1.14 (1.02, 1.26)	1.10 (0.94, 1.28)	0.44	0.08
Urogenital system	6	0.93 (0.81, 1.05)	0.96 (0.69, 1.34)	0.81	0.001
Nervous system	5	1.15 (0.97, 1.36)	1.02 (0.72, 1.47)	0.71	0.01
Adjustment					
Full	3	1.05 (0.98, 1.12)	1.04 (0.97, 1.12)	0.00	0.50
Incomplete	18	1.06 (1.00, 1.12)	1.06 (1.00, 1.12)	0.00	0.84
Quality score					
≥ 4	12	1.07 (1.01, 1.13)	1.07 (1.01, 1.13)	0.00	0.78
< 4	9	1.04 (0.97, 1.12)	1.04 (0.97, 1.12)	0.00	0.70
Macrolide exposure period					
First trimester	16	1.06 (1.01, 1.11)	1.06 (1.01, 1.11)	0.00	0.95
Third trimester	4	1.12 (0.93, 1.35)	1.15 (0.85, 1.56)	0.62	0.05
Geographic location					
Europe	10	1.12 (1.03, 1.22)	1.12 (1.03, 1.22)	0.00	0.86
North America	9	1.03 (0.98, 1.09)	1.03 (0.98, 1.09)	0.00	0.74
Type of treatment					
Erythromycin	9	0.96 (0.91, 1.01)	1.00 (0.88, 1.14)	0.79	0.00
Azithromycin	6	1.09 (1.00, 1.19)	1.09 (1.00, 1.19)	0.00	0.73
Clarithromycin	5	0.96 (0.86, 1.07)	0.96 (0.86, 1.07)	0.00	0.97
Roxithromycin	5	1.63 (0.96, 2.75)	1.66 (0.95, 2.89)	0.08	0.36

*CI: Confidence Interval; OR: Odds Ratio; *Ri: Proportion of total variance due to between-study variance*

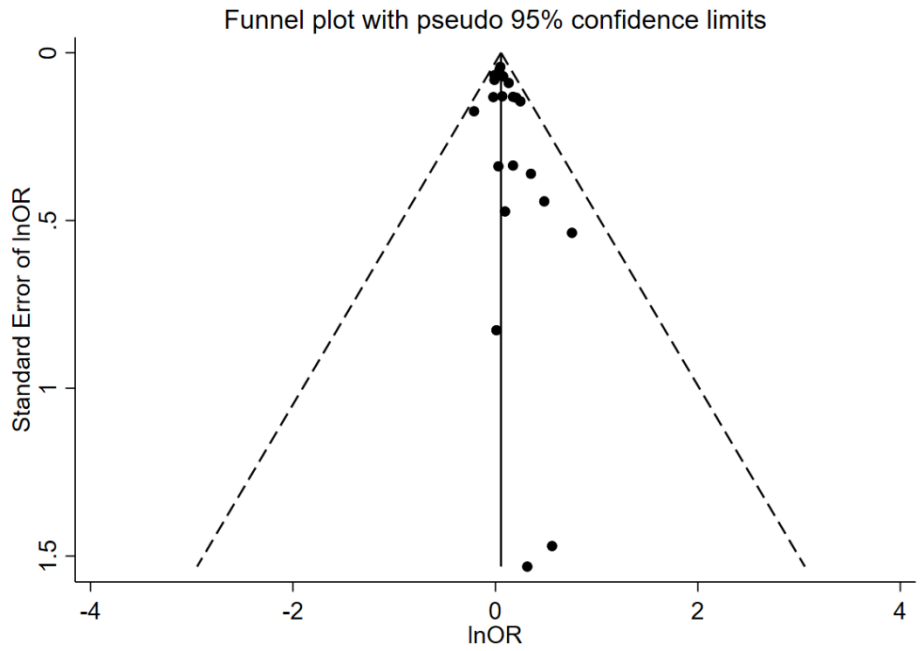

Figure 17 Funnel plot of studies included in the meta-analysis about macrolides and congenital malformation

6. DISCUSSION

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Discussion

Antibiotic resistance has long been recognized as an international public health crisis. Dependence and addiction on tranquilizers is another growing international public health concern, yet it remains insufficiently recognized by the scientific community. Both problems are derived from the misuse of antibiotics and tranquilizers. They are associated with elevated mortality and morbidity rates as well as with heavy social, economic, and clinical burdens.

Knowledge, *Attitude* and *Practice* (KAP) questionnaires are the corner stone of prevention programs aimed at improving the rational use of medicines. These instruments are used at baseline to assess the need for intervention programs, and will later be used in the design of these programs, based on the characteristics of the population. KAP questionnaires are also applied in the post-intervention period to measure the effectiveness of the prevention programs. Accordingly, it is crucial that the pre- and post-interventions be based on validated instruments that ensure the quality of the data.

To the best of our knowledge:

1) none of the studies published before the present work on the association of *Knowledge* and *Attitudes* with *Practices* of antibiotic misuse by the general population applied a fully validated questionnaire. Moreover, all KAP studies about antibiotics were of cross-sectional design.

2) instruments to measure the association of *Knowledge* and *Attitudes* with *Practices* of tranquilizer misuse as well as related epidemiological studies are not available.

Accordingly, the present work aimed at filling these gaps. It was divided into three phases: **1)** development and validation of KAP questionnaires about antibiotic and tranquilizer use, **2)** application of the developed questionnaires in countries with different socioeconomic and public health indicators, and **3)** meta-analyses of determinants of misuse.

6.1. Development and validation of KAP questionnaires about antibiotic and tranquilizer use

Six questionnaires were developed and validated in the present thesis; three KAP questionnaires on antibiotic misuse in Galician, Arabic and French; and other three KAP questionnaires on tranquilizer misuse in the same three languages. The Galician versions of the questionnaires were tested in Galicia, while those in Arabic and French were tested in Lebanon. The validation was carried out in full for each of the six questionnaires. The content and the scale validity indexes of the questionnaires confirmed their *content validity*. The test-retest *reliability* assessment proved the *stability* of the questionnaires over time to generate *reproducible* results. The confirmatory factorial analysis proved the *construct validity* of the questionnaires in Galician and French. However, the CFA analysis could not be undertaken for the questionnaires in Arabic due to the presence of missing answers that affected the structure of the collected data. Though, the sample size of the population who answered the questionnaire in Arabic was relatively large, a larger sample size is needed to demonstrate the construct validity of this version of the questionnaire. The Cronbach´s alpha value was slightly below the optimally accepted value for the questionnaire about antibiotics in French, which could be due to the reduced number of items after the exclusion of Q7 and Q9 during model configuration along with the multidimensionality of the questionnaire [260]. The internal reliability of a questionnaire is also influenced by sociodemographic properties of the population, thus it is

expected that the same questionnaire yield different reliability results in different settings [137]. Importantly, the questionnaires in Galician and French were highly *accepted* by the general adult population in Galicia as well as in Lebanon, as reflected by the high response rates and the low percentage of unanswered questions.

The availability of *reliable* and *construct-valid* instruments is essential for epidemiological studies that aim to measure associations between *Knowledge*, *Attitudes*, and antibiotic or tranquilizer misuse *Practices*. The use of non-validated questionnaires may introduce measurement error in the ascertainment of the exposure and the outcome, while the availability of validated questionnaire in the same *language* as that of the study population and the tailoring of the questionnaire to the *socio-demographic* characteristics of the population ensure higher quality of data.

Knowledge and *Attitudes* are considered stable variables that are unlikely to change in a short period. In the three versions of the questionnaires about antibiotics and tranquilizers, overall, the test-retest *reliability* of *Knowledge* and *Attitude* items showed that they generate reproducible results, except for the item Q5 in the questionnaire in Galician about antibiotics *"It is good to be able to get antibiotics from relatives or friends without having to see a medical doctor".* The low ICC for this item (Q5) could be induced by the sample distribution [261], as the large majority of participants totally disagreed (answered 0) with this statement in the two waves of the test-retest. Accordingly, item Q5 is likely to be reliable and therefore it was retained in the questionnaire.

The questionnaires were designed to measure the level of *Knowledge* and *Attitudes* of the participants irrespective of their antibiotic or tranquilizer use in the last two months. Consequently, the questionnaires could aid in obtaining data from both users and non-users of those drugs, a crucial aspect in epidemiologic related studies.

The *construct validity* assessment showed that the adopted models of the questionnaires on antibiotics and tranquilizers have a good to excellent fit. The distribution of the *Knowledge* and *Attitude* items, based on logical and theoretical grounds, across the three factors, "*Knowledge*", "*Attitude-Personal*" and "*Attitude-Healthcare provider*" supported further the adequacy of the chosen model [133]. In the developed questionnaires, some items showed cross-load, i.e., loaded in more than one factor. This observation was expected as the questionnaires were designed to measure more than one factor, and thus they include multidimensional constructs [262]. The structure of the data confirmed further the presence of three differentiated factors. Although the models of the questionnaires validated in Galicia as well as in Lebanon showed correlation between one or more factors, the structure of those correlated factors was distinct which ensures their specificity.

The two factors "*Knowledge*" and "*Attitude-Personal*" correlated in all models of questionnaires about antibiotics and tranquilizers. This correlation was expected because personal *Attitudes* toward medicines are in part driven by the *Knowledge* of the individuals of that medicine. For instance, item Q6 in the questionnaire on antibiotics "*When I have a sore throat, I prefer to use an antibiotic*" loaded significantly on "*Knowledge*" and "*Attitude-Personal*" in both versions of the questionnaire, Galician and French, explaining further the existing association between the two factors.

"*Knowledge*" and "*Attitude-Healthcare provider*" factors did not correlate in the Galician and French versions of the antibiotic questionnaire, nor in the Galician version of the tranquilizer questionnaire. The absence of this correlation between the two factors reveals that the items designed to measure participants' *Knowledge* about antibiotics or tranquilizers are not related to those intended to explore the relation between patients and healthcare providers, which confirms the specificity and uniqueness of the factors. Nonetheless, "*Knowledge*" and "*Attitude-Healthcare provider*" showed a weak positive association in the data collected in Lebanon about tranquilizers, which could be due to the sociodemographic and psychometric characteristics of the population, i.e., Lebanese individuals with better socioeconomic class have a higher level of *Knowledge*, a better access to healthcare, and thus might have a better communication with their healthcare providers.

The developed questionnaires measured the associations between *Attitudes* towards healthcare providers and antibiotic or tranquilizer misuse *Practices*. Various reports had highlighted the importance of a good healthcare provider-patient relationship for an adequate therapeutic adherence [263, 264]. Furthermore, the data collected in Galicia suggested the presence of a negative and weak correlation between "*Attitude-Personal*" and "*Attitude-Healthcare provider*" meaning that Galician individuals who have more negative *Attitudes* towards their healthcare provider are more susceptible to have medically disapproved *Attitudes*. For instance, in the questionnaire about tranquilizers, there was a cross-load of item Q13 "*If I believe that I need a tranquilizer and the doctor did not prescribe it, I will get it at the pharmacy without a prescription"* on the two *Attitude* factors. This could be explained by the fact that patients' willingness to use tranquilizers without a prescription is generated from their personal *Attitudes* towards tranquilizers as well as from their low degree of trust in the treating physician. Regarding the questionnaires tested in Lebanon, the two factors "*Attitude-Personal*" and "*Attitude-Healthcare provider*", correlated probably due to socioeconomic differences and worse access to healthcare.

As the assessment of exposure to a drug depends on the memory of the participants, the *Practice* block of the questionnaires was designed to measure antibiotic or tranquilizer use in the past two months, i.e., in a short recall period. This would help decrease the risk of recall bias and allows for comparability between studies, since differences in the time unit (past year, past month, lifetime) is widely observed in the literature. Most available studies inquire about the use of drugs without prescription, leaving the other aspects of misuse undetermined. Therefore, we designed the *Practice* questions to tackle all aspects of misuse (unprescribed use, shortened treatment, changed dose, taking a skipped dose upon recall or doubling the subsequent dose, and storing or sharing drug leftover). This would allow for better examination of misuse and thus, will help orienting the prevention programs. Finally, the provided choices to answer the *Practice* questions were based on an extensive literature review to include any possible answer, and therefore avoid leaving questions unanswered.

The developed instruments showed high *acceptability* rates by the general population in Galicia and Lebanon, which reflect the feasibility of their application in different settings and cultures. Various characteristics that were taken into consideration during the study design had helped in increasing the response rate. The time required to completely answer a questionnaire was within the ideal range (10 minutes) [265]. Long questionnaires negatively influence the response rate and the quality of data [266]. Another factor that could have enhanced the

response rate is that the questionnaire was issued from a research and academic institution [267].

The absence of previously validated KAP questionnaires on antibiotic or tranquilizer use and the unavailability of an instrument that is superior to the ones validated in the present thesis (gold standard), made us unable to compare the concurrent validity of our questionnaires with other instruments.

6.2. Application of the developed questionnaires in countries with different socioeconomic and public health indicators: Galicia and Lebanon

The questionnaires developed in the present study were applied to measure the association of *Knowledge* and *Attitudes* with antibiotic and tranquilizer misuse *Practices* in Galicia and Lebanon. Two cohort studies were carried out in Galicia, and other two cross-sectional studies were undertaken in Lebanon. In addition, to verify the appropriateness of cross-sectional design in drawing correct conclusions from KAP based studies, we compared findings from cross-sectional and longitudinal approaches using data collected from the same individuals. In this regard, two additional studies were carried out: one about antibiotic misuse and another about tranquilizer misuse.

The ***novelty*** of these epidemiological studies lies in that, to the best of our knowledge, they encompass:

1) The **first** study in Lebanon to measure through effect (or association) measures the relation between *Knowledge*, *Attitudes* and antibiotic misuse *Practices*.
2) The **first** cohort study ***worldwide*** about *Knowledge*, *Attitudes* and antibiotic misuse *Practices.*
3) The **first** study ***worldwide*** to investigate the association between *Knowledge, Attitudes* and *Practices* of tranquilizer misuse.
4) The **first *methodological assessment*** of cross-sectional and longitudinal studies about *Knowledge, Attitudes* and misuse *Practices* of antibiotics as well as tranquilizers.

Our studies about antibiotics and tranquilizers showed a substantial association between the level of *Knowledge* and *Attitudes* and misuse *Practices* of these drugs. These are common to the Galician and Lebanese populations, yet the comparison study between cross-sectional and longitudinal approaches using data collected from the same individuals in Galicia showed divergent findings.

In Lebanon, lack of *Knowledge* about **antibiotics** was associated with higher odds of misuse of these drugs. Our data about the Lebanese population showed a considerable misunderstanding of the role of antibiotics. Half of the participants thought that antibiotics are effective against viral infections while three-quarters expected an antibiotic prescription in case of common cold and preferred to keep antibiotics at home for a potential future need. We also found substantial associations between *Personal Attitudes* towards antibiotics and their misuse *Practices* by the Lebanese people. For instance, individuals who would agree to get antibiotics without prescription or who would accept curtailing the course of antibiotics treatment upon improvement are more likely to misuse antibiotic.

*In **Galicia,*** we assessed the association of *Knowledge* and *Attitudes* with **antibiotic** misuse *Practices* using **cross-sectional** and **longitudinal** approaches of data collected from the same individuals. Cross-sectional data analysis indicated similar findings to that obtained in Lebanon about the association of poor *Knowledge* and certain *Attitudes* with increased odds of antibiotic misuse. However, these findings were not sustained by the longitudinal approach since only three *Knowledge* and *Attitude* items showed association with antibiotic misuse in Poisson regression analysis and only one item showed an association in GLMM analysis.

In ***Galicia*** and ***Lebanon***, we observed higher odds of **tranquilizer** misuse *Practices* for individuals with medically inappropriate *Personal Attitudes* towards tranquilizers such as accepting the use of these drugs in order to sleep better, enjoy themselves with their families, or work better. ***Lebanon*** has been continuously experiencing a series of dramatic events related to war, conflicts and economic crisis over the past three decades, [268]. In ***Galicia***, the majority of the participants were in the working age, but one-third of the individuals who misused tranquilizers were unemployed. These social and economic stressors increase the likelihood of tranquilizer misuse [269]. For instance, unemployment negatively influences the psychological state and mental health of the working-age population, hence increases predisposition to tranquilizer use [270, 271]. An additional contributor to the use of tranquilizers is the distinct perception that people have of prescription drugs compared to illicit drugs. The acceptance of individuals to use a certain drug is influenced by their *Knowledge* of the extent of harm associated with the use or the misuse of that drug [272]. Prescription drugs are perceived as being safer, socially accepted and easily accessed [273, 274]. This is consistent with our finding about a lower likelihood of tranquilizer misuse by the Lebanese individuals who knew that tranquilizers reduce people's control over what they do, increase the risk of traffic accidents, and/or affect the children's learning abilities. In Galicia, *Knowledge* about tranquilizers was not associated with their misuse *Practices*.

The preference of the population to store antibiotic or tranquilizer leftovers for a potential need in the future was identified as an *Attitude* leading to misuse in ***Galicia and Lebanon***. Easy access to drugs shapes individual's pattern of use and perception towards those drugs and promote their misuse [275-277]. ***In Lebanon***, a patient's past use of a medication is identified as the most frequent motive for self-treating with that medicine [278]. This is in line with our finding that more than half of the study population did not always consult a doctor in case of sickness. These figures are alarming for various motives. **Concerning antibiotics**, *first*, the dispensing of these drugs is not strictly regulated in Lebanon and can be obtained without prescription, though this action is unlawful; *second,* a considerable proportion of the pharmacists in Lebanon believe that some antibiotics are harmless and recommend these drugs to their clients without referring them to a physician; and *third*, the Lebanese population accepts receiving antibiotics prescribed by pharmacists [279], while these pharmacists blatantly report their interest in retaining customers by delivering antibiotics without medical prescription to increase their economic benefit [280]. **Regarding antibiotics and tranquilizers**, the health care system in Lebanon is not centralized. Hence a patient can obtain several prescriptions from various physicians, and/or use an old prescription to repetitively purchase a more controlled drug that requires prescription such as tranquilizers. Some physicians also serve as an outlet for their own social network, i.e., families and friends [278]. It was also reported that the physicians' decision about tranquilizer prescription does not only depend on the patient's medical situation but is also affected by the physicians' specialty and their personal experience with those drugs [281]. ***In Galicia,*** though the healthcare system is centralized, and antibiotics and tranquilizers cannot be purchased without prescription, misuse can still take place by failing

to adhere to the treatment guidelines, and/or storing or sharing tranquilizer leftover. The prevalence of self-medication is increasing in Spain [282], and old prescriptions and social network were recognized as frequent sources of drugs [6]. Moreover, a recent study showed that antibiotic dispensing without prescription still occurs in North-West Spain [90].

We found that negative *Attitudes toward the health-care provider* are associated with higher odds of antibiotic and tranquilizer misuse *Practices* in Galicia and Lebanon. Examples of these *Attitudes* include: distrusting the physician´s decision about prescribing or not prescribing antibiotics or tranquilizers, believing that the physician does not clearly explain the motives for prescription/non-prescription and believing that the pharmacist does not clearly explain the importance of correct therapeutic compliance. Previous reports also showed that the concordance between the patient and the physician influences patients' acceptance of and adherence to a treatment, as well as attendance of follow-up visits or new consultations [283].

The misuse of antibiotics and tranquilizers is associated with severe health consequences, increments hospitalization rates, healthcare expenses, morbidity and mortality rates and implies hefty economic and social burdens [14, 94, 284-286]. Misuse of antibiotics heavily exacerbates the international problem of antibiotic resistance, limits treatment options and causes the death of more than 700000 individuals each year [14]. Likewise, misuse of tranquilizers contributes to serious health consequences. It complicates the management of comorbid diseases, increases the risk of traffic accidents, and worsens the quality of life [94, 284-286]. We found that Galician and Lebanese individuals who would accept prolonging the use of tranquilizers even after improving are at higher odds of tranquilizer misuse. Beyond the one-month use, tranquilizers cause physical dependence on these drugs [287, 288], as they affect the central nervous system, and their mechanisms of action is similar to that of other addiction drugs [289-291]. Accordingly, preventive actions are required in both countries to improve the rationale use of antibiotics and reduce the risk of dependence and addiction to tranquilizers.

Unlike in the comparison study about antibiotics in Galicia, both **cross-sectional** and **longitudinal** approaches showed an association between *Knowledge* and *Attitudes* and tranquilizer misuse *Practices*, albeit with certain differences regarding the magnitude of some associations, in particular those concerning *Practices* of tranquilizer misuse such as unprescribed use or shortened treatment. In general, cross-sectional and longitudinal designs are expected to generate different conclusions [292-295], and the former approach is often deemed misleading, yet in the context of KAP based studies, biases associated with both designs should be inspected [296].

KAP studies about medicine misuse are routinely carried out using cross-sectional approaches as they require less resources and time. Our cohort study was the first to be carried out on KAP associations regarding antibiotic. Simultaneity bias is a main concern in cross-sectional studies as both exposure and outcome are measured at the same time, hence it cannot be assured whether the inadequate level of *Knowledge* or inappropriate *Attitude* (exposure) was acquired at the time of the misuse (outcome) or before [297]. In addition, the two designs, cross-sectional and longitudinal, assess different epidemiological concepts and readers could misinterpret a prevalence odds ratio measured by cross-sectional studies as a proxy of relative risk determined by cohort studies [298].

We discuss different sources biases that could have contributed to inconsistent findings from cross-sectional and longitudinal approaches in the comparison studies about antibiotics and tranquilizers. **1) *Social desirability bias*:** in the longitudinal studies, follow-up assessments were carried out by phone calls due to logistic reasons. During phone assessment, participants

are less likely to declare a medically disapproved *Practice* than during a self-administered questionnaire [299]. Though socially accepted responses might be present in both designs, cross-sectional and longitudinal, it is more probable that the social desirability bias has greater effect in the phone-based follow-up than during self-administered questionnaires. **2) *Hawthorne effect*:** individuals participating in research studies tend to improve their behaviour (*Practices* towards the medicine), which might result in a fewer number of outcomes during the follow-up. In our settings, enough observations were obtained in cross-sectional and longitudinal approaches, in both antibiotic and tranquilizer misuse studies; **3) *Selection bias:*** individuals with a lower level of *Knowledge* are more likely to abandon research studies because of a poorer adherence to treatment [300]. Hence, loss to follow-up or dropouts is a concern in longitudinal studies. Our data from the antibiotic and the tranquilizer studies showed that the level of *Knowledge* and *Attitudes* of participants who were lost to follow-up was similar to those who completed at least one follow-up assessment. It is then unlikely that our results are influenced by selection bias.

6.3. Meta-analyses of socioeconomic determinants of antibiotic misuse *Practices*

To the best of our knowledge, no previous meta-analysis had assessed the dose-response association of socioeconomic indicators with antibiotic misuse. Due to lack of studies that report socioeconomic index, we carried out two dose-response meta-analyses of the socioeconomic indicators: ***income*** and ***education***.

Data from both meta-analyses accorded well with a flat linear association between the dose (income or education) and the response (antibiotic misuse).

The dose-response meta-analysis of ***income*** and antibiotic misuse showed that, overall, there was no association between the two variables. However, subgroup analyses uncovered a dose-response association of medium and high income levels with specific *Practices* of antibiotic misuse; i.e. storage of drug leftover and non-adherence, country wealth, WHO geographic region and study period.

Likewise, we reported that there was no association between a one-year increase in ***education*** level and antibiotic misuse. The categorical analysis revealed that the odds of antibiotic misuse is, in general, lower in individuals with high education than in those with low education level. Nevertheless, opposite findings were obtained for studies carried out in Europe and for the misuse *Practice* "storage of antibiotics".

The main findings of the two meta-analysis suggests that the odds of antibiotic misuse is the same for poor and wealthy people and for individuals with low and high education levels. Notably, the odds of *antibiotic storage* at home for future need is larger for medium income and for highly educated people than for those with low income or low education level.

The literature review revealed that individuals tend to self-medicate irrespective of their income or education level. People with low education level are more vulnerable to comorbidities and hence, they are more susceptible to use medicines than individuals with higher education [301]. The education level of the individuals is strongly associated with their socioeconomic status, especially with income [302]. On the one hand, under constrained financial resources, especially in settings with limited access to health facilities, self-medication is most often the only available option of healthcare [303]. By self-medicating, low income people avoid medical

consultation fees and laboratory tests. Forgone care is more frequently reported by low income than by high income households [304]. Due to financial motives, low income individuals often cut-back basic needs and take less medication than recommended [305, 306], justifying therefore our finding about higher likelihood of adherence to antibiotic treatment by high income than by low income people. On the other hand, individuals with higher socioeconomic status; i.e. high income and education levels, have: **1)** better economic affordability to buy and store non-reimbursed medicines [307], **2)** a wider social network that increases their access to unprescribed medicines [307] and **3)** a better access to health information especially through the internet [308].

We showed a higher likelihood of antibiotic misuse by high-income individuals in upper-middle wealth countries. We also reported that in Africa, people with medium income have a higher likelihood of antibiotic misuse than those with low income. In line with these results, a previous report about the economy of self-medication in general, concluded that the demand for self-medication declines with rising the income of those with high income, but increases with incrementing the income of low income individuals, resulting in a null pooled effect between income and self-medication [303]. Regulations about antibiotic dispensing should be further enforced since more than half of the antibiotics worldwide are dispensed without prescription [37].

Health literacy significantly influences health status and medicine use [309]. Individuals with low education level have poorer health literacy aptitudes than those with high education [310]. The lack of access to healthcare of less educated people also reduces their health literacy [311]. Nonetheless, limited health literacy skills is not only a characteristic of low educated people but also a feature of highly educated individuals [311]. In wealthy countries such as Europe the prevalence of low health literacy oscillates between 30% and 60% [312]. In these meta-analyses, we also found a higher likelihood of antibiotic misuse by high income and by highly educated individuals in Europe. Certainly, the health literacy of the population is also influenced by several factors other than socioeconomic indicators. The simplicity degree of the available health related information to be easily understood by the public [313] as well as the proficiency of the healthcare provider in communicating the information to the patient [311, 314] are factors that condition the health literacy rate of the population. In the specific context of antibiotics, insufficient health literacy level about antibiotic use was reported among highly educated people in specific settings [315]. Lack of knowledge about antibiotics was reported both in low- and high-wealth countries [30, 316].

The likelihood of antibiotic misuse by highly educated people decreased after 2015, which could be due to the efforts exerted by WHO and antibiotic stewardship programs [31]. Inversely, we observed a marginal increase in the odds of antibiotic misuse by medium and high income individuals after 2015 than before this period. This could stem from two main motives; *first* the expenditure on health is growing at a faster pace than economies, resulting in a doubling of the out-of-pocket spending and enlarging the differences between high- and low-wealth countries regarding health expenditure [317]; and *second,* measures to control antibiotic dispensing are not strictly applied in all countries, allowing therefore individuals with better financial resources to continue using unprescribed antibiotics. Under the need for better control of antibiotic use, in 2019, the WHO placed a new urgent call to control the antibiotic resistance crisis [318].

The two meta-analyses have various strengths. Besides being the **first** meta-analyses to examine dose-response association between ***income*** and ***education,*** and antibiotic misuse, the

dose was standardized to allow for comparability across studies. The income was standardized in two approaches: GDP per capita based on PPP and adjusted net national income per capita. The education level was standardized to years of education according to the education system of each country. We reported summary estimates of association per 1-unit increase of income or education. Finally, we presented various stratified analyses, especially the subgroup analysis by country wealth as proxy of socioeconomic status.

These meta-analyses also suffered from limitations. In the income meta-analysis, all eligible studies were of cross-sectional design, and in the education meta-analysis, all except two studies were of this design. The cross-sectional design, theoretically, limits any causal inference. However, income and education are relatively stable variables through time, which mitigates this limitation.
Furthermore, not all studies provided measures of association adjusted for potential confounders or reported restriction, matching or confounding variables. In the ***income*** meta-analysis, higher OR estimates were obtained from studies that did not control for age, gender, education level and household size than from studies with complete adjustment. This reveals that our findings about income could be overestimated due to incomplete adjustment. In the ***education*** meta-analysis, pooled estimates from studies that controlled for age and gender yielded a summary estimate closer to the null value than studies that did not control for any or none of those variables. Further studies that control adequately for all potentially related socio-demographic variables are required.

One-sixth of studies included in the ***income*** meta-analysis, did not employ a pretested or validated questionnaire to ascertain the exposure (income) and the outcome (antibiotic misuse). Nevertheless, this limitation was unlikely to affect our results as restricting the analysis to studies that applied validated instruments did not introduce any change in the overall effect. As for the education meta-analysis, one-third of included studies used non-validated questionnaires to ascertain exposure and outcome. Summary estimates from those studies were farther from the null value than those of studies with validated instruments.

The two meta-analyses were based on random-effect models to account for heterogeneity between studies [319-321]. Indeed, heterogeneity was expected in these studies due to variations in the defined levels of income or education, period of antibiotic use (for example, use in the past month [170], past three months [179] and past year [197]), and settings. Experts in meta-analysis point out that heterogeneity is an expectation in any meta-analysis rather than an exception [322] and that no amount of heterogeneity is considered unacceptable as long as the inclusion criteria are clearly defined and the data are correctly analysed [319].

The findings of ***income*** meta-analysis are unlikely to be affected by publication bias as revealed by the negative result of Egger's test and the trim-and-fill analysis that did not suggest imputation of any additional study. The same applies for the meta-analysis on ***education.*** Although some elements of publication bias were observed in studies that assessed the association of high education with antibiotic misuse, the trim-and-fill analysis did not suggest any additional study.

6.4. Macrolides, an alternative treatment to penicillin resistant infections. A meta-analysis of macrolides prenatal exposure and congenital malformation

Around one-tenth of women, especially those with poor socioeconomic situation, need antibiotic treatment during pregnancy to eliminate urinary tract infections [67, 68]. As a consequence of resistance, penicillin antibiotics are no longer recommended for asymptomatic bacteriuria [67]. Instead, ***macrolides*** are widely prescribed during pregnancy [68]. Data regarding birth defects from macrolides exposure during pregnancy is inconsistent. Therefore, we undertook a meta-analysis to summarize the association of prenatal exposure to macrolides with congenital abnormalities and to determine whether this effect varies according to the type of macrolide and gestational age.

We observed a weak association between prenatal exposure to macrolides and congenital malformations in the approach that applied mixed comparators (foetuses unexposed to any drug and foetuses exposed to other non-macrolide drugs). This association was restricted to exposure in early pregnancy, and to digestive and musculoskeletal systems.

Our findings coincide with that of a previous report that showed increased odds of digestive system congenital malformations based on data collected from two studies [323].

Erythromycin is a class of macrolides that acts as a motilin agonist, provoking strong gastric contractions which consequently contributes to digestive system malformations [324]. We reported an association between prenatal exposure to macrolides and musculoskeletal birth defects, but there is lack of information to explain this association. In the approach that applied the comparator group 2 (exposure to non-macrolides antibiotics), we observed that the likelihood of occurrence of congenital malformation in foetuses exposed to macrolides is lower than that in those exposed to other antibiotics; which means that macrolides could be safer than other antibiotics when used during pregnancy. Another meta-analysis about the cardiovascular safety of macrolides as compared to penicillin did not find any association between macrolides and the risk of arrhythmia or cardiovascular mortality [325], revealing that the risk of cardiovascular events does not differ between exposure to macrolides or penicillin.

We reported that the association between macrolides and congenital malformation varies by populations, where there could be higher odds of malformation in the European population than in the North American one. Congenital anomalies differ across ethnic group [326].

We detected asymmetry in the funnel plot and the trim and fill analysis suggested the addition of six studies, which indicate the presence of publication. the corrected OR based on the trim-and-fill analysis favoured the absence of association between macrolides and congenital malformation.

It is remarkable that only three out the 21 studies included in this meta-analysis had adjusted the measure of association for age and urinary tract infections, two factors that are known to contribute to increased risk of non-chromosomal congenital abnormalities [70, 327]. Nonetheless, pooled estimates from those three fully adjusted studies did not differ from that of incompletely adjusted studies.

Misclassification of congenital malformation is unlikely to take place. Exposure to macrolides was ascertained through medical records in more than half of the included studies. Restricting

the analysis to those studies that used medical records did not alter the summary OR estimated from all studies.

In this meta-analysis we could not provide a dose-response analysis due to the lack of data. Moreover, we could not consider congenital malformation outcomes in abortions or stillbirths due to absence of data. Accordingly, the mutagenic effect of macrolides that could have induced abortions or stillbirths cannot be ruled out.

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7. CONCLUSIONS

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Conclusions

1. Validated instruments to measure the association of *Knowledge* and *Attitudes* with **antibiotic** and **tranquilizer** misuse *Practices* are now available for the first time.

2. The questionnaires were validated in three languages: Galician, Arabic and French, and tested in two socio-economically different settings: Galicia and Lebanon. They were highly acceptable by the Galician and Lebanese populations.

3. Low knowledge and misconceptions about the role of antibiotics and about the hazards of tranquilizers are associated with misuse *Practices* of these drugs.

4. Medically inappropriate *Attitudes* including tendency to curtailing or extending the treatment duration other than prescribed, willingness to obtain antibiotics and tranquilizers without prescription, and acceptance to use tranquilizers to improve sleep, work or mood, are associated with higher odds of antibiotic and tranquilizer misuse *Practices.*

5. Negative attitudes towards healthcare provider are associated with higher odds of antibiotic and tranquilizer misuse *Practices.*

6. Drug availability and accessibility were identified as risk factors for drug misuse.

7. Misuse of antibiotics and tranquilizers take place in settings without a centralized healthcare system such as in Lebanon as well as in settings with centralized systems such as Galicia.

8. Cross-sectional and longitudinal approaches yield distinct results with respect to the association of *Knowledge* and *Attitudes* with *Practices* of antibiotic and tranquilizer misuse. None is free from bias and results from both approaches should be carefully scrutinized to obtain sound conclusions in KAP studies.

9. Dose-response meta-analysis revealed that antibiotic misuse takes place by all individuals irrespective of their income level and their education level.

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10. A meta-analysis showed a marginal association between macrolides prenatal exposure and congenital malformation. Risk–benefit research is needed to address the question of whether macrolide prescription should be restricted during pregnancy.

8. REFERENCES

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9. ANNEXES

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Annex I. Various languages of *Knowledge, Attitude* and *Practice* questionnaires about antibiotic and tranquilizers

English version of *Knowledge, Attitude* and *Practice* questionnaire about antibiotic use

KNOWLEDGE, ATTITUDES AND PRACTICES TOWARDS THE PERSONAL USE OF ANTIBIOTICS

Code of the questionnaire: _____ **Date:** _____

To choose an answer, please fill in COMPLETELY the corresponding circle(s): CORRECTLY answered: ● INCORRECTLY answered: ⊗ ∅

Please answer on the following questions about **ANTIBIOTICS** (Amoxicillin, Cefixime, Ciprofloxacin, Levofloxacin, Penicillin, etc.)

On a scale of 0 to 10 points, choose a number representing your level of agreement on the statements below. "0" (zero) means you totally disagree while "10" means that you agree completely.

Please evaluate the below statements **REGARDLESS** of whether you are currently using *antibiotics* **OR NOT**

Example: Practicing sports benefits health ⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ● ⑨ ⑩

	Disagree ← → Agree
1. ***Antibiotics*** **are effective against viruses**	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
2. **When I get a cold, I take *antibiotics* to help me feel better faster**	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
3. **If I feel better after a few days, I sometimes stop taking my *antibiotics* before completing the course of treatment**	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
4. **I expect my doctor to prescribe *antibiotics* if I suffer from common cold or flu symptoms**	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
5. **It is good to be able to get *antibiotics* from relatives or friends without having to see a medical doctor**	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
6. **When I have a sore throat, I prefer to use an *antibiotic***	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
7. **Each type of infection needs a different *antibiotic***	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
8. **If I feel side effects during a course of treatment of *antibiotics*, I should stop taking them as soon as possible**	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
9. **I take the *antibiotics* according to the doctor's instructions**	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
10. **If *antibiotics* are consumed in excess, they will not work when they are really needed**	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
11. **I prefer to keep *antibiotics* at home in case there is a need for them later**	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
12. **I trust the doctor's decision if s/he decides to prescribe or not prescribe *antibiotics***	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
13. **If I believe that I need an *antibiotic* and the doctor did not prescribe it, I will get it at the pharmacy without a prescription**	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
14. **Doctors often explain clearly to the patient the reasons for prescribing or not prescribing *antibiotics***	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
15. **Doctors often explain clearly to the patient the instructions for the use of *antibiotics***	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
16. **When you buy *antibiotics*, the pharmacist tells you about the importance of correct therapeutic compliance/adherence**	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩

KNOWLEDGE, ATTITUDES AND PRACTICES TOWARDS THE PERSONAL USE OF ANTIBIOTICS

Code of the questionnaire: _____ **Date:** _____

17. In the past two months, did you take antibiotics? ○ Yes (please move to question 18) ○ No (please move to question 28)

Answer the following questions about your consumption of ANTIBIOTICS IN THE PAST TWO MONTHS

18. How long was the duration of your last treatment with *antibiotics*?

Number of Days ☐☐

Number of Months ☐☐

19. Who prescribed or recommended you the use of *antibiotics*? (You can choose more than one answer)

○ The doctor
○ Friends
○ The family
○ The pharmacist
○ I had them at home

20. The last time you had to take *antibiotics*, did you complete the course of treatment?

○ Yes
○ No
○ Still using them

21. What did you do with the *antibiotics* that were left unused? (You can choose more than one answer)

○ I kept them to be used the next time I am sick
○ I disposed of them in the garbage or sewage system
○ I gave them to someone
○ I returned them to the pharmacy
○ I didn't have any remaining *antibiotics*

22. The last time you had to take *antibiotics*, did you forget to take any of the doses?

○ Never (please move to question 24)
○ Sometimes (please move to question 23)
○ Often (please move to question 23)

23. What did you do when you skipped a dose of your *antibiotics*?

○ I continued the following doses normally
○ I doubled/increased the following dose
○ I took it as soon as I remembered

24. The last time you had to take *antibiotics*, did you change the dose on your own (without medical advice)?

○ Never (please move to question 28)
○ Sometimes (please move to question 25)
○ Often (please move to question 25)

25. What did you do when you changed your dose of *antibiotics* on your own (without medical advice)?

○ I took more of it (please answer question 26 and then 28)
○ I took less of it (please move to question 27)
○ Sometimes I took more, and sometimes I took less of it (please answer questions 26 and 27)

26. Why did you increase the dose of *antibiotics* on your own (without medical advice)? (You can choose more than one answer)

○ I forgot to take the previous dose
○ I felt very sick
○ I didn't feel a notable improvement
○ I felt better but wanted to improve even more

27. Why did you reduce the dose of *antibiotics* on your own (without medical advice)? (You can choose more than one answer)

○ I was worried about the medication's side effects
○ I was tired, and I forgot
○ I felt that I was taking too many medicines
○ I was in a hurry and I forgot
○ I don't like to take medicines at night
○ I was feeling better

KNOWLEDGE, ATTITUDES AND PRACTICES TOWARDS THE PERSONAL USE OF ANTIBIOTICS

Code of the questionnaire: _____ **Date:** _____

General Demographic Characteristics

28. Indicate your gender

○ Male ○ Female

29. Indicate your age _____

30. What is your highest educational level?

○ I did not go to school

○ Primary

○ Secondary

○ University

31. Are you currently working?

○ Yes

○ No

32. How many members live in your house, including you?

○ 2 ○ 3-4 ○ 5-6 ○ More than 6

33. Do you consult a doctor when you are sick?

○ Never

○ Rarely

○ Sometimes

○ Always

34. Have you ever received a medical prescription over the phone?

○ Yes

○ No

Thank you very much for your time and collaboration!

English version of *Knowledge*, *Attitude* and *Practice* questionnaire about tranquilizer use

Knowledge, Attitudes and Practices towards the Use of Tranquilizers

Please answer the following questions about ***TRANQUILIZERS*** (medicines that include sleeping or nerve pills, for example Alprazolam, Bromazepam, Diazepam, Ambien, Xanax, and Valium)

On a scale of 0 to 10 points, choose a number representing your level of agreement on the statements below. "0" (zero) means you totally disagree while "10" means that you agree completely.

Please evaluate the below statements **REGARDLESS** of whether you are using *tranquilizers* **OR NOT**

Example: Practicing sports benefits health ⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ● ⑨ ⑩

	Disagree ←	→ Agree
1. I would agree to take *tranquilizers* in order to sleep better	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩	
2. If I feel better after a few days, I will keep taking my *tranquilizers* even after completing the prescribed course of treatment	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩	
3. I would take *tranquilizers* in order to enjoy myself with my family	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩	
4. I would agree to take *tranquilizers* when I feel down and sad in order to work better	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩	
5. *Tranquilizers* reduce people's control over what they do	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩	
6. People taking *tranquilizers* are at increased risk of traffic accidents	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩	
7. Psychotropic drugs (such as *tranquilizers*) may affect children's learning abilities when prescribed to them	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩	
8. If I feel side effects during a course of treatment of tranquilizers, I should stop taking it as soon as possible	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩	
9. I would take the *tranquilizers* according to the doctor's instructions	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩	
10. If *tranquilizers* are consumed in excess, they won't work when they are really needed	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩	
11. I prefer to keep *tranquilizers* at home in case there was a need for them later	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩	
12. I will trust the doctor's decision if s/he decided to prescribe or not prescribe *tranquilizers*	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩	
13. If I believe that I need a *tranquilizer* and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩	
14. I think that doctors often explain clearly to the patients the reasons for prescribing or not prescribing *tranquilizers*	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩	
15. I think that doctors often explain clearly to the patients the instructions for the use of *tranquilizers*	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩	
16. I think that, when dispensing *tranquilizers*, the pharmacists tell the customers about the importance of correct therapeutic compliance/adherence	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩	

17. **In the past two months, did you take *tranquilizers*?** ○ Yes (please move to question 18) ○ No (please move to question 28)

Knowledge, Attitudes and Practices towards the Use of Tranquilizers

Answer the following questions about your consumption of *TRANQUILIZERS* IN THE PAST TWO MONTHS

18. How long was the duration of your last treatment with *tranquilizers*?

Number of Days ☐☐

Number of Months ☐☐

Number of Years ☐☐

19. Who prescribed or recommended you the use of *tranquilizers*? (You can choose more than one answer)

- ○ The doctor
- ○ Friends
- ○ The family
- ○ The pharmacist
- ○ I had them at home

20. Last time you had to take *tranquilizers*, did you complete the course of treatment?

- ○ Yes
- ○ No

21. What did you do with the *tranquilizers* that were left unused? (You can choose more than one answer)

- ○ I kept them to be used the next time I am sick
- ○ I disposed of them in the garbage or sewage system
- ○ I gave them to someone
- ○ I returned them to the community pharmacy
- ○ I didn´t have any remaining *tranquilizers*

22. Last time you had to take *tranquilizers*, did you forget to take any of the doses?

- ○ Never (please move to question 24)
- ○ Sometimes (please move to question 23)
- ○ Often (please move to question 23)

23. What did you do when you skipped a dose of your *tranquilizers*?

- ○ I continued the following doses normally
- ○ I doubled/increased the following dose
- ○ I took it as soon as I remembered

24. Last time you had to take *tranquilizers*, did you change the dose on your own (without medical advice)?

- ○ Never (please move to question 28)
- ○ Sometimes (please move to question 25)
- ○ Often (please move to question 25)

25. What did you do when you changed your dose of *tranquilizers* on your own (without medical advice)?

- ○ I took more of it (please answer question 26 and then 28)
- ○ I took less of it (please move to question 27)
- ○ Sometimes I took more, and sometimes I took less of it (please answer questions 26 and 27)

26. Why did you increase the dose of *tranquilizers* on your own (without medical advice)? (You can choose more than one answer)

- ○ I forgot to take the previous dose
- ○ I felt very sick
- ○ I didn't feel a notable improvement
- ○ I felt better but wanted to improve even more
- ○ I was going through a stressful time (stress, problems, etc.)

27. Why did you reduce the dose of *tranquilizers* on your own (without medical advice)? (You can choose more than one answer)

- ○ I was worried about the medication's side effects
- ○ I was tired, and I forgot
- ○ I felt that I was taking too many medicines
- ○ I was in a hurry and I forgot
- ○ I don't like to take medicines at night
- ○ I was feeling better

Knowledge, Attitudes and Practices towards the Use of Tranquilizers

General Demographic Characteristics

28. Indicate your gender

○ Male ○ Female

29. Indicate your age _____

30. What is your highest educational level?

○ I did not go to school
○ Primary
○ Secondary
○ University

31. Are you currently working?

○ Yes
○ No

32. How many members live in your house, including you?

○ 2 ○ 3-4 ○ 5-6 ○ More than 6

33. Do you consult a doctor when you are sick?

○ Never
○ Rarely
○ Sometimes
○ Always

34. Have you ever received a medical prescription over the phone?

○ Yes
○ No

35. How often do you drink alcohol?

○ Never
○ On special occasions
○ Only on weekends
○ 3-5 times a week
○ Every day

Thank you very much for your time and collaboration!

Galician version of *Knowledge*, *Attitude* and *Practice* questionnaires about antibiotic and tranquilizer use in Galicia

USC FACULTADE DE MEDICINA E ODONTOLOXÍA

COÑECEMENTOS, CRENZAS E USO DE ANTIBIÓTICOS E TRANQUILIZANTES EN GALICIA

Código do cuestionario: _____

Eu, (nome e apelidos)..... con número de teléfono (móbil).....

- **Lin a folla de información ao participante do estudo arriba mencionado que se me entregou, puiden conversar con: ..... e facer toda las preguntas sobre o estudo.**
- **Comprendo que a miña participación é voluntaria, e que podo retirarme do estudo cando queira, sen ter que dar explicacións e sen que isto repercuta nos meus coidados médicos.**
- **Accedo a que se utilicen os meus datos nas condicións detalladas na folla de información ao participante.**
- **Presto libremente a miña conformidade para participar neste estudo.**

	O/a participante	O/a investigador/a que solicita o consentimento
Nome e Apelidos		
Fdo		
Data		

CUESTIONARIO

Para marcar a resposta encha **COMPLETAMENTE** o círculo: **CORRECTAMENTE:** ● **INCORRECTAMENTE:** ∅ ⊗

Datos de participantes

1. **Cal é o seu sexo?** ○ Home ○ Muller
2. **Por favor escriba a súa idade:** _____ anos
3. **Está de acordo con que o chamemos cada dous meses durante un ano para facer un seguimento do uso de antibióticos e / ou tranquilizantes?** ○ Si ○ Non
4. **Que día da semana e a que hora prefire que o chamemos?** Día: _____ Hora: _____

Responda as seguintes preguntas sobre os ANTIBIÓTICOS (Amoxicilina, Ciprofloxacino, Doxiciclina, Penicilina, Lincosamidas, etc.)

Nunha escala de 0 a 10 puntos, elixa un número que represente o seu nivel de acordo nas seguintes afirmacións. "0" (cero) significa que está totalmente en desacordo mentres que "10" significa que está de acordo completamente.
Por favor responda todas as seguintes preguntas, **independentemente** de se está a usar antibióticos **ou non**.
Exemplo: Practicar deporte beneficia a saúde ⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ● ⑨ ⑩

5. Os antibióticos son efectivos contra os virus	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
6. Cando teño un catarro ou gripe tomo antibióticos	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
7. Se me sinto mellor despois duns días, ás veces deixo de tomar os meus antibióticos antes de completar o curso do tratamento	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
8. Espero que o meu médico prescriba antibióticos se padezo síntomas comúns de catarro ou gripe	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
9. É bo poder obter antibióticos de familiares ou amigos sen ter que ver un médico	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
10. Cando teño unha dor de gorxa prefiro usar un antibiótico	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
11. Cada infección necesita un antibiótico diferente	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
12. Os antibióticos poden matar as bacterias que normalmente viven na pel e no intestino	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
13. Se sinto efectos secundarios durante un tratamento de antibióticos, debería deixar de tomalo o máis axiña posible	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩

USC FACULTADE DE MEDICINA E ODONTOLOXÍA

COÑECEMENTOS, CRENZAS E USO DE ANTIBIÓTICOS E TRANQUILIZANTES EN GALICIA

Código do cuestionario: _____

14. Tomo os antibióticos de acordo coas instrucións do médico	0 1 2 3 4 5 6 7 8 9 10
15. Se os antibióticos se consumen en exceso, non funcionarán cando realmente sexan necesarios	0 1 2 3 4 5 6 7 8 9 10
16. Prefiro gardar os antibióticos na casa por se hai necesidade de máis tarde	0 1 2 3 4 5 6 7 8 9 10
17. Confío na decisión do médico se decide prescribir ou non prescribir antibióticos	0 1 2 3 4 5 6 7 8 9 10
18. Se eu creo que necesito un antibiótico e o médico non o prescribiu, obtereino na farmacia sen receita médica	0 1 2 3 4 5 6 7 8 9 10
19. Os médicos a miúdo explican ben e claramente os motivos para prescribir ou non prescribir antibióticos	0 1 2 3 4 5 6 7 8 9 10
20. Os médicos a miúdo explican claramente as instrucións de uso dos antibióticos	0 1 2 3 4 5 6 7 8 9 10
21. Cando vostede compra antibióticos, o farmacéutico infórmao sobre a importancia do correcto cumprimento / adherencia terapéutica	0 1 2 3 4 5 6 7 8 9 10

22. Nos ÚLTIMOS DOUS MESES, tomou vostede antibióticos? ○ Si (pase á pregunta 23) ○ Non (pase á pregunta 33)

Responda as seguintes preguntas sobre o seu consumo de antibióticos nos <u>ÚLTIMOS DOUS MESES</u>

23. Canto tempo durou o seu último tratamento con antibióticos?

Número de días ☐☐ Número de meses ☐☐

24. Quen prescribiu ou recomendou o uso de antibióticos? (Pode escoller máis dunha resposta)

○ O médico ○ Amigos ○ A familia

○ O farmacéutico ○ Eu tiñaos na casa

25. A última vez que tivo que tomar antibióticos, rematou o curso do tratamento?

○ Si ○ Non

26. Que fixo vostede cos antibióticos que non foron utilizados? (Pode escoller máis dunha resposta)

○ Gardeinos para usalos a próxima vez que estea enfermo

○ Desfíxenme deles no lixo ou o sistema de alcantarillado

○ Deillos a alguén

○ Non tiña ningún antibiótico restante

○ Díxolles á farmacia

27. A última vez que tivo que tomar antibióticos, esqueceuse de tomar calquera das doses?

○ Nunca (pase á pregunta 29)

○ Ás veces (pase á pregunta 28)

○ Moitas veces (pase á pregunta 28)

28. Que fixo cando saltou unha dose dos seus antibióticos?

○ Continuei coas seguintes doses normalmente

○ Dobrei / aumentei a seguinte dose

○ Tomeina en canto o lembrei

29. A última vez que tivo que tomar antibióticos, cambiou a dose por conta propia (sen consellos médicos)?

○ Nunca (pase á pregunta 33)

○ Ás veces (pase á pregunta 30)

○ Moitas veces (pase á pregunta 30)

30. Que fixo vostede cando modificou a dose de antibióticos por conta propia (sen consellos médicos)?

○ Tomei máis (vaia á pregunta 31 e despois á pregunta 33)

○ Tomei menos (vaia á pregunta 32)

○ Ás veces tomei máis, e ás veces tomei menos (responda as preguntas 31 e 32)

31. Por que aumentou a dose de antibióticos por conta propia (sen consellos médicos)? (Podes escoller máis dunha resposta)

○ Esquecín tomar a dose anterior

○ Sentinme moi enfermo

○ Eu non sentín unha mellora notable

○ Sentinme mellor e quería mellorar aínda máis

32. Por que reduciu a dose de antibióticos por conta propia (sen consellos médicos)? (Podes escoller máis dunha resposta)

○ Estaba preocupado polos efectos secundarios do medicamento

○ Non me gusta tomar medicamentos pola noite

○ Sentín que tomaba demasiados medicamentos

○ Tiña présa e esqueceume

○ Estaba canso e esquecín

○ Sentíame mellor

USC FACULTADE DE MEDICINA E ODONTOLOXÍA

COÑECEMENTOS, CRENZAS E USO DE ANTIBIÓTICOS E TRANQUILIZANTES EN GALICIA

Código do cuestionario: _____

Responda as seguintes preguntas sobre os TRANQUILIZANTES
(medicamentos que inclúen o pílulas para o sono ou os nervios: Alprazolam, Diazepam, Lorazepam, Lormetazepam, Valium etc.)**?**

Nunha escala de 0 a 10 puntos, elixa un número que represente o seu nivel de acordo nas seguintes afirmacións. "0" (cero) significa que está totalmente en desacordo mentres que "10" significa que está de acordo completamente.
Por favor responda todas as seguintes preguntas, **independentemente** de se está a usar tranquilizantes **ou non**.
Exemplo: Practicar deporte beneficia a saúde ⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ● ⑨ ⑩

33. Aceptaría tomar tranquilizantes para durmir mellor	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
34. Se me sinto mellor despois duns días, ás veces sigo tomando os tranquilizantes mesmo despois de completar o curso prescrito	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
35. Tomaría tranquilizantes para gozar coa miña familia	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
36. Aceptaría tomar tranquilizantes para traballar mellor	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
37. Os tranquilizantes reducen o control das persoas sobre o que fan	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
38. As persoas que toman tranquilizantes están en maior risco de accidentes de tráfico	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
39. Os medicamentos psicotrópicos (como os tranquilizantes) poden afectar as habilidades de aprendizaxe dos nenos cando se lles prescriban	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
40. Se sinto efectos secundarios durante un tratamento de tranquilizantes, debería deixar de tomalo o máis axiña posible	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
41. Tomo os tranquilizantes de acordo coas instrucións do médico	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
42. Se os tranquilizantes se consumen en exceso, non funcionarán cando realmente son necesarios	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
43. Prefiro gardar os tranquilizantes na casa por se hai necesidade de máis tarde	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
44. Confío na decisión do médico se decide prescribir ou non prescribir tranquilizantes	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
45. Se eu creo que necesito un tranquilizante e o médico non o prescribiu, obtereino na farmacia sen receita médica	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
46. Os médicos a miúdo explican ben e claramente os motivos para prescribir ou non prescribir tranquilizantes	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
47. Os médicos a miúdo explican claramente as instrucións de uso dos tranquilizantes	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
48. Cando vostede compra tranquilizantes, o farmacéutico infórmao sobre a importancia do correcto cumprimento / adherencia terapéutica	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩

49. Nos ÚLTIMOS DOUS MESES, tomou vostede tranquilizantes?

○ Si (pase á pregunta 50) ○ Non (pase á pregunta 60)

USC FACULTADE DE MEDICINA E ODONTOLOXÍA

COÑECEMENTOS, CRENZAS E USO DE ANTIBIÓTICOS E TRANQUILIZANTES EN GALICIA

Código do cuestionario: _____

Responda as seguintes preguntas sobre o seu consumo de tranquilizantes nos ÚLTIMOS DOUS MES

50. Canto tempo durou o último tratamento con tranquilizantes?

Número de días ☐☐

Número de meses ☐☐

Número de anos ☐☐

51. Quen prescribiu ou recomendou o uso de tranquilizantes? (Podes escoller máis dunha resposta)

○ O médico ○ Amigos ○ A familia

○ O farmacéutico ○ Eu tiñaos na casa

52. A última vez que tivo que tomar tranquilizantes, rematou o curso do tratamento?

○ Si ○ Non

53. Que fixo vostede cos tranquilizantes que non foron utilizados? (Podes escoller máis dunha resposta)

○ Gardeinos para usalos a próxima vez que estea enfermo

○ Desfíxenme deles no lixo ou o sistema de alcantarillado

○ Deillos a alguén

○ Non tiña ningún tranquilizante restante

○ Díxolles á farmacia

54. A última vez que tivo que tomar tranquilizantes, esqueceuse de tomar calquera das doses?

○ Nunca (pase á pregunta 56)

○ Ás veces (pase á pregunta 55)

○ Moitas veces (pase á pregunta 55)

55. Que fixo cando saltou unha dose dos seus tranquilizantes?

○ Continuei coas seguintes doses normalmente

○ Dobrei / aumentei a seguinte dose

○ Tomeina en canto o lembrei

56. A última vez que tivo que tomar tranquilizantes, cambiou a dose por conta propia (sen consellos médicos)?

○ Nunca (pase á pregunta 60)

○ Ás veces (pase á pregunta 57)

○ Moitas veces (pase á pregunta 57)

57. Fixo vostede cando modificou a dose de tranquilizantes por conta propia (sen consellos médicos)?

○ Tomei máis (vaia a pregunta 58 e despois a pregunta 60)

○ Tomei menos (pase á pregunta 59)

○ Ás veces tomei máis, e ás veces tomei menos (responda as preguntas 58 e 59)

58. Por que aumentou a dose de tranquilizantes por conta propia (sen consellos médicos)? (Podes escoller máis dunha resposta)

○ Esquecín tomar a dose anterior

○ Sentinme moi enfermo

○ Eu non sentín unha mellora notable

○ Sentinme mellor e quería mellorar aínda máis

○ Estaba pasando por un tempo estresante (estrés, problemas, etc.)

59. Por que reduciu a dose de tranquilizantes por conta propia (sen consellos médicos)? (Podes escoller máis dunha resposta)

○ Estaba preocupado polos efectos secundarios do medicamento

○ Non me gusta tomar medicamentos pola noite

○ Sentín que tomaba demasiados medicamentos

○ Tiña présa e esqueceume

○ Estaba canso e esquecín

○ Sentíame mellor

Características xerais demográficas

60. Está a traballar actualmente? ○ Si ○ Non

61. Cantos membros viven na súa casa, incluíndo vostede?

○ 1 ○ 2 ○ 3 – 4

○ 5 – 6 ○ Máis de 6

62. Consulta con un médico cando está enfermo?

○ Nunca ○ Ás veces

○ Raramente ○ Sempre

63. Algunha vez recibiu unha receita médica por teléfono?

○ Si ○ Non

64. Cal é o maior nivel de estudos que ten?

○ Sen estudos ○ Primaria

○ Secundaria ○ Superior

65. Cantas veces bebe alcohol?

○ Nunca ou menos que unha vez ao mes

○ Unha vez por semana

○ Só os fins de semana

○ 3 - 5 veces por semana

○ Todos os días

Moitas grazas polo seu tempo e colaboración!

Arabic version of *Knowledge, Attitude* and *Practice* questionnaires about antibiotic and tranquilizer use in Lebanon

أمّي، أبي، شاركوا في هذا الإستبيان وساعدوا في جعل مُجتمعنا أكثر صحّة!

الأهالي الأعزاء،
تدعوكم جامعة سانتياغو دي كومبوستيلا في إسبانيا والجامعة الأمريكيّة للعلوم والتكنولوجيا في لبنان للمُشاركة في أوّل دراسة حول تحديد العوامل الرئيسيّة الّتي تُؤدّي إلى إساءة إستخدام المُضادّات الحَيَويّة والمُهَدّئات.

لماذا يجب عليكم المشاركة؟
أنتم، الأهالي، تمثّلون جزءاً كبيراً ومهمّاً من الشّعب اللّبنانيّ. لذلك، فنحن نشجّعكم بشدّةٍ على المشاركة في دراستنا هذه. بمشاركتكم سوف تُساعدون السُّلطات المعنيَّة في وضع الإستراتيجيّات الصحيَّة الّتي من شأنها أن تقلّل من مشكلة إساءة إستخدام الأدوية المتعمَّدة وغير المتعمّدة. **سينعكس ذلك بشكلٍ إيجابيٍّ على صحّتكم وعلى صحّة أطفالكم.** كل ما نحتاجه منكم هو القليل من وقتكم!

كيف يُمكنكم المُشاركة؟
للمُشاركة في هذه الدراسة، يُرجى منكم الإجابة على الإستبيان وإعادته إلى المدرسة. **يُمكنكم الرَّد على الإستبيان بِغَضّ النَّظر عمّا إذا كُنتم تستخدمون الأدوية بشكلٍ صحيح أم لا. لن يتمّ سؤالكم عن إسمكم أو عنوانكم أو عن أيّة معلوماتٍ الّتي من شأنها أن تكشف عن هويّتكم.** بالإضافة، سوف تُدمج الإجابات المُتلقاة من جميع المشتركين في قاعدة بيانات **مستترة الهويّة**، كما **سيتمُّ الحفاظ على سرّيّة** جميع المعلومات المُعطاة ومن ثُمّ سيتمُّ تلفها في نهاية الدراسة.

يجب على أحد الوالدين فقط (الأم أو الأب) الإجابة على الإستبيان. إنّ المشاركة في هذه الدّراسة هي **طوعيّة**، كما وإنّها **لا تفرض** أي **تكاليف ماليّة**.

إنّ إجابتكم على هذا الإستبيان تعني بأنّكم تعطون موافقتكم على المشاركة في هذه الدراسة.

شكراً لكم على المُشاركة!

المَعرفَة وَالإعتِقَاد وَإستِخدَام المُضَادَات الحَيَويَّة والمُهَدِّئَات في لبنان
رمز الإستبيان:_____ **التَّاريخ:**_____

للإجابة على سؤال، رجاءً إملأ الدَّائرة المقابلة بالكامل: **أجيبَ بِشَكْلٍ صَحيح :** ● **أجِيبَ بِشَكْلٍ خاطئ:** ∅ ⊗

يُرْجَى الإجَابَة عَلَى الأسئِلَة التَّالِيَة حَوْلَ *المُضَادَّات الحَيَويَّة* (مثلاً: أموكسيسيلين، سيفيكسيم، سيبروفلوكساسين، ليفوفلوكساسين، بنسلين، إلى آخره) ؟

على مقياس من "⓪" (صفر) إلى "⑩"(عشر) نقاط، إختر رقم يعبر عن درجة موافقتك على العبارات التّالية، بحيث أن الرقم "⓪" (صفر) يعني إنّك ترفض كُليّاً والرقم "⑩" (عشرة) يعني إنّك توافق تماماً
يُرجى تقييم العبارات التّالية **بصرف النّظر** عمّا إذا كُنت تستخدم *المُضَادَّات الحَيَويَّة* **أم لا**

مثلاً: مُمارسة ا لرِّياضة تُفيد الصِّحّة ⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ● ⑨ ⑩

	أوافق ←										→ لا أوافق
١) *المُضَادَّات الحَيَويَّة* فعَّالة ضدَّ الفيروسات	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
٢) عندما أُصاب بنزلات البرد أو الإنفلونزا أتناول *المُضَادَّات الحَيَويَّة* لمساعدتي على التحسُّن بشكل أسرع	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
٣) إذا شعرت بالتحسُّن بعد بضعة أيّام، أتوقف أحيانًا عن تناول *المُضَادَّات الحَيَويَّة* قبل إنتهاء فترة العلاج	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
٤) أتوقّع أن يصف لي الطّبيب *المُضَادَّات الحَيَويَّة* إذا كنت أشعر بعوارض نزلات البرد أو الإنفلونزا	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
٥) مِن الجَيِّد أن تكون قادراً على الحصول على *المُضَادَّات الحَيَويَّة* من الأقارب أو الأصدقاء دون الحاجة إلى زيارة الطّبيب	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
٦) عِنْدَمَا أشعر بالْتِهَاب في الحَلْق، أفضّل إسْتِخْدام *مُضَادّ حَيَوِيّ*	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
٧) كل نوع من الإلتهاب يحتاج إلى نوع مختلف من *المُضَادَّات الحَيَويَّة*	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
٨) *المُضَادَّات الحَيَويَّة* تقتل البكتيريا التي تعيش عادةً على الجلد أو في المُمْرَان	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
٩) إذا شعرت بآثار جانبيّة خلال فترة العلاج *بالمُضَادَّات الحَيَويَّة* يجب أن أتوقف عن إستعماله في أقرب وقت ممكن	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
١٠) أستعمل *المُضَادَّات الحَيَويَّة* حسب تعليمات الطّبيب	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
١١) إذا تمّ إستهلاك *المُضَادَّات الحَيَويَّة* بكثرة، فلن تنفع عند الحاجة إليها حقًّا	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
١٢) أُفضّل أن أُبقي *مُضَادَّات حَيَويَّة* إضافيّة في المنزل، في حال الحاجة إليها لاحقاً	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
١٣) أثق بقرار الطّبيب سواء قرّر وصف أو عدم وصف *المُضَادَّات الحَيَويَّة*	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
١٤) إذا كنت أعتقد أنّني بحاجة إلى *المُضَادَّات الحَيَويَّة* ولم يصفها الطّبيب، سأحصل عليها من الصَّيْدَليَّة بدون وصفة	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
١٥) غَالِبًا مَا يَشرَح الأَطبَّاء بِوُضوح للمريض أسباب وصف أَوْ عدم وصف *المُضَادَّات الحَيَويَّة*	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
١٦) غَالِبًا مَا يَشرَح الأَطبَّاء بِوُضوح للمريض كيفية إستخدام *المُضَادَّات الحَيَويَّة*	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
١٧) عند شراء *المُضَادَّات الحَيَويَّة*، يُبلغك الصَّيْدَلي عن أهميّة التَّقيُّد الصَّحيح بالعلاج	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩

المَعرفَة وَالإعتِقَاد وَإسْتِخدَام المُضَادَات الحَيَوِيَّة والمُهَدِّئَات في لبنان
رمز الإستبيان:_____ **التَّاريخ:**_____

١٨) **في الشّهر الماضي، هل إستعملت *المُضَادَّات الحَيَوِيَّة*؟** ○ نعم (رجاءً إنتقل إلى االسُّؤال ١٩) ○ كلا (رجاءً إنتقل إلى االسُّؤال ٢٩)

أَجِب على الأَسْئِلَةِ التَّالِيَة عن إستهلاكك من المُضَادَّات الحَيَوِيَّة *في الشّهر الماضي*

١٩) **كم كانت مُدَّة آخر علاج *بالمُضَادَّات الحَيَوِيَّة*؟**

عدد الأيَّام: ☐☐ عدد الأشهر: ☐☐

٢٠) **من الَّذي وصف لك أو نصحك بإستخدام *المُضَادَّات الحَيَوِيَّة*؟** (بإمكانك إختيار أكثر من إجابة)

○ الطَّبيب ○ الأَصْدِقاء ○ العائلة

○ الصَّيْدَلِيّ ○ كانَ عندي في المنزل

٢١) **في آخر مَرَّة كان عليك أن تتناول *المُضَادَّات الحَيَوِيَّة*، هل أكملت كُلّ دورة العلاج؟**

○ نعم ○ كلا

٢٢) **ماذا فعلت *بالمُضَادَّات الحَيَوِيَّة* الّتي تُركت دون إستعمال؟** (بإمكانك إختيار أكثر من إجابة)

○ إحتفظت بها لكي أَستَعمِلُهَا عندما أمرض في المَرَّة القادمة

○ رميتها في الزباله أو في مياه الصَّرف الصِّحّيّ

○ أُعطيتها لأحد

○ لم يتبقى لديّ أي مُضَادَّات الحَيَوِيَّة

٢٣) **في آخر مَرَّة كان عليك أن تتناول *المُضَادَّات الحَيَوِيَّة*، هل نسيت أن تأخذ أي من الجرعات؟**

○ أبداً (رجاءً إنتقل إلى االسُّؤال٢٥)

○ أحياناً (رجاءً إنتقل إلى االسُّؤال٢٤)

○ في كثيرٍ من الأحيان (رجاءً إنتقل إلى االسُّؤال ٢٤)

٢٤) **ماذا فعلت عندما تخطّيت/لم تتناول جُرْعة من *المُضَادَّات الحَيَوِيَّة*؟**

○ تابعت الجُرعات التَّالِيَة بشكلٍ طبيعيّ

○ ضاعفت أو زدت الجُرعة الثانيّة

○ تَناولتُهَا عندما تذكَّرت

٢٥) **في آخر مَرَّة كان عليك أن تتناول *المُضَادَّات الحَيَوِيَّة*، هل قمت بتغيير عيار الجُرعة من تِلْقَاء نفسك** (بدُون إسْتِشَارَةٍ طِبِّيَّةٍ)؟

○ أبداً (رجاءً إنتقل إلى االسُّؤال ٢٩)

○ أحياناً (رجاءً إنتقل إلى االسُّؤال ٢٦)

○ في كثيرٍ من الأحيان (رجاءً إنتقل إلى االسُّؤال ٢٦)

٢٦) **ماذا فعلت عندما غَيَّرتْ عيار *المُضَادَّات الحَيَوِيَّة* من تِلْقَاء نفسك** (بدُون إسْتِشَارَةٍ طِبِّيَّةٍ)؟

○ تناولت منها أكثر (رجاءً إنتقل إلى االسُّؤال ٢٧ ومن ثُمّ إلى السُّؤال ٢٩)

○ تناولت منها أقل (رجاءً إنتقل إلى االسُّؤال ٢٨)

○ أحياناً تناولت منها أكثر وأحياناً أُخرى أقل (رجاءً أجِب على السُّؤالين ٢٧ و ٢٨)

٢٧) **لماذا قُمت بزيادة عيار جُرعة *المُضَادَّات الحَيَوِيَّة* من تِلْقَاء نفسك** (بدُون إسْتِشَارَةٍ طِبِّيَّةٍ)؟ (بإمكانك إختيار أكثر من إجابة)

○ نسيت أن أتناول الجُرعة السَّابقة

○ شعرت بأَنّني مريضٌ جِدًّا

○ لم أشعر بتحسُّن ملحوظ

○ تحسَّنت ولكن أردت أن أتحسَّن أكثر

٢٨) **لماذا قُمت بتخفيض عيار جُرعة *المُضَادَّات الحَيَوِيَّة* من تِلْقَاء نفسك** (بدُون إسْتِشَارَةٍ طِبِّيَّةٍ)؟ (بإمكانك إختيار أكثر من إجابة)

○ كنتُ قَلِقًا من آثار الدواء الجانبيَّة

○ كنتُ مُتعبًا ونسيت

○ شعرت بأَنّني أتناول الكثير من الدواء

○ كنتُ على عجلةٍ ونسيت

○ لا أُحبُّ تناول الأَدْوِيَة في اللَّيْل

○ شعرتُ بتحسُّن

المَعرفَة وَالإعتِقَاد وَإستِخدَام المُضَادَات الحَيَوِيَّة والمُهَدِّئَات في لبنان
رمز الإستبيان:_____ **التَّارِيخ:**_____

يُرْجَى الإجَابَة عَلَى الأسئِلَة التَّالِيَة حَوْلَ *المُهَدِّئَات* (أدويه تتَضَمَّن: المنوّم أو حبوب الأعصاب، مثلاً: ألبرازولام، برومازيبام، ديازيبام، أمبين، زاناكس، فاليوم، إلى آخره)؟

على مقياس من "⓪" (صفر) إلى "⑩"(عشر) نقاط، إختر رقم يعبر عن درجة موافقتك على العبارات التّالية، بحيث أن الرقم "⓪" (صفر) يعني إنّك ترفض كُلِيّاً والرقم "⑩" (عشرة) يعني إنّك توافق تماماً
يُرجى تقييم العبارات التّالية **بصرف النّظر** عمّا إذا كُنت تستخدم *المُهَدِّئَات* **أم لا**

مثلاً: مُمارسة ا لرّياضة تُفيد الصّحّة⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ● ⑨ ⑩

	أوافق ←									→ لا أوافق
٢٩) من الممكن أن أوافق على إستعمال *المُهَدِّئَات* لكي أنام بشكل أفضل	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨ ⑩
٣٠) إذا شعرت بتحسن بعد بضعة أيّام أتابع إستعمال *المُهَدِّئَات* حتى بعد إنتهاء فترة العلاج المقرّرة	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨ ⑩
٣١) من الممكن أن أستعمل *المُهَدِّئَات* لأستمتع أكثر مع عائلتي	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨ ⑩
٣٢) من الممكن أن أوافق على إستعمال *المُهَدِّئَات* إذا كنت محبط وحزين، لكي أعمل بشكلٍ أفضل	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨ ⑩
٣٣) *المُهَدِّئَات* تخفف من قدرة النّاس على التّحكم بتصرّفاتهم	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨ ⑩
٣٤) الأشخاص الذين يتناولون *المُهَدِّئَات* معرّضين بشكل أكبر لخطر حدوث حوادث السّير	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨ ⑩
٣٥) قد يكون للأدوية التي تؤثّر على الأعصاب مثل *المُهَدِّئَات* تأثير على قدرات الأطفال التعليميّة عند وصفها لهم	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨ ⑩
٣٦) إذا شعرت بآثار جانبيّة خلال فترة العلاج *بالمُهَدِّئَات* يجب أن أتوقف عن إستعماله في أقرب وقت ممكن	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨ ⑩
٣٧) أستعمل *المُهَدِّئَات* حسب تعليمات الطّبيب	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨ ⑩
٣٨) إذا تمّ إستهلاك *المُهَدِّئَات* بكثرةٍ، فلن تنفع عند الحاجة إليها حقّاً	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨ ⑩
٣٩) أُفضّل أن أُبقي *مُهَدِّئَات* إضافيّة في المنزل، في حال الحاجة إليها لاحقاً	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨ ⑩
٤٠) أثق بقرار الطّبيب سواء قرّر وصف أو عدم وصف *المُهَدِّئَات*	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨ ⑩
٤١) إذا كنت أعتقد أنّني بحاجة إلى *المُهَدِّئَات* ولم يصفها الطبيب، سأحصل عليها من الصّيْدَليّة بدون وصفة	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨ ⑩
٤٢) غالبًا مَا يشرَح الأطبّاء بوُضوح للمريض أسباب وصف أَوْ عدم وصف *المُهَدِّئَات*	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨ ⑩
٤٣) غالبًا مَا يشرَح الأطبّاء بوُضوح للمريض كيفيّة إستخدام *المُهَدِّئَات*	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨ ⑩
٤٤) عند شراء *المُهَدِّئَات*، يُبلغك الصّيْدَلي عن أهميّة التّقيّد الصّحيح بالعلاج	⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨ ⑩

المَعرفَة وَالإعتِقَاد وَإستِخدَام المُضَادَات الحَيَوِيَّة والمُهَدِّئَات في لبنان
رمز الإستبيان:_____ التَّارِيخ:_____

٤٥) **في الشّهر الماضي، هل إستعملت *المُهَدِّئَات*؟** ○ نعم (رجاءً إنتقل إلى االسُّؤال ٤٦) ○ لا (رجاءً إنتقل إلى االسُّؤال ٥٦)

أجِب على الأسْئِلَةِ التَّالِيَة عن إستهلاكك من *المُهَدِّئَات* في الشّهر الماضي

٤٦) **كم كانت مُدَّة آخر علاج *بالمُهَدِّئَات*؟**

عدد الأيَّام: ☐☐ عدد الأشهر: ☐☐ عدد السّنين: ☐☐

٤٧) **من الّذي وصف لك أو نصحك بإستخدام *المُهَدِّئَات*؟** (بإمكانك إختيار أكثر من إجابة)

○ الطَّبيب ○ الأصْدِقَاء
○ العائلة ○ الصَّيْدَلِيّ
○ كانَ عندي في المنزل

٤٨) **في آخر مَرَّة كان عليك أن تتناول *المُهَدِّئَات*، هل أكملت كُلّ دورة العلاج؟**

○ نعم ○ كلا

٤٩) **ماذا فعلت بالمُهَدِّئَات الّتي تُركت دون إستعمال؟** (بإمكانك إختيار أكثر من إجابة)

○ إحتفظت بها لكي أستَعملَها عندما أمرض في المَرَّة القادمة
○ رميتها في الزباله أو في مياه الصَّرف الصِّحّيّ
○ أُعطيتها لأحد
○ لم يتبقى لديّ أي من المُهَدِّئَات

٥٠) **في آخر مَرَّة كان عليك أن تتناول *المُهَدِّئَات*، هل نسيت أن تأخذ أي من الجرعات؟**

○ أبداً (رجاءً إنتقل إلى االسُّؤال ٥٢)
○ أحياناً (رجاءً إنتقل إلى االسُّؤال ٥١)
○ في كثير من الأحيان (رجاءً إنتقل إلى االسُّؤال ٥١)

٥١) **ماذا فعلت عندما تخطّيت/لم تتناول جُرْعَة من المُهَدِّئَات؟**

○ تابعت الجُرعات التَّالِيَة بشكل طبيعي
○ ضاعفت أو زدت الجُرعة الثانيّة
○ تناولتها عندما تذكرت

٥٢) **في آخر مَرَّة كان عليك أن تتناول *المُهَدِّئَات*، هل قمت بتغيير عيار الجُرعة من تِلْقَاء نفسك** (بِدُون إسْتِشَارَةٍ طِبِّيَّةٍ)؟

○ أبداً (رجاءً إنتقل إلى االسُّؤال ٥٦)
○ أحياناً (رجاءً إنتقل إلى االسُّؤال ٥٣)
○ في كثيرٍ من الأحيان (رجاءً إنتقل إلى االسُّؤال ٥٣)

٥٣) **ماذا فعلت عندما غيَّرتْ عيار جُرعة *المُهَدِّئَات* من تِلْقَاء نفسك** (بِدُون إسْتِشَارَةٍ طِبِّيَّةٍ)؟

○ تناولت منها أكثر (رجاءً إنتقل إلى االسُّؤال ٥٤ ومن وثمّ السُّؤال ٥٦)
○ تناولت منها أقل (رجاءً إنتقل إلى االسُّؤال ٥٥)
○ أحياناً تناولت منها أكثر وأحياناً أخرى أقل (رجاءً أجب على السُّؤالين ٥٤ و٥٥)

٥٤) **لماذا قُمت بزيادة عيار جُرعة *المُهَدِّئَات* من تِلْقَاء نفسك** (بِدُون إسْتِشَارَةٍ طِبِّيَّةٍ)؟ (بإمكانك إختيار أكثر من إجابة)

○ نسيت أن أتناول الجُرعة السَّابقة
○ شعرت بأنّني مريضٌ جِدًّا
○ لم أشعر بتحسُّن ملحوظ
○ تحسَّنت ولكن أردت أن أتحسَّن أكثر
○ كُنتُ أمر بمرحلةٍ عصيبةٍ (ضغوطات، مشاكل،إلى آخره)

٥٥) **لماذا قُمت بتخفيض عيار جُرعة المُهَدِّئَات من تِلْقَاء نفسك** (بِدُون إسْتِشَارَةٍ طِبِّيَّةٍ)؟ (بإمكانك إختيار أكثر من إجابة)

○ كُنتُ قلقاً من آثار الدواء الجانبيّة
○ كُنتُ متعباً ونسيت
○ شعرت بأنّني آخذ الكثير من الدّواء
○ كُنتُ على عجلة ونسيت
○ لا أحب تناول الأدْوِيَة في اللَّيْل
○ شعرت بتحسُّن

المَعرفَة وَالإعتِقَاد وَإستِخدَام المُضَادَات الحَيَوِيَّة والمُهَدِّئَات في لبنان
رمز الإستبيان:_____ التَّارِيخ:_____

الخَصَائِص الدِّيمُوغْرَافِيَّة العَامَّة

٥٦) حدِّد جِنسك ○ ذكر ○ أنثى

٥٧) ما هو تاريخ ميلادك؟ (يُرجى كتابة الأرقام المقابلة في الفراغات أدناه)

اليَوْم	الشَّهْر	السَّنَة

٥٨) ما هو أعلى مستوى تعليميّ لديك؟

○ لم أدخل إلى المدرسة
○ إبتدائيّ (الصّف الأول إلى الصّف السادس)
○ مُتَوَسِّط (الصف السَّابع إلى الصف التَّاسع)
○ ثانويّ (الصف العَاشِر إلى الصف الثَّاني عَشَر)
○ جامعة

٥٩) هل تعمل حاليًا؟ ○ نعم ○ كلا

٦٠) ماذا يُغَطِّي تَأْمِينُكَ الصِّحِّيّ؟ (بإمكانك إختيار أكثر من إجابة)

○ ليس لديّ تأمين صِحِّيّ
○ الكُلفة أو جزء من تكلفة الإستشارة الطبيّة
○ الكُلفة أو جزء من تكلفة الأدويّة

٦١) يُرجى الإشارة إلى وضعك العائلي؟

○ متزوج/متزوجة (رجاءً إنتقل إلى االسُّؤال رقم ٦٢)
○ مطلّق/مطلّقة (رجاءً إنتقل إلى السُّؤال رقم ٦٤)
○ أرمل/أرملة (رجاءً إنتقل إلى االسُّؤال رقم ٦٤)
○ منفصل/منفصلة عن الزوجة/الزوج ولكن لستما مطلقين (رجاءً إنتقل إلى االسُّؤال رقم ٦٢)

٦٢) ما هو أعلى مستوى تعليمي لزوجك/لزوجتك؟

○ لم يدخل/تدخل إلى المدرسة
○ إبتدائيّ (الصف الأول إلى الصف السادس)
○ مُتوسِّط (الصف السَّابع إلى الصف التَّاسع)
○ ثانويّ (الصف العَاشِر إلى الصف الثَّاني عَشَر)
○ جامعة

٦٣) هل زوجك/زوجتك يعمل/تعمل حاليًا؟ ○ نعم ○ كلا

٦٤) ما هو عدد الأفراد الذين يعيشون في منزلك، بما في ذلك أنت؟

○ ٢ ○ ٣- ٤ ○ ٥- ٦ ○ أكثر من ٦

٦٥) هل توجد أيّة مراكز رعاية صِحِّيَّة (مثلاً مستوصفات أو مستشفيات)، موجودة بالقرب من منطقة سكنك؟

○ نعم ○ كلا

٦٦) ما هو مجموع دخل الأسرة الشّهري (مجموع الدخل المُكتسب من جميع الأفراد الذين يعيشون في منزلك)؟

○ أقل من ٥٠٠ دولارٍ أمريكيٍّ في الشّهر
○ بين ٥٠٠ و٩٩٩ دولارٍ أمريكيٍّ في الشّهر
○ بين ١٠٠٠ و ١٤٩٩ دولارٍ أمريكيٍّ في الشّهر
○ بين ١٥٠٠ و ١٩٩٩ دولارٍ أمريكيٍّ في الشّهر
○ بين ٢٠٠٠ و ٢٥٠٠ دولارٍ أمريكيٍّ في الشّهر
○ أكثر من ٢٥٠٠ دولارٍ أمريكيٍّ في الشّهر

٦٧) هل تستشير الطّبيب عندما تكون مريضًا؟

○ أَبَدًا ○ نَادِرًا
○ أَحْيَانًا ○ دَائِمًا (رجاءً إنتقل إلى االسُّؤال رقم ٦٩)

٦٨) ما هو سبب عدم إستشارتك للطّبيب بشكلٍ دائم؟ (بإمكانك إختيار أكثر من إجابة)

○ لا حاجة للطّبيب
○ الخوف من الطّبيب
○ عدم توفر المال الكافي
○ عدم توفر الوقت الكافي لزيارة الطّبيب
○ فترة الإنتظار الطويلة ليَتمّ فحص المريض من قبل الأطبّاء
○ عدم وجود عيادة بالقرب من منزلي

٦٩) هل سبق لك أن تَلَقَّيتَ وَصْفَةً طِبِّيَّةً عبر الهاتف؟

○ نعم ○ كلا

٧٠) هل تتناول الكُحول أو المشروبات الروحيّة ؟

○ نعم (رجاءً إنتقل إلى االسُّؤال رقم ٧١)
○ كلا (شكرًا لك! لقد أكملت الإجابة على الإستبيان)

٧١) كم مرة تشرب الكُحول أو المشروبات الروحيّة؟

○ في المُناسبات الخاصّة ○ ٣ - ٥ مرات في الأسبوع
○ مَرّة واحدة في الأسبوع ○ يوميًّا
○ في نهاية الأسبوع فقط

شكرًا جزيلاً لوقتكم وتعاونكم!

French version of *Knowledge*, *Attitude* and *Practice* questionnaires about antibiotic and tranquilizer use in Lebanon

Maman, Papa, Participez à cette Enquête et Contribuez à Rendre notre Société plus Saine!

Chers Parents,
L'Université de Santiago de Compostela en Espagne et l'American University of Science and Technology au Liban, vous invitent à participer à la première étude cherchant à identifier les facteurs principaux conduisant au mauvais usage des antibiotiques et tranquillisants.

Pourquoi devriez-vous participer?
Vous, les parents, représentez une proportion importante de la population Libanaise. Par conséquent, nous vous encourageons à participer à notre étude afin que les parties concernées puissent établir des stratégies de santé ciblées qui conduiront à réduire les problèmes liés aux mauvais usages, intentionnels ou involontaires, de médicaments. **Cela impacterait positivement votre santé ainsi que celle de vos enfants.** Tout ce dont nous avons besoin de votre part est d'un peu de temps!

Comment pouvez-vous participer?
Pour participer à cette étude, il vous suffit de répondre à ce questionnaire et de le rendre à l'école. **Vous pouvez répondre à ce questionnaire indépendamment du fait que vous consommiez des médicaments correctement ou pas.** Il ne vous sera demandé de fournir **ni** votre nom, **ni** votre adresse, **ni** toute autre information permettant de révéler votre identité. Par ailleurs, les réponses fournies par les participants seront rassemblées dans une même base de données anonyme. Elles seront gardées confidentielles et seront supprimées à la fin de l'étude.

Seul un des parents (la maman ou le papa) doit répondre au questionnaire. Votre participation est volontaire, anonyme, n'impose aucuns frais financiers.

En nous renvoyant ce questionnaire avec vos réponses, vous donnez votre accord pour participer à cette étude.

Merci de votre participation!

CONNAISSANCES, CROYANCES ET UTILISATION D'ANTIBIOTIQUES ET DE TRANQUILLISANTS AU LIBAN
Code du questionnaire:_____ **Date:**_____

Pour choisir une réponse, veuillez remplir <u>COMPLÈTEMENT</u> le(s) cercle(s) correspondant(s): CORRECTEMENT répondu: ● INCORRECTEMENT répondu: ⊘ ∅

Veuillez répondre aux questions suivantes sur les *ANTIBIOTIQUES* (Amoxicillin, Cefixime, Ciproflaxin, Levoflaxin, Penicillin, etc…)

Sur une échelle de 0 à 10 points, sélectionnez un chiffre représentant votre niveau d'accord avec les affirmations ci-dessous. "0" (zéro) veut dire que vous n'êtes pas du tout d'accord et "10" représente un accord maximum.

Veuillez indiquer votre niveau d'accord **<u>QUE VOUS</u>** utilisiez des *antibiotiques* **<u>OU PAS</u>**

Exemple: Faire du sport est bénéfique pour la santé ⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ● ⑨ ⑩

		Pas d'accord ← → D'accord
1.	Les *antibiotiques* sont efficaces contre les virus	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
2.	Quand je suis enrhumé(e) ou j'ai une grippe, je prends des *antibiotiques* pour m'aider à me sentir mieux plus vite	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
3.	Si je me sens mieux après quelques jours de prise d'*antibiotiques*, il m'arrive d'arrêter mon traitement avant de le finir	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
4.	J'attends de mon médecin qu'il me prescrive des *antibiotiques* quand j'ai des symptômes de rhume ou une grippe	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
5.	Il est bon de pouvoir obtenir des *antibiotiques* de parents ou amis sans devoir voir un médecin	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
6.	Quand j'ai un mal de gorge, je préfère prendre un *antibiotique*	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
7.	Chaque type d'infection a besoin d'un *antibiotique* différent	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
8.	Les *antibiotiques* peuvent tuer les bactéries qui vivent habituellement sur la peau et dans les intestins	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
9.	Si je ressens des effets secondaires durant un traitement d'antibiotiques, je dois arrêter de prendre le médicament dès que possible	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
10.	Je prends les *antibiotiques* en suivant les instructions du médecin	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
11.	Quand les *antibiotiques* sont consommés de façon excessive, ils n'auront plus d'effet au moment où l'on en a vraiment besoin	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
12.	Je préfère garder des *antibiotiques* chez moi au cas où j'en aurais besoin plus tard	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
13.	Je fais confiance au médecin s'il /si elle décide de prescrire ou pas des *antibiotiques*	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
14.	Si je pense que j'ai besoin d'un *antibiotique* et que le médecin ne me le prescrit pas, je vais à la pharmacie pour me le procurer sans ordonnance	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
15.	Les médecins expliquent souvent clairement au patient les raisons de prescrire ou de ne pas prescrire des antibiotiques	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
16.	Les médecins expliquent souvent clairement au patient les instructions d'utilisation des *antibiotiques*	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
17.	Quand le patient achète un *antibiotique*, le pharmacien lui explique l'importance d'une bonne adhésion thérapeutique	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩

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Code du questionnaire:_____ **Date:**_____

18. Au cours du mois dernier, avez-vous pris des *antibiotiques*?

○ Oui (passer à la question 19) ○ Non (passer à la question 29)

Veuillez répondre aux questions suivantes sur votre consommation des *ANTIBIOTIQUES* AU COURS DU MOIS DERNIER

19. Quelle a été la durée de votre dernier traitement aux *antibiotiques*?

Nombre de jours ☐☐ Nombre de mois ☐☐

20. Qui vous a prescrit ou recommandé les *antibiotiques*? (Vous pouvez choisir plusieurs réponses)

○ Le médecin ○ Des amis

○ La famille ○ Le pharmacien

○ Je les avais chez moi

21. Avez-vous pris jusqu'au bout votre dernier traitement aux *antibiotiques*?

○ Oui ○ Non

22. Qu'avez-vous fait des *antibiotiques* que vous n'avez pas utilisés? (Vous pouvez choisir plusieurs réponses)

○ Je les ai gardés pour les utiliser la prochaine fois que je suis malade

○ Je m'en suis débarrassé(e) dans la poubelle ou les eaux usées

○ Je les ai donnés à quelqu'un d'autre

○ Il ne me restait plus d'antibiotique

23. Au cours de votre dernier traitement aux *antibiotiques*, vous est-il arrivé d'oublier de les prendre?

○ Jamais (passer à la question 25)

○ Parfois (passer à la question 24)

○ Souvent (passer à la question 24)

24. Qu'avez-vous fait quand vous avez oublié de prendre une dose de vos *antibiotiques*?

○ J'ai continué de prendre les doses suivantes normalement

○ J'ai doublé/augmenté la dose suivante

○ Je l'ai prise dès que je m'en suis souvenu(e)

25. Au cours de votre dernier traitement aux antibiotiques, avez-vous changé la dose sur votre propre décision (sans avis médical)**?**

○ Jamais (passer à la question 29)

○ Parfois (passer à la question 26)

○ Souvent (passer à la question 26)

26. Comment avez-vous vous-même changé votre dose d'*antibiotiques* (sans avis médical)**?**

○ J'en ai pris plus (passer à la question 27 puis 29)

○ J'en ai pris moins (passer à la question 28)

○ Parfois j'en ai pris plus et parfois moins (passer à la question 27 puis 28)

27. Pourquoi avez-vous vous-même décidé d'augmenter votre dose d'*antibiotiques* (sans avis médical)**?** (vous pouvez choisir plusieurs réponses)

○ J'ai oublié de prendre la dose précédente

○ Je me suis senti(e) très malade

○ Je n'ai pas senti de réelle amélioration

○ J'ai senti une amélioration mais voulais me sentir encore mieux

28. Pourquoi avez-vous décidé vous-même de réduire votre dose d'*antibiotiques* (sans avis médical)**?** (vous pouvez choisir plusieurs réponses)

○ J'avais peur des effets secondaires

○ J'étais fatigué(e) et j'ai oublié

○ J'ai pensé que j'en prenais trop

○ J'étais pressé(e) et j'ai oublié

○ Je n'aime pas prendre de médicaments la nuit

○ Je me sentais mieux

CONNAISSANCES, CROYANCES ET UTILISATION D'ANTIBIOTIQUES ET DE TRANQUILLISANTS AU LIBAN
Code du questionnaire:_____ **Date:**_____

Veuillez répondre aux questions suivantes sur les *TRANQUILLISANTS (médicaments incluant somnifères ou calmants: Alprazolam, Bromazepam, Diazepam, Ambien, Xanax, Valium, etc.)*?

Sur une échelle de 0 à 10 points, sélectionnez un chiffre représentant votre niveau d'accord avec les affirmations ci-dessous. "0" (zéro) veut dire que vous n'êtes pas du tout d'accord et "10" représente un accord maximum.

Veuillez indiquer votre niveau d'accord **QUE VOUS** utilisiez des *tranquillisants* **OU PAS**

Exemple: Faire du sport est bénéfique pour la santé ⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ● ⑨ ⑩

		Pas d'accord ← → D'accord
29.	J'accepterais de prendre des *tranquillisants* pour mieux dormir	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
30.	Si je me sens mieux après quelques jours, je continue parfois de prendre des *tranquillisants* même après avoir fini le traitement prescrit	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
31.	J'accepterais de prendre des *tranquillisants* pour pouvoir profiter du temps passé avec ma famille	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
32.	J'accepterais de prendre des *tranquillisants* quand je suis abattu(e) et triste pour pouvoir mieux travailler	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
33.	Les *tranquillisants* diminuent le contrôle des personnes sur ce qu'elles font	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
34.	Les personnes qui prennent des *tranquillisants* ont un plus grand risque d'avoir un accident de la route	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
35.	Lorsqu'ils sont prescrits à des enfants, les médicaments psychotropes (comme par exemple les *tranquillisants*), peuvent affecter leur capacité d'apprentissage	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
36.	Si je ressens des effets secondaires durant un traitement de tranquillisants, je dois arrêter de prendre le médicament dès que possible	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
37.	Je prends les *tranquillisants* en suivant les instructions du médecin	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
38.	Quand les *tranquillisants* sont consommés de façon excessive, ils n'auront plus d'effet au moment où l'on en a vraiment besoin	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
39.	Je préfère garder des *tranquillisants* chez moi au cas où j'en aurais besoin plus tard	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
40.	Je fais confiance au médecin s'il /si elle décide de prescrire ou pas des *tranquillisants*	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
41.	Si je pense que j'ai besoin d'un *tranquillisant* et que le médecin ne me le prescrit pas, je vais à la pharmacie pour me le procurer sans ordonnance	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
42.	Les médecins expliquent souvent clairement au patient les raisons de prescrire ou de ne pas prescrire des tranquillisants	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
43.	Les médecins expliquent souvent clairement au patient les instructions d'utilisation des *tranquillisants*	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩
44.	Quand le patient achète un *tranquillisant*, le pharmacien lui explique l'importance d'une bonne adhésion thérapeutique	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩

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Code du questionnaire:_____ **Date:**_____

45. Au cours du mois dernier, avez-vous pris des *tranquillisants?*

○ Oui (passer à la question 46) ○ Non (passer à la question 56)

Veuillez répondre aux questions suivantes sur votre consommation des TRANQUILLISANTS AU COURS DU MOIS DERNIER

46. Quelle a été la durée de votre dernier traitement aux *tranquillisants*?

Nombre de jours ☐☐
Nombre de mois ☐☐
Nombre d'années ☐☐

47. Qui vous a prescrit ou recommandé les *tranquillisants*? (Vous pouvez choisir plusieurs réponses)

○ Le médecin ○ Des amis
○ La famille ○ Le pharmacien
○ Je les avais chez moi

48. Avez-vous pris jusqu'au bout votre dernier traitement aux *tranquillisants*?

○ Oui ○ Non

49. Qu'avez-vous fait des tranquillisants que vous n'avez pas utilisés? (Vous pouvez choisir plusieurs réponses)

○ Je les ai gardés pour les utiliser la prochaine fois que je suis malade
○ Je m'en suis débarrassé(e) dans la poubelle ou les eaux usées
○ Je les ai donnés à quelqu'un d'autre
○ Il ne me restait plus des tranquillisants

50. Au cours de votre dernier traitement aux tranquillisants, vous est-il arrivé d'oublier de les prendre?

○ Jamais (passer à la question 52)
○ Parfois (passer à la question 51)
○ Souvent (passer à la question 51)

51. Qu'avez-vous fait quand vous avez oublié de prendre une dose de vos tranquillisants?

○ J'ai continué de prendre les doses suivantes normalement
○ J'ai doublé/augmenté la dose suivante
○ Je l'ai prise dès que je m'en suis souvenu(e)

52. Au cours de votre dernier traitement aux tranquillisants, avez-vous changé la dose sur votre propre décision (sans avis médical)**?**

○ Jamais (passer à la question 56)
○ Parfois (passer à la question 53)
○ Souvent (passer à la question 53)

53. Comment avez-vous changé vous-même votre dose de tranquillisants (sans avis médical)**?**

○ J'en ai pris plus (passer à la question 54 puis à la question 56)
○ J'en ai pris moins (passer à la question 55)
○ Parfois j'en ai pris plus et parfois moins (passer à la question 54 puis 55)

54. Pourquoi avez-vous vous-même décidé d'augmenter votre dose de tranquillisants (sans avis médical)**?** (Vous pouvez choisir plusieurs réponses)

○ J'ai oublié de prendre la dose précédente
○ Je me suis senti(e) très malade
○ Je n'ai pas senti de réèlle amélioration
○ J'ai senti une amélioration mais voulais me sentir encore mieux
○ Je vivais une période stressante (stress, problèmes, etc…)

55. Pourquoi avez-vous vous-même choisi de réduire votre dose de *tranquillisants* (sans avis médical)**?** (vous pouvez choisir plusieurs réponses)

○ J'avais peur des effets secondaires du médicament
○ J'étais fatigué(e) et j'ai oublié
○ J'ai pensé que j'en prenais trop
○ J'étais pressé(e) et j'ai oublié
○ Je n'aime pas prendre de médicaments la nuit
○ Je me sentais mieux

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Code du questionnaire:_____ **Date:**_____

Caractéristiques Démographiques Générales

56. Indiquez votre sexe ○ Homme ○ Femme

57. Quelle est votre date de naissance? (Veuillez inscrire les chiffres dans les espaces alloués)

☐☐ ☐☐ ☐☐☐☐
Jour **Mois** **Année**

58. Quel est votre niveau d'éducation académique.

○ Je n'ai pas été à l'école
○ Elémentaire/ Primaire (maternelle jusqu'à la 6ème)
○ Complémentaire (5ème à la 3ème)
○ Secondaire (2nde à la terminale)
○ Universitaire

59. Actuellement, avez-vous une activité professionnelle?

○ Oui ○ Non

60. Qu'est-ce qui est couvert par votre assurance santé? (Vous pouvez choisir plus d'une réponse).

○ Je n'ai pas d'assurance santé
○ Le coût ou une partie des coûts des consultations médicales
○ Le coût ou une partie des coûts de mes médicaments

61. Veuillez indiquer votre statut marital:

○ Marié(e) (passer à la question 62)
○ Divorcé(e) (passer à la question 64)
○ Veuf/Veuve (passer à la question 64)
○ Séparé(e) de mon épouse/époux, mais non divorcé(e) (passer à la question 62)

62. Quel est le niveau d'éducation académique de votre époux/épouse?

○ Il/Elle n'a pas été à l'école
○ Elémentaire/ Primaire (maternelle jusqu'à la 6ème)
○ Complémentaire (5ème à la 3ème)
○ Secondaire (2nde à la terminale)
○ Universitaire

63. Actuellement, votre époux/épouse travaille-t-il/elle?

○ Oui ○ Non

64. Combien de personnes vivent sous votre toit, inclus vous-même?

○ 2 ○ 3 – 4 ○ 5 – 6 ○ Plus de 6

65. Y a-t-il des instituts de santé, tels que des dispensaires ou hôpitaux, situés près de votre lieu de résidence?

○ Oui ○ Non

66. Quel est le total des revenus familiaux (quel est le revenu total perçu par tous les membres de la famille vivant sous le même toit)?

○ Moins de 500US$ par mois
○ Entre 500 et 999US$ par mois
○ Entre 1000 et 1499US$ par mois
○ Entre 1500 et 1999US$ par mois
○ Entre 2000 et 2500US$ par mois
○ Plus de 2500US$ par mois

67. Consultez-vous un médecin lorsque vous êtes malade?

○ Jamais ○ Rarement
○ Parfois ○ Toujours (passer à la question 69)

68. Quelle est la raison pour laquelle vous ne consultez pas toujours un médecin? (Vous pouvez choisir plus d'une réponse).

○ Je n'ai pas besoin de médecin
○ J'ai peur des médecins
○ Par manque d´argent
○ Je n'ai pas le temps de le consulter
○ L'attente avant d'être examiné(e) est longue
○ La clinique est située loin de ma maison

69. Avez-vous déjà reçu une prescription médicale par téléphone?

○ Oui ○ Non

70. Buvez-vous de l'alcool?

○ Oui (passer à la question 71)
○ Non (Merci! Vous avez fini de répondre au questionnaire)

71. A quelle fréquence consommez-vous de l'alcool?

○ Aux occasions spéciales
○ Une fois par semaine
○ Les weekends seulement
○ 3 à 5 fois par semaine
○ Tous les jours

Merci d'avoir participé à cette étude !

Annex II. Publications derived from the thesis

Mallah N, Rodríguez-Cano R, Figueiras A, Takkouche B. Design, reliability and construct validity of a knowledge, attitude and practice questionnaire on personal use of antibiotics in Spain. Scientific Reports 2020, 10(1):20668. (Journal Ranking: first quartile)

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Design, reliability and construct validity of a Knowledge, Attitude and Practice questionnaire on personal use of antibiotics in Spain

Narmeen Mallah[1,2], Rubén Rodríguez-Cano[3], Adolfo Figueiras[1,2,4] & Bahi Takkouche[1,2,4]✉

Numerous questionnaires are available on Knowledge, Attitudes, and Practices (KAP) towards antibiotics' use by adults, but none of these questionnaires is fully validated. We undertook an exhaustive literature review to design a comprehensive KAP questionnaire concerning the personal use of antibiotics in Galicia, North Spain. The Item Content Validity Index (I-CVI) and modified Kappa statistic (K*), confirmed the content validity of the questions (0.78 ≤ I-CVI ≤ 1.00 and 0.78 ≤ K* ≤ 1.00). The S-CVI statistic showed the content validity of the scale (S-CVI/Ave: 0.95). Following face validity and pilot testing, the Test–Retest Reliability in a sample of 145 adults confirmed the reliability of the questions. We carried out Confirmatory Factor Analysis using cross loadings and modification indices to choose the most adequate model in data collected from 844 adults. We estimated the indicators of model fit and demonstrated that the selected model has a good to excellent fit, thus establishing the construct validity. The final version of the questionnaire was highly accepted by the general adult population as reflected by the response rate (95.85%) and the low percentage of unanswered questions (0.4–2.7%). Our fully validated questionnaire could prove useful for research as it permits generating high quality data and reducing measurement error.

Antibiotic resistance remains a global public health threat, despite the exerted regional and international efforts to defeat this problem. In Europe, the burden of infections due to antibiotic-resistant bacteria is comparable to that of influenza, tuberculosis and HIV/AIDS combined[1]. Each year, Europe records 670,000 new infections due to resistance and 33,000 deaths as a direct consequence of these infections. A recent report from the Center of Disease Control showed that the burden of antibiotic resistance remains important in the United States, with 2.8 million antibiotic-resistant infections and more than 35,000 related deaths every year[2]. It is foreseen that the situation by 2050 will deteriorate even more, with 10 million attributable annual deaths and a cumulative cost of 100 trillion USD, if no proactive solutions are found to slow down the expansion of antibiotic resistance[3].

Health strategies to tackle antibiotic resistance were already defined by the Word Health Organization and encompass interventions that are oriented to health and research centers as well as to community settings[4]. Increasing awareness and changing behaviors towards a proper use of antibiotics are essential elements in the community intervention package[4]. In this context, intervention programs to improve the use of antibiotics apply a specific questionnaire pre- and post-intervention in order to measure changes in Knowledge, Attitudes and Practices (KAP) in the target population. KAP modeled questionnaires are instruments that assess the following three dimensions: Knowledge (what the respondents know about antibiotics), Attitude (what the respondents think or believe about antibiotics) and Practice (what they do regarding antibiotics)[5].

As data obtained from KAP studies are fundamental in assessing the need, planning and implementing public health programs, it is of paramount importance to use reliable and valid instruments in order to ensure a good research quality[6]. Nonetheless, despite the long-standing recognition of antibiotic resistance, the

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literature revealed that to-date, no fully validated KAP questionnaire is available for antibiotics' use by the general population[7]. A recent systematic review of surveys about knowledge and/or attitudes towards antibiotic use by the general population reported that 11 studies tested the validity and the reliability of the used questionnaire[8], but the validity of these questionnaires was only partially assessed and limited to face and/or content validity. Other studies claimed using "previously similar validated questionnaires"[9], nonetheless the cited studies were not found to include validated questionnaires. Alumran and colleagues developed and validated the construct of a questionnaire about the parents' perceptions on the use of antibiotics for children with upper respiratory tract infections[10]. However, this questionnaire cannot be applied in a straightforward fashion to assess knowledge and attitudes of adults concerning their own use of antibiotics, as parents are usually more judicious with antibiotics' use for children than for themselves[11].

Accordingly, to fill this gap, we aimed in the present study to design and validate a questionnaire for the assessment of Knowledge and Attitude related to Practices of personal use of antibiotics in the general population. We describe the development process of this questionnaire and report the assessment of its face, content and construct validity. We also examine the questionnaire reliability, responsiveness, and acceptability in North Spain.

Results

Content validity. The process of items' selection for retaining in the questionnaire to be validated is summarized in Fig. 1. The Item-Content Validity Index (I-CVI) estimations for the 28 KAP items that were retained after the initial evaluation of the panelists ranged between 0.78 and 1.00, indicating that these items were considered clear, understandable, and relevant to the questionnaire. For all items, modified Kappa (K') values were excellent (> 0.75), revealing that the agreement between experts was not due to chance. Scale Content Validity Index (S-CVI/Ave) was 0.95, confirming the content validity of the scale.

Face validity and pilot testing. All the 30 adults who participated in the pilot testing answered the questionnaire in its totality. Two participants reported that they misunderstood 0 and 10 being the lowest and highest levels of agreement. We, therefore, added an additional indication using arrows to help the participants remember the direction of agreement. We also provided an answered example ("practicing sports benefits health") to facilitate the understanding of the 0–10 Likert Scale concept. One participant declared that it was not clear whether the Knowledge and Attitudes items should be answered in case the respondent did not use antibiotics. Therefore, we added this statement "Please evaluate the below statements REGARDLESS of whether you are using antibiotics OR NOT". For the question, "The last time you had to take antibiotics, did you complete the course of treatment?", the participants suggested adding one additional answer ("still using them"). The questionnaire took 8–10 min to be completed, and the participants showed satisfaction about the questionnaire length.

Test–retest reliability. Out of the 145 adults invited to participate in the test–retest reliability test, 140 answered the questionnaire in the two occasions. The Intraclass Correlation Coefficient (ICC) assessment showed that the reliability was acceptable for 4 items ($0.40 \leq ICC \leq 0.58$), good for 9 items ($0.60 \leq ICC \leq 0.70$), and excellent for an item ($ICC = 0.82$) (Table 1). Three items (Q5, Q10 and Q11) showed ICC values below 0.4 (Table 1). Since low ICC could be due to lack of sample heterogeneity for these items, we calculated their Spearman's correlation coefficient in order to explore further their reliability. Spearman coefficient showed that answers in the first and second rounds are weakly correlated for Q5 (Spearman regression coefficient, $r_s = 0.193$; $p = 0.022$) and moderately correlated for Q10 ($r_s = 0.433$; $p < 0.0001$) and Q11 ($r_s = 0.405$; $p < 0.0001$).

Construct validity. We explored the construct validity by distributing the initial 17 items of the Knowledge and Attitude construct into 2 dimensions: Knowledge about antibiotics (Knowledge), and Attitude towards antibiotics (Attitude), based on theoretical grounds and then by confirming the structure of the 2-factors model (Model 0) using Confirmatory Factor Analysis (CFA). This model showed an unacceptable model fit as reflected by the goodness of fit indicators (Table 2).

In Model 0, Q8 did not load significantly in the Knowledge factor, and the items "Q10, Q13, Q15, Q16, Q17" loaded negatively in the Attitude factor. These five attitude items dealt with the patient-health care provider relationship and therefore they were attributed to a new factor (Attitude-Healthcare provider).

The new model (Model 1.0) included "Q1, Q2, Q4, Q6, Q7, Q8 and Q11" in the Knowledge factor; "Q3, Q5, Q9, Q12, Q14" in Attitude-Personal factor and "Q10, Q13, Q15, Q16, Q17" in Attitude-Healthcare provider factor. Model 1.0 showed better fit than Model 0, however it still was not acceptable (Table 2).

Therefore, we made various iterations based on cross-loadings, modification indices and analyzed correlations between items' residuals in order to improve the goodness of fit. Accordingly, we eliminated Q8 "Antibiotics can kill the bacteria that normally live on the skin and in the gut" from Model 1.0, and named the modified model "Model 1.1". Table 3 summarizes the loadings of the 16 retained items on their corresponding factor. Significant correlations were observed between the residuals of Q10 and Q13 ($r = 0.18$, $p < 0.0001$), Q11 and Q10 ($r = 0.20$, p-value < 0.0001), Q13 and Q14 ($r = -0.13$, p-value $= 0.001$) and Q4 and Q7 ($r = 0.12$, p-value $= 0.001$) (Fig. 2).

The indicators of the goodness of fit assessment of the Model 1.1 showed an adequate fit. (Table 2). The χ^2 difference test between Model 1.0 and Model 1.1 showed that they are statistically different ($\Delta\chi^2 = 331.97$, $\Delta df = 22$, $p = 0.0001$) (Table 2). Accordingly, we adopted Model 1.1 for this questionnaire.

Knowledge was significantly positively correlated with Attitude-Personal factor ($r = 0.56$, $p < 0.0001$), whereas it was not correlated with Attitude-Healthcare provider ($r = 0.04$, $p = 0.417$). Attitude-Personal and Attitude-Healthcare provider were weakly negatively correlated ($r = -0.11$, $p = 0.023$) (Fig. 1).

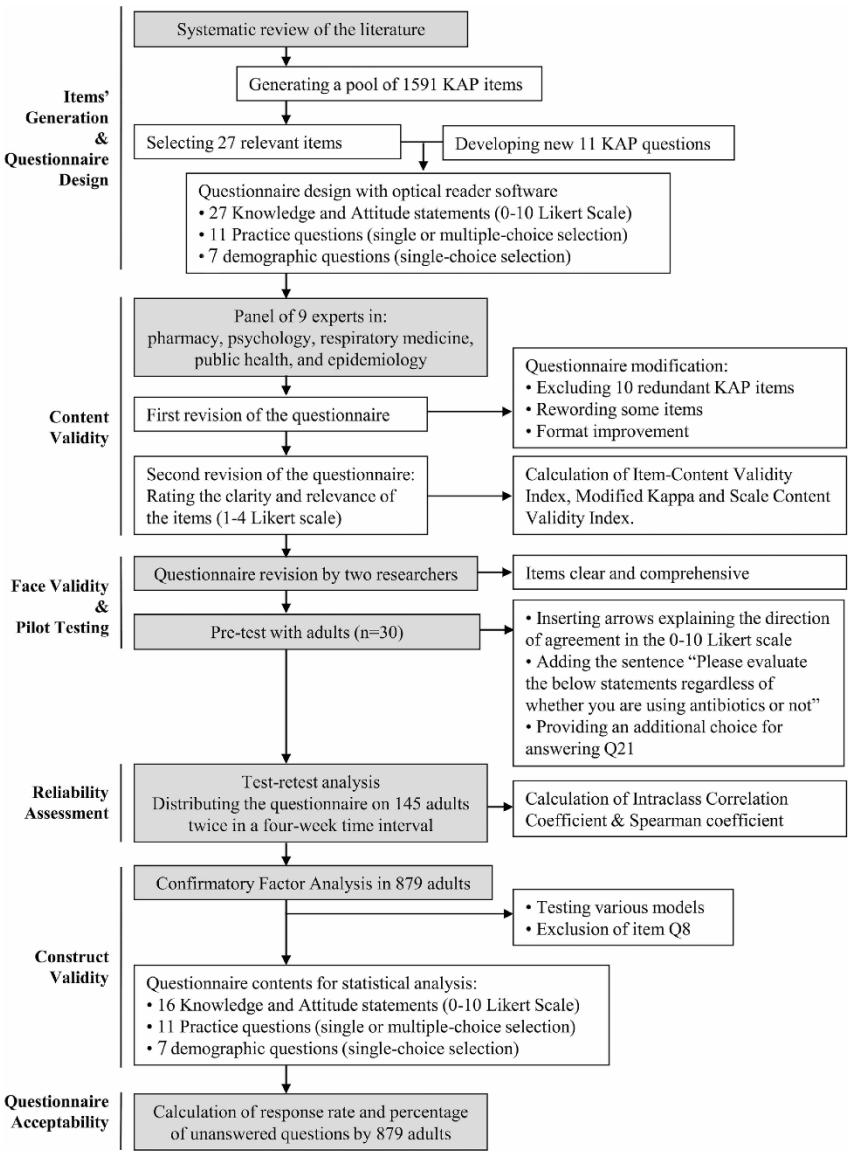

Figure 1. Flow diagram describing the steps followed to develop and validate the KAP questionnaire.

Final version of the questionnaire. According to the findings from the validation steps mentioned above, we provide the final version of the questionnaire which consists of three blocks (see Supplementary Information S1). The first block encompasses the 16 retained items after the CFA analysis and that underlie 3 factors: Knowledge about antibiotics, Attitude towards the personal use of antibiotics and Attitude towards health care providers. The second block includes a series of 11 questions that intend to measure the different practices of personal misuse of antibiotics. The third block entails the demographic characteristics and consists of seven

Item	N	ICC (95% CI)
Q1. Antibiotics are effective against viruses	137	0.82 (0.75, 0.87)
Q2. When I get a cold, I take antibiotics to help me feel better faster	140	0.62 (0.48, 0.73)
Q3. If I feel better after a few days, I sometimes stop taking my antibiotics before completing the course of treatment	139	0.40 (0.17, 0.57)
Q4. I expect my doctor to prescribe antibiotics if I suffer from common cold or flu symptoms	138	0.68 (0.55, 0.77)
Q5. It is good to be able to get antibiotics from relatives or friends without having to see a medical doctor	140	0.06 (− 0.32, 0.32)
Q6. When I have a sore throat, I prefer to use an antibiotic	138	0.62 (0.46, 0.73)
Q7. Each type of infection needs a different antibiotic	138	0.67 (0.54, 0.77)
Q8. Antibiotics can kill the bacteria that normally live on the skin and in the gut	130	0.67 (0.54, 0.77)
Q9. If I feel side effects during a course of treatment of antibiotics, I should stop taking them as soon as possible	136	0.60 (0.44, 0.72)
Q10. I take the antibiotics according to the doctor's instructions	139	0.36 (0.10, 0.54)
Q11. If antibiotics are consumed in excess, they will not work when they are really needed	137	0.19 (0.14, 0.42)
Q12. I prefer to keep antibiotics at home in case there is a need for them later	139	0.58 (0.41, 0.70)
Q13. I trust the doctor's decision if s/he decides to prescribe or not prescribe antibiotics	138	0.50 (0.29, 0.64)
Q14. If I believe that I need an antibiotic and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	138	0.50 (0.29, 0.64)
Q15. Doctors often explain clearly to the patient the reasons for prescribing or not prescribing antibiotics	134	0.70 (0.58, 0.79)
Q16. Doctors often explain clearly to the patient the instructions for the use of antibiotics	138	0.65 (0.51, 0.75)
Q17. When you buy antibiotics, the pharmacist tells you about the importance of correct therapeutic compliance/adherence	139	0.63 (0.48, 0.74)

Table 1. Test–retest reliability assessment of Knowledge and Attitudes items of the questionnaire. *N* number of participants who answered the corresponding item in the two-time occasions, *ICC* intra-class correlation coefficient.

Indicator	Model 0	Model 1.0	Model 1.1
χ^2	1037.074	580.45	248.49
df	118	116	94
p	< 0.0001	< 0.0001	< 0.0001
RSMEA (90% CI)	0.096 (0.091, 0.102)	0.069 (0.063, 0.075)	0.044 (0.038, 0.051)
CFI	0.55	0.77	0.92
TLI	0.49	0.74	0.90
AIC	67,594.035	67,141.414	62,873.317
BIC	67,840.296	67,397.146	63,147.993
aBIC*	67,675.160	67,225.659	62,963.803
SRMR	0.088	0.073	0.047

Table 2. Comparison of the goodness of fit parameters between models. Model 0 encompassed two factors (Knowledge and Attitude), Model 1.0 consisted of three factors (Knowledge, Attitude-Personal and Attitude-Healthcare provider) and Model 1.1 involved the same factors as Model 1.0 but excluding Q8. χ^2 Chi-square value, *df* Degree of Freedom, *p* p-value (Chi-square), *RSMEA* Root Mean Squared Error Approximation, *CFI* Comparative Fit Index, *TLI* Tucker-Lewis Index, *AIC* Akaike Information Criterion, *BIC* Bayesian Information Criterion, *aBIC* sample-size adjusted BIC, *SRMR* Standardized Root Mean Square Residual.

questions. The questions of the second and the third blocks are responded by selecting one or several answers from a list of possible answers, except for "age" which is introduced as a number by the participants.

Questionnaire overall reliability. The overall reliability was reflected by the Cronbach's alpha of 0.62, which is deemed acceptable given that our questionnaire assesses distinct dimensions uncorrelated with each other.

Items and questionnaire acceptability. 844 out of 879 participants accepted answering the questionnaire, yielding a participation rate of 95.85%. The percentage of missing or blank answers was between 0.4% and 2.7%, revealing a high item-response rate. These figures indicate high acceptability of the questionnaire by the population.

Item	Loading estimate	Standard error	P-value	Standard loading estimate
Knowledge				
Q1. Antibiotics are effective against viruses	1.65	0.09	< 0.0001	0.60
Q2. When I get a cold, I take antibiotics to help me feel better faster	1.46	0.08	< 0.0001	0.81
Q4. I expect my doctor to prescribe antibiotics if I suffer from common cold or flu symptoms	1.22	0.09	< 0.0001	0.40
Q6. When I have a sore throat, I prefer to use an antibiotic	0.49	0.09	< 0.0001	0.26
Q7. Each type of infection needs a different antibiotic	0.12	0.08	0.014	0.09
Q11. If antibiotics are consumed in excess, they will not work when they are really needed	− 0.38	0.06	< 0.0001	− 0.25
Attitude-personal				
Q3. If I feel better after a few days, I sometimes stop taking my antibiotics before completing the course of treatment	1.55	0.09	< 0.0001	0.55
Q5. It is good to be able to get antibiotics from relatives or friends without having to see a medical doctor	0.66	0.05	< 0.0001	0.56
Q6. When I have a sore throat, I prefer to use an antibiotic	0.84	0.12	< 0.0001	0.37
Q9. If I feel side effects during a course of treatment of antibiotics, I should stop taking them as soon as possible	0.62	0.11	< 0.0001	0.21
Q10. I take the antibiotics according to the doctor's instructions	− 0.40	0.05	< 0.0001	− 0.39
Q12. I prefer to keep antibiotics at home in case there is a need for them later	1.28	0.09	< 0.0001	0.48
Q13. I trust the doctor's decision if s/he decides to prescribe or not prescribe antibiotics	− 0.34	0.08	< 0.0001	− 0.18
Q14. If I believe that I need an antibiotic and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	0.90	0.06	< 0.0001	0.54
Attitude-healthcare provider				
Q10. I take the antibiotics according to the doctor's instructions	0.12	0.04	0.004	0.11
Q13. I trust the doctor's decision if s/he decides to prescribe or not prescribe antibiotics	0.39	0.06	< 0.0001	0.23
Q15. Doctors often explain clearly to the patient the reasons for prescribing or not prescribing antibiotics	1.76	0.08	< 0.0001	0.77
Q16. Doctors often explain clearly to the patient the instructions for the use of antibiotics	1.69	0.08	< 0.0001	0.82
Q17. When you buy antibiotics, the pharmacist tells you about the importance of correct therapeutic compliance/adherence	1.05	0.07	< 0.0001	0.41

Table 3. Factors loadings and standard errors from the three-factors model (Model 1.1).

Discussion

To-date none of the studies that measured the association of Knowledge and Attitudes with Practices of use of antibiotics in the general population applied a fully validated questionnaire[8]. Therefore, to fill this gap, we designed and validated the psychometric properties of a KAP questionnaire about antibiotics' use by the adult general population. The content and the scale validity indices confirmed the content validity of our questionnaire. Moreover, the test–retest reliability and the confirmatory factor analysis proved the reliability and the construct validity of the questionnaire. Importantly, the questionnaire was accepted by the general population as reflected by the high response rate and the low percentage of unanswered questions.

The *availability* of a reliable and construct-valid instrument is fundamental for epidemiological studies that aim to measure associations between Knowledge, Attitudes, and Practices toward the personal use of antibiotics, as the use of a non-validated questionnaire may induce measurement error in the exposure and the outcome. In particular, the availability of a validated KAP questionnaire is crucial for the design of interventions aimed at improving the Knowledge and modifying Attitudes and Practices towards a proper use of antibiotics.

Knowledge and Attitudes are considered stable variables that are not likely to be changed rapidly. The test–retest *reliability* of these questions showed that they generate reproducible results, except for the item Q5 "It is good to be able to get antibiotics from relatives or friends without having to see a medical doctor". The low ICC for Q5 could be due to the fact that the sample distribution was concentrated in the extreme lower end of the agreement scale[12], where the overwhelming majority of the population answered by 0 (totally disagree) in the two test rounds. Moreover, an extremely large proportion of participants showed disagreement with the statement Q5. Accordingly, item Q5 is likely to be reliable and should be retained in the questionnaire.

The *construct validity* assessment showed that the adopted model has a good to excellent fit. The logical and the theoretical distribution of the questions across the three factors, Knowledge, Attitude-Personal and Attitude-Healthcare provider, in Model 1.1 supported further the adequacy of the model[13]. In our questionnaire, some items loaded in more than one factor (cross-load). This was expected since our instrument encompasses a multidimensional construct[14]. Knowledge factor correlated significantly with Attitudes towards the personal use of antibiotics (Attitude-Personal). Knowledge and Attitude-Personal include item Q6 "When I have a sore throat, I prefer to use an antibiotic" that loaded significantly on both factors, explaining further the existing association. Such findings were expected, as personal Attitudes toward the use of antibiotics in case of sore throat infections are in part driven by patients' knowledge on this topic. On the other side, Knowledge was not correlated with Attitudes towards health-care provider (Attitude-Healthcare provider), revealing that the items designed to measure participants' Knowledge about antibiotics are not related to those intended to explore the relation between patients and healthcare providers. This confirms that the questions included in each of these two factors

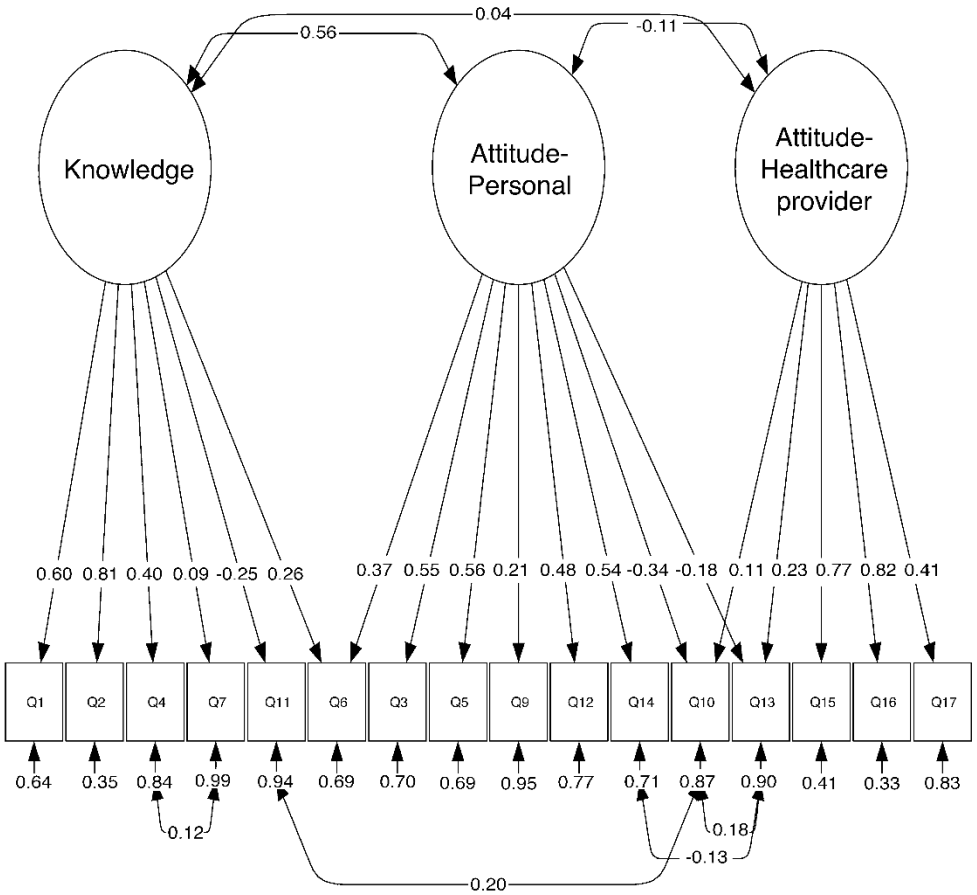

Figure 2. Representation of the model selected by CFA analysis (Model 1.1). Each of the three factors (Knowledge, Attitude-Personal and Attitude-Healthcare provider) is represented with its corresponding standardized items loadings and their residuals. "Knowledge" includes items the explore the knowledge of the adults towards antibiotics. "Attitude-Personal" encompasses statements about attitudes towards the personal use of antibiotics. "Attitude-Healthcare provider" involves phrases about the patient-healthcare provider relationship with respect to antibiotics. The double-sided arrows represent correlations between the variables. Q1–Q7 and Q9–Q17 are items of the Knowledge and Attitude construct (Q8 was deleted in a previous step). The single headed arrows represent the correlation of the items and their respective factors.

are specific and measure unique and unrelated dimensions. Our CFA results indicate that including the factor Attitude-Healthcare provider in the questionnaire is essential as various reports highlighted on the influence of healthcare provider-patient relationship on proper therapeutic compliance[15,16], and in specific with respect to the proper use of antibiotics[17,18]. Consequently, KAP questionnaires should not be limited to knowledge and personal attitudes only, but should also examine attitudes towards healthcare-providers. In addition, a negative and weak correlation existed between Attitude-Personal and Attitude-Healthcare provider, suggesting that individuals who tend to have higher agreement with Attitude-Healthcare provider statements are also more prone to disagree or to agree to a lesser extent with the items included in Attitude-Personal factor. This demonstrates that trust and communication between patients and their healthcare providers have a substantial impact on patients' attitudes toward antibiotics. Explaining the motives for prescribing or not prescribing antibiotics and giving instructions of their use by the physicians to the patients is associated with lower odds of antibiotics' misuse[18]. Testing these associations in other populations would further validate our findings.

In general, an assessment of past intake of antibiotics relies on the memory of the participants. Therefore, to decrease the risk of recall bias we have included a time limit in the design of the "Practice" questions by asking

about the use in the past two months. The questionnaire encompasses 11 questions that are elaborated to determine any aspect of misuse. Moreover, the provided choices of answers were based on an extensive literature review to include any possible answer, and therefore avoid leaving questions unanswered.

The questionnaire was designed to measure the participants' Knowledge and Attitudes regardless of their consumption of antibiotics in the last 2 months. Therefore, our questionnaire could prove useful in obtaining data both from users and non-users of antibiotics, which represent a crucial issue in epidemiologic studies involving Knowledge, Attitudes and Practices in antibiotic use.

The high *acceptability* of the questionnaire by the general population reflects the feasibility of its application in general population settings. In fact, the time taken to answer our questionnaire was within the ideal range (10 min), which therefore aided in increasing the response rate[19]. Questionnaires with a long list of questions negatively influence the participation rate and the quality of data[20]. Another factor that could have enhanced the response rate is the fact of being issued from a research and academic institution[21]. The same questionnaire was translated forward and backward into English, Arabic and French in a previous study that targeted the general population[18]. The translated versions were also pilot tested. This favors the application of the questionnaire in non-English speaking populations.

Our study has an important limitation. In epidemiologic studies, an important step in the validation process involves comparing the results obtained from the questionnaire being validated to a superior method, deemed "gold standard". However, to the best of our knowledge, to date, a gold standard to assess the proper use or the misuse of antibiotics does not exist and therefore, our instrument could not be compared against any previous reference method. Due to this limitation, we consider that the present questionnaire is reliable and has construct validity, but future research is needed to provide a gold standard for KAP questionnaire about antibiotics. Another limitation of our validation study is that the construct was validated in the Spanish population only, therefore our questionnaire needs to be further tested in different settings and populations.

Conclusion

This study presents a step forward towards the validation of a knowledge, attitude, and practice questionnaire about the personal use of antibiotics. Moreover, taking into consideration the inconsistent reporting of validation methodologies across studies and the abuse of the term validation, as well as the exhaustive review of the methodology carried out in the current manuscript, we believe that this study would help validating KAP pharmacologic studies on other drugs than antibiotics.

Methods

Items' generation. We comprehensively reviewed the literature to identify published KAP questionnaires about the personal use of antibiotics in the general population. We applied the following search syntax in Medline from inception until September 2018: ((''Anti-Bacterial Agents''[Mesh] OR ''Anti-Bacterial Agents''[Pharmacological Action]) AND (''Surveys and Questionnaires''[Mesh]) AND (''Attitude to Health''[Mesh] OR ''Health Knowledge, Attitudes, Practice''[Mesh] OR ''Knowledge''[Mesh] OR beliefs OR perception OR ''Health Behavior''[Mesh] OR ''Awareness''[Mesh]) AND (misuse or overuse or use or abuse)). We also searched conference papers in the Conference Proceedings Citation Index-Science (CPCI-S) as well as the reference list of relevant studies. In addition, we reviewed reports about the determinants of self-medication with antibiotics as well as aspects of medicine's misuse. Subsequently, we generated a pool of 1591 published items (questions or statements) about 3 dimensions: knowledge, attitudes, or practices towards antibiotics. After removing duplicated or very similar questions, we selected 27 items based on their relevancy to the topic, and tailored their wordings as needed. We also created 11 additional KAP questions in order to draft a comprehensive questionnaire on the mentioned dimensions. We included seven questions about demographic characteristics. The 45-item questionnaire was originally written in English and then forward and backward translated to Spanish/Galician language by bilingual researchers. The translated version of the questionnaire was then reviewed by a native language specialist. The questionnaire was designed using OMR Remark Office software (Remark Office OMR 2014, version 9.2.0.20, GRAVIC, PA, USA).

Content validity. The content validity of the questionnaire is an assessment of the adequateness and the comprehensiveness of the items of the questionnaire to measure the target construct and is routinely performed by a panel of 3–10 experts[22,23].

Our panel of experts consisted of 9 members with experience in questionnaire design and who were specialized in at least one of the following fields: pharmacy, psychology, respiratory medicine, public health, and epidemiology. At first, we provided the panel of experts with the 45-item questionnaire and collected their feedback about the items' clarity, relevance, and ease of understanding as well as the comprehensiveness of the questionnaire. The experts received the Spanish/Galician version of the questionnaire, as Spanish/Galician is their native language. They were also requested to identify deficient areas, suggest any additional potentially relevant item and/or possible answer, and make suggestions for improvement. The questionnaire was then modified by discarding any unnecessary item, rephrasing any ambiguous question, and making the necessary changes in the format. The modified questionnaire was circulated among the panelists for a second evaluation. At this stage, each of the nine experts, evaluated the content of the questionnaire by rating each item, using a 1–4 Likert scale. 1 and 4 represented the lowest and the highest levels of clarity and relevance, respectively. We calculated the Item Content Validity Index (I-CVI) by dividing the number of experts rating that item ≥ 3 by the total number of experts. As our panel consisted of nine experts, items with I-CVI ≥ 0.78 were retained in the questionnaire[24].

We then calculated the Scale Content Validity Index (S-CVI/Ave) which represents the average of I-CVIs of all items of the scale. S-CVI/Ave > 0.90 is considered to reveal a content-valid scale[24].

To take into account the agreement by chance between experts we estimated a modified Kappa (k*)[25]. The probability of agreement by chance (P_c) was calculated using the formula: $P_c = (N/A\ (N - A) \times 0.5^N$, where N is the total number of experts, A is the number of experts that rated the item by ≥ 3. K^* is calculated as follows: $K^* = (I\text{-}CVI - P_c)/(1 - P_c)$[25].

Face validity and pilot testing. Face validity entails an examination of the questionnaire by the research group in order to determine whether the included items are appropriate and relevant and whether the questionnaire measures what it is intended to be measured; i.e. Knowledge, Attitudes and Practices towards antibiotics[22]. Therefore, subsequent to content validity, two members of the group (N.M. and B.T.) subjectively checked the face validity of the questionnaire by reviewing the clarity and the completeness of the questions to measure the target outcome.

The questionnaire was then tested in a sample of 30 adults from the general population who were not related to the medical field. We asked the participants to provide feedback about the clarity and the understandability of the questions, the questionnaire design, the ease of answering and finally on the time taken to answer the questionnaire.

Test–retest reliability. Reliability is concerned with measurement error and it reflects the stability of the measurement process over time[22,26]. Stability is routinely evaluated through test–retest procedure. It involves administering the same questionnaire to the same participants on two occasions, provided that the measured characteristic does not change during the testing period[26]. Since Knowledge and Attitudes are considered stable characteristics over time, we examined the stability of these domains by conducting a test–retest reliability assessment in a sample of 145 adults. The participants were randomly recruited from the administrative staff at the University of Santiago de Compostela, Spain. Participants were unrelated to the health or medical fields. We administered the same questionnaire to the same participants within a 4-week time interval. The participants were informed about the study objective and they agreed to answer the questionnaire on the two occasions.

We assessed the reliability by calculating the Intraclass Correlation Coefficients (ICCs) with their 95% Confidence Interval (CI) relative to the average measure of the two-way mixed-effects model as recommended for test–retest settings[27]. Items with ICC ≥ 0.4 were considered reliable[28].

Construct validity. Construct validity is an assessment of the extent to which a questionnaire measures a target construct, i.e. Knowledge and Attitudes. Factorial validity represents an empirical assessment of the construct validity by applying factor analysis statistical models. A factor is a combination of items that are thought to measure the same dimension or trait (such as knowledge)[22]. This step is carried out when the construct of the questionnaire is intended to measure more than one dimension. The Knowledge and Attitude construct was designed to comprise two dimensions of 17 items. These variables were measured in a 0–10 Likert Scale.

We carried out a Confirmatory Factor Analysis (CFA) to test the construct validity of the questionnaire. CFA assesses the relationships between the items and their corresponding factor. We distributed the questionnaire in a population of 879 adult individuals from the general population. The participants consisted of subjects accompanying a next-of-kin to primary care consultations at the University Hospital of Santiago de Compostela, Spain. All subjects visiting the consultations during the recruitment period that took place between May and December 2019 were contacted. They were informed that the questions are about personal use of antibiotics, and not about the use in the offspring, in order to avoid any misunderstanding.

We structured the factorial model by assigning each item to its specific dimension (factor) according to theoretical grounds[29–32]. We started by distributing the 17 items of the construct into two factors. Items that tested the knowledge about antibiotics' role and specificity were assigned to the Knowledge factor. Items that inspected the agreement of the participants about certain attitudes towards the use of antibiotics and patient-health care provider relationship were placed in the Attitude factor. Subsequently we tested the correlation of the items with their corresponding factors.

We explored the normality of the distribution of each item included in the construct and then undertook CFA using the Maximum Likelihood Robust estimation method. Missing data were handled by applying Full Information Maximum Likelihood (FIML). The factors were standardized by constraining them to a mean of 0 and to a variance of 1. To improve the fit of the model, we inspected standardized residual correlations between items and applied modification indices method in order to better select the items to be added to a factor[13,33]. Standardized factor loadings represent the correlation between an item and its corresponding factor. We ran three CFA and compared the fit of the models against each other.

We assessed the goodness of fit of the models using the following statistics: RSMEA, CFI, TLI and SRMR. We also compared AIC, BIC and aBIC. AIC indicates the relative amount of information lost by a model. Lower AIC values indicate higher quality of the model. BIC is an indicator similar to AIC, however it penalizes the model more than AIC[34].

RMSEA values are considered "excellent" if < 0.06 and acceptable if RMSEA < 0.08. CFI and TLI values ≥ 0.95 indicate excellent fit and values between 0.90 and 0.94 indicate acceptable fit. SRMR values < 0.08 indicate acceptable fit[35].

Questionnaire overall reliability. We calculated Cronbach's coefficient alpha to check the overall reliability of the questionnaire using data collected from the 844 adult individuals[36]. A reliability index ≥ 0.6 is considered acceptable[36,37].

Items and questionnaire acceptability. We explored the acceptability of the questionnaire in the cohort of 879 individuals by calculating the response rate, i.e. the percentage of individuals who accepted answering the questionnaire. We also inspected the item-response rate by computing the percentage of missing data for each item[38–42].

All statistical analyses were carried out using IBM SPSS 20.0. CFA was analyzed with R (version 4.0.0)[43], and R package: lavaan (version 0.6–6)[44].

The flow diagram of the full validation procedure is summarized in Fig. 1.

Ethics. Our study was approved by the ethics committee of the University of Santiago de Compostela (R00002, No. 2019/179). It was also authorized by the Spanish Agency for Medication and Healthcare Products (AEMPS, Reference AFG-ANT-2018-01). The study was conducted in compliance with the general requirements of the ethics committee and with the General Data Protection Regulation (Regulation (EU) 2016/679 and Organic Law 3/2018). Written informed consent form was obtained from the participants and the data were anonymized before analysis.

Data availability

The dataset generated and analysed during the current study is available in the (FigShare) repository, (https://figshare.com/s/d8bbd91b657d9a468aaa).

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Author contributions
N.M. performed the literature review, designed the questionnaire, collected, analyzed, and interpreted the data, and conceived and wrote the manuscript. R.R.-C. participated in data analysis. A.F. and B.T. supervised the questionnaire design. B.T. supervised data analysis and interpretation. All authors reviewed and revised the manuscript and counted responsible for its content.

Competing interests
The authors declare no competing interests.

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Development and validation of a knowledge, attitude and practice questionnaire of personal use of tranquilizers

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ABSTRACT

Background: Tranquilizer misuse is insufficiently acknowledged as a public health problem despite its alarming consequences. Instruments to measure psychosocial factors related to tranquilizer misuse are lacking. We aimed to develop and validate a Knowledge, Attitude and Practice questionnaire of tranquilizer misuse by adults in Spain.

Methods: The questionnaire was designed after an extensive literature review and several meetings with experts. We assessed face and content validity, and pilot tested the questionnaire. We examined its reliability by test-retest analysis in a sample of 145 adults. We distributed the questionnaire to 879 individuals, tested the construct validity through Confirmatory Factor Analysis (CFA), measured its overall reliability and determined its acceptability.

Results: The Item Content Validity Index (I-CVI from 0.78 to 1.00), the Scale Content Validity Index, using the averaging method (S-CVI/Ave = 0.95) and the fact that the modified Kappa statistic for each of the Knowledge, Attitude and Practice items was equal to I-CVI demonstrated the content validity of the questionnaire. The Intra-Class Correlation coefficients for Knowledge and Attitude items were > 0.5, establishing their reliability. The Knowledge and Attitude construct was modeled using CFA and the model showed a good fit, thus establishing its validity. The overall reliability of the construct was revealed by Cronbach's alpha values > 0.6. The questionnaire was highly accepted (response rate = 95 % and item non-response ≤ 4%).

Conclusions: The validity of the developed questionnaire was established. Its availability will stimulate the initiation of research on tranquilizer misuse and will consequently help in designing related public health interventions.

1. Introduction

Tranquilizer misuse, defined as the use of this drug family without prescription or with medical prescription but without complying with the physician's instructions, is highly prevalent worldwide (United Nations Office on Drugs and Crime (UNODC)., 2011, 2019). Tranquilizers represent the third most frequently misused prescription drug in the United States, with a prevalence of 2.2 %, almost identical to that reported for cocaine use (United Nations Office on Drugs and Crime (UNODC)., 2019; Votaw et al., 2019).

Tranquilizers share with illicit drugs the ability to drive to addiction and to generate substance use disorders (Shmulewitz et al., 2015; Poznyak et al., 2018). In the United States, deaths from drug overdose, including tranquilizers, experienced a 10-fold increase between 1999 and 2017, and emergency room visits for benzodiazepine overdose doubled in the same time (Day, 2014; National Institute on Drug Abuse (NIDA), 2021). The co-ingestion of benzodiazepines with other drugs like opioids drastically increases the frequency of deaths by overdose at all ages (Day, 2014; National Institute on Drug Abuse (NIDA), 2021). In Europe, 11 % of the population has used tranquilizers without prescription at some point of their lives (Novak et al., 2016). Tranquilizer

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abuse is also frequent in developing countries (Puangkot et al., 2010; Babakhanian et al., 2012; Nattala et al., 2014; Abbasi-Ghahramanloo et al., 2015; Tabatabaei et al., 2018).

Benzodiazepines are the most frequently misused tranquilizers (United Nations Office on Drugs and Crime, 2019). Although the efficiency of benzodiazepines and the tolerance of their short-term use have been firmly established, these drugs were associated with pharmacological and physiological dependence when used for long term and in high doses (O'Brien, 2005; Ashton, 2005). The use of tranquilizers, such as benzodiazepines, is strongly associated with motor vehicle accidents, falls and fractures due to psychomotor impairment (Brandt and Leong, 2017).

Except from scarce studies that pinpointed the potential role of certain demographic attributes and psychiatric conditions, the determinants of tranquilizer misuse are understudied (Opaleye et al., 2013; Tahiri et al., 2017; Lembke et al., 2018; Votaw et al., 2019).

Knowledge, Attitude and Practices (KAP) questionnaires were widely used in the assessment of psychosocial properties related to the misuse of medicines such as antibiotics (Kosiyaporn et al., 2020; Mallah et al., 2020a,b). KAP questionnaires rely on declarative statements that are designed to gather information about conceptions (i.e., knowledge) and opinions (i.e., attitudes) of a population regarding a specific topic (Médecins du Monde, 2011). As individuals' perception of the risk associated with a certain drug and the social acceptance of that drug influence the decision concerning its use (Von Wartburg, 1984; Mainous et al., 2001), the use of KAP based instruments will help understand individuals' level of knowledge and attitudes towards these drugs. In this line, tranquilizers are generally perceived as safer and more socially accepted drugs than illicit substances (Gilbert et al., 2006; Weyandt et al., 2009; Sirdifield et al., 2017). KAP questionnaires also encompass a series of items about the respondents' performance regarding that topic, such as how the respondents behave in relation to a particular medicine and whether they adhere to the doctor's instructions of use (i.e., practice). Findings generated from KAP questionnaires can help identify psychosocial determinants of a problem and consequently allow to design and assess related intervention programs (World Health Organization (WHO)-Working group on Monitoring & Evaluation., 2014).

Accordingly, we aimed to develop and validate the first questionnaire to explore Knowledge, Attitude and Practices of the general adult population towards the use of tranquilizers. The availability of a validated instrument might help develop studies to measure psychosocial determinants of tranquilizer misuse.

2. Materials and methods

2.1. Setting

The study was undertaken in the general adult population in Galicia, a north-western region of Spain. All participants in the various stages of this study were susceptible of consuming tranquilizers. In Spain, the dispensation of psychoactive drugs is strictly controlled. Nonetheless, self-medication with psychoactive drugs can still take place through the use of old prescriptions or sharing of medicines (Carrasco-Garrido et al., 2014; Busto et al., 2020).

Our study was approved by the Ethics Committee of the University of Santiago de Compostela (R00002, No. 2019/179), and authorized by the Spanish Agency for Medication and Healthcare Products (AEMPS, Reference AFG-ANT-2018-01). It was carried out in compliance with the general requirements of the Ethics Committee and with the General Data Protection Regulation (Regulation (EU) 2016/679 and Organic Law 3/2018).

2.2. Study population

2.2.1. Pilot testing

Data was collected from a sample of 30 adults from the general adult population. Participants were selected from different occupations, unrelated to the medical sector (i.e., accounting, catering industry, hairdressing industry, administration, etc.).

2.2.2. Test-retest reliability

One-hundred fourty-five adults were recruited from the administrative staff of the University of Santiago de Compostela.

2.2.3. Confirmatory factorial analysis (CFA)

Eight-hundred seventy-nine attendants of primary care clinics at the University Hospital Complex of Santiago de Compostela, the largest public hospital in the region of Galicia, were contacted.

2.3. Questionnaire development and validation

The flow diagram of the complete validation procedure is presented in Fig. 1, and the validated questionnaire is available in English and Spanish versions (Supplementary Files S1 and S2). The procedure of each validation step is explained in the subsequent sections.

2.3.1. Item generation

An exhaustive literature review was carried out to identify potential psychosocial determinants of tranquilizer misuse. We searched for potential studies in Medline using the following combination of free-text words: "(tranquilizers) AND ((misuse OR non-medical use OR self-prescription))" from inception of this database until September 2018. Additionally, we searched specific drug classes such as benzodiazepines. We also explored conference papers in the Conference Proceedings Citation Index- Science (CPCI-S) and manually checked the reference lists of related studies. Subsequently, we adapted some questions from previous reports (Helbling et al., 2006; Lazaratou et al., 2007; Lankenau et al., 2012; Martin et al., 2013), inspired from KAP studies about the misuse of other drugs (Mallah et al., 2020a), and carried out several meetings with experts in psychology, pharmacology, public health, medicine and KAP questionnaires in order to develop a comprehensive list of questions.

In KAP questionnaires dealing with medicine misuse, Knowledge and Attitudes are not clearly differentiated constructs. Therefore, the items measuring these variables are usually represented in the same set of questions. Accordingly, the initial questionnaire consisted of 54 items that were distributed in three domains: 1) Knowledge and Attitudes, 2) Practice, and 3) demographic characteristics. The Knowledge and Attitudes domain comprised 26 statements that were designed to measure the participants' knowledge about tranquilizers and their consequences, and the participants' attitudes towards the use of tranquilizers as well as towards the healthcare providers with respect to tranquilizer prescription. The level of agreement with these statements is rated using a 0–10 Likert scale, where 0 and 10 correspond to the lowest and the highest levels of agreement, respectively. For ease of understanding of the 0–10 Likert scale, arrows were inserted above the scale to indicate the direction of agreement and an answered example unrelated to tranquilizer use was provided *(Practicing sports benefits health)*. In addition, to emphasize that these questions (statements) should be answered by both users and nonusers of tranquilizers, the following statement was added *"Please evaluate the statements below **REGARDLESS** of whether you are using tranquilizers **OR NOT**"*.

The Practice domain consisted of a series of 11 questions about the use of tranquilizers in the past two months, the source of tranquilizers (prescription, family, etc.), and about whether the tranquilizers were used according to the physician's instructions with respect to duration, timing and dosage.

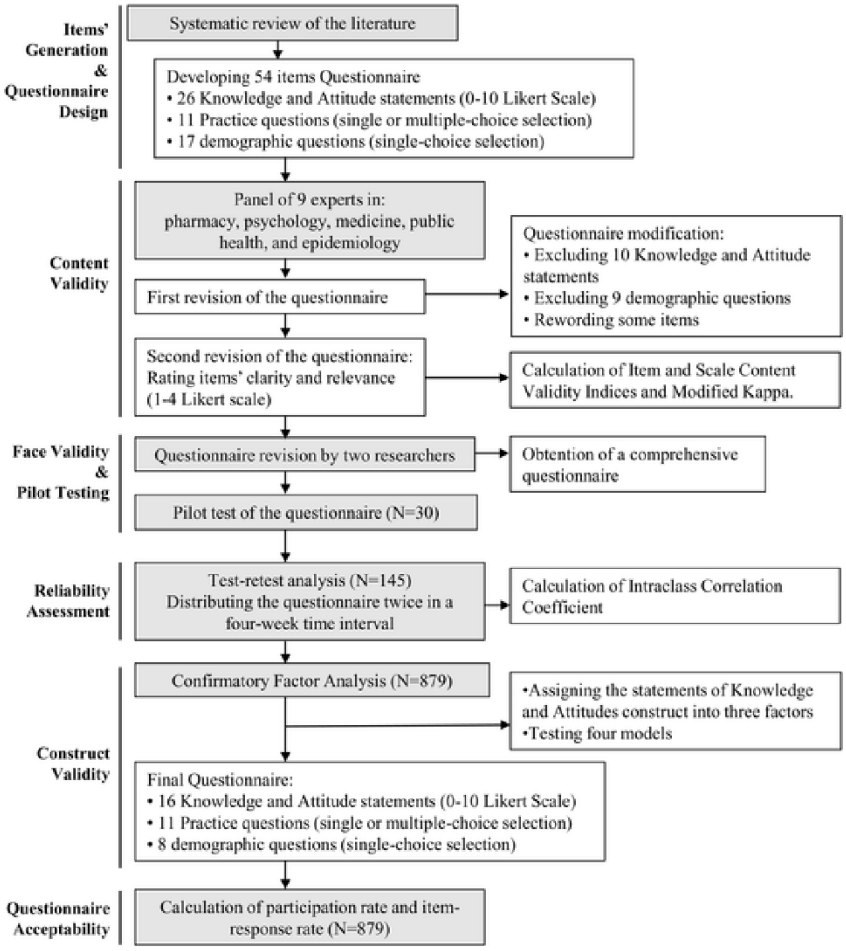

Fig. 1. Flow diagram of the process of questionnaire validation.

The demographic characteristics block included 17 questions about general attributes such as age, gender, educational level, employment status, family size, use of health care system and alcohol consumption.

The questionnaire was originally written in English and then forward and backward translated into Spanish, by bilingual researchers. The translated questionnaire was then reviewed by a native language specialist.

2.3.2. Content validity

A panel of nine experts examined the appropriateness and the comprehensiveness of the questionnaire to measure Knowledge, Attitudes and Practices of the general population towards the use of tranquilizers. The panelists were specialists in at least one of these areas: epidemiology, medicine, pharmacy, psychology and public health.

At first, the panelists were provided with a version of the questionnaire in Spanish, their native language. They were asked to: 1) review the 54-item questionnaire, 2) provide their feedback about the clarity and comprehensiveness of the items, as well as about the questionnaire length, design, and format; 3) identify any deficient questions; and propose new questions or choices for possible answers. Next, items that were considered redundant or unnecessary were removed, and the wording of other questions was tailored. The amended questionnaire was then sent for a second evaluation by the experts. At this stage, the experts were requested to formally assess the relevance and the clarity of each item by rating it on a 4-point Likert scale, where 1 and 4 represented the lowest and highest level of relevancy and clarity. These ratings were used to estimate the Item Content Validity Index (I-CVI) and the Scale Content Validity Index, using the averaging method (S-CVI/Ave). I-CVI is the ratio of the number of experts who rated an item ≥ 3 to the total number of experts. Items with I-CVI ≥ 0.78 were kept in the questionnaire (Polit and Beck, 2006). S-CVI/Ave is the average of I-CVIs of all items in a scale. S-CVI/Ave > 0.90 reflects a content-valid scale (Polit and Beck, 2006). Modified Kappa (K*) was also calculated to explore the agreement by chance between experts, using the formula: $K^* = (I\text{-}CVI - P_c)/(1 - P_c)$; where P_c is the probability of agreement by chance (Polit et al., 2007). $P_c = (N/A\,(N - A) \times 0.5^N$, where N and A represent the total number of experts and the number of those who rated an item ≥3, respectively (Polit et al., 2007).

2.3.3. Face validity and pilot testing

After reviewing content validity, two researchers (NM and BT) reviewed the clarity and the comprehensiveness of the items that formed the KAP questionnaire. Face validity is established when the researchers verify that the items retained in the questionnaire are adequate, relevant, and conclusive to measure the target outcome (McDowell, 2006).

A pilot testing of the questionnaire was undertaken in a sample of 30 adults who were requested to give feedback about item clarity, format, ease of answering, as well as on the length of the questionnaire.

2.3.4. Reliability testing

This step of the validation process entails an assessment of the capability of the questionnaire to generate reproducible measurements over time. Questionnaire stability or reproducibility is routinely explored through a test-retest procedure (DeVellis, 2003; McDowell, 2006). This step was carried out by distributing the questionnaire twice within a four-week time interval to a sample of 145 adults. Participants were aware of the study objective and provided their consent to participate in the reliability testing. The Intraclass Correlation Coefficient (ICC) was estimated with its 95 % Confidence Interval (CI) relative to the average measure, using a two-way mixed-effects model (Shrout and Fleiss, 1979). Only those individuals who answered the questionnaire on the two occasions were considered in the analysis. ICC values ≥ 0.4 reflect an acceptable reliability of the item (Cicchetti and Sparrow, 1981).

2.3.5. Construct validity

To establish the validity of a construct, researchers examine through factorial analysis the extent to which the items of that construct measure a targeted latent variable. In our questionnaire the Knowledge and Attitudes construct was designed to measure knowledge about tranquilizers, and attitudes towards the use of tranquilizers as well as towards the healthcare provider.

CFA was carried out to measure the relation between each item and the assigned factor, as well as the relation between the distinct factors included in the construct. Eight-hundred thirty-six individuals completely answered the questionnaire and were included in the analysis.

The normality of the distribution of the answers to each item included in the construct was inspected and the Maximum Likelihood Robust Estimation method was used to estimate the CFA. The distribution of the answers was standardized by constraining it to a mean of 0 and a variance of 1. Missing data were handled using Full Information Maximum Likelihood (FIML).

The fit of various CFA models was evaluated by examining the change of the χ^2 statistic for the nested models (i.e., χ^2 Difference Test) and the following indexes: Root Mean Squared Error Approximation (RSMEA), accepted if < 0.08; Comparative Fit Index (CFI), accepted if in the range 0.90–0.94; Tucker-Lewis Index (TLI), accepted if in the range 0.90–0.94; and Standardized Root Mean Square Residual (SRMR), accepted if < 0.08 (Little, 2013). Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and sample-size adjusted BIC (aBIC) were also compared to inspect the relative amount of information lost by each model (Vrieze, 2012). A higher quality of the model is achieved when AIC and BIC values are smaller (Vrieze, 2012). To determine the best model that explains the structure of the data, different iterations were made based on modification statistics and theoretical grounds (Little, 1997; Brown, 2006).

2.3.6. Questionnaire and item acceptability

The acceptability of the questionnaire by the general population was determined using the proportion of individuals who accepted answering the questionaire in the sample of attendants of primary care clinics.

The acceptability of each item was also inspected by calculating the proportion of missing answers for that item (Statistical Policy Office, Federal Committee on Statistical Methodology, 2001; Burkell 2003; Galesic and Bosnjak, 2009; Egleston et al., 2011; Rosenberg et al., 2014).

2.3.7. Questionnaire overall reliability

The overall reliability of the questionnaire was tested by calculating Cronbach's alpha coefficient, using data of the completed questionnaires returned by attendants of primary care clinics (N = 836). A reliability index ≥ 0.6 is considered acceptable (Ursachi et al., 2015; Taber 2018).

Statistical analyses were carried out using IBM SPSS Statistics for Windows, Version 20.0: IBM Corp. Armonk, NY, USA, R (version 4.0.0) (R Core Team, 2021), and R package: lavaan (version 0.6–6) (Rosseel, 2012).

3. Results

3.1. Content validity

After the initial revision of the 54-item questionnaire, the panel of experts found that 10 KAP items were redundant and nine demographic questions were not deemed relevant for the Spanish population. Therefore, these 19 items were eliminated from the questionnaire.

The panel reevaluated the amended 35-item questionnaire. The estimated item and scale content validity indices reflected the content validity of the amended instrument with acceptable to excellent I-CVI values that ranged between 0.78 and 1.00, and S-CVI/Ave of 0.95. K* estimates ranged between 0.78 and 1.00. For all items, K* and I-CVI values were equal, providing evidence that the observed agreement between the panelists was not due to chance.

3.2. Face validity and pilot testing

We concluded that the 35-item questionnaire was comprehensive, and that the questions were directly related to the topic, establishing therefore the face validity of the questionnaire (Supplementary Files S1 and S2 and Table 1).

All subjects who participated in the pilot testing answered the questionnaire completely. The participants reported that the questions were easy to understand and that the duration of the questionnaire was adequate (8–10 min).

3.3. Test retest reliability

137 out of 145 participants answered the questionnaire on the two occasions. ICC estimates were > 0.5 for all Knowledge and Attitude items, indicating that these items are reliable and generate reproducible results (Table 1).

3.4. Construct validity

The demographic characteristics of individuals included in the CFA analysis (N = 836) are presented in Supplementary File S1. According to theoretical grounds, we initially allocated the 16 items to two separate factors: Knowledge and Attitude (Model 1). The "Knowledge" factor encompassed those items that measure the participants' level of knowledge about tranquilizers (Q5-Q8 and Q10), while the "Attitude" factor included statements that explore the participants' attitudes towards the use of tranquilizers as well as towards the healthcare provider (Q1-Q4, Q9, and Q11-Q16). Model 1 showed poor fit indicators (Table 2). The inspection of the factor loadings of Model 1 showed that items Q9 and Q14-Q16 did not load significantly on the Attitude factor. A further exploration of the item content and the correlation matrix suggested the creation of a new factor, defined by the partici-

Table 1
Intraclass Correlation Coefficients (ICCs) and 95 % Confidence Intervals (CIs) of the Knowledge and Attitudes items of the questionnaire.

Item	N	ICC (95 % CI)
Q1. I would agree to take tranquilizers in order to sleep better	137	0.84 (0.77, 0.88)
Q2. If I feel better after a few days, I will keep taking my tranquilizers even after completing the prescribed course of treatment	126	0.72 (0.60, 0.80)
Q3. I would take tranquilizers in order to enjoy myself with my family	136	0.77 (0.67, 0.83)
Q4. I would agree to take tranquilizers when I feel down and sad in order to work better	134	0.73 (0.62, 0.81)
Q5. Tranquilizers reduce people's control over what they do	130	0.68 (0.55, 0.78)
Q6. People taking tranquilizers are at increased risk of traffic accidents	136	0.71 (0.59, 0.79)
Q7. Psychotropic drugs (such as tranquilizers) may affect children's learning abilities when prescribed to them	130	0.71 (0.59, 0.80)
Q8. If I feel side effects during a course of treatment of tranquilizers, I should stop taking it as soon as possible	132	0.60 (0.43, 0.71)
Q9. I would take the tranquilizers according to the doctor's instructions	127	0.77 (0.67, 0.84)
Q10. If tranquilizers are consumed in excess, they won't work when they are really needed	129	0.59 (0.42, 0.71)
Q11. I prefer to keep tranquilizers at home in case there is a need for them later	132	0.69 (0.56, 0.78)
Q12. I will trust the doctor's decision if s/he decides to prescribe or not prescribe tranquilizers	135	0.82 (0.74, 0.87)
Q13. If I believe that I need a tranquilizer and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	135	0.53 (0.34, 0.67)
Q14. I think that doctors often explain clearly to the patients the reasons for prescribing or not prescribing tranquilizers	131	0.65 (0.51, 0.75)
Q15. I think that doctors often explain clearly to the patients the instructions for the use of tranquilizers	130	0.63 (0.47, 0.74)
Q16. I think that, when dispensing tranquilizers, the pharmacists tell the customers about the importance of correct therapeutic compliance/adherence	126	0.650.51, 0.76)

N: number of participants who answered the questionnaire on the two occasions.

pants' attitude towards healthcare provider with respect to the prescription and recommendations of tranquilizers use.

Accordingly, in a new model (Model 2), the items of the "Attitude" factor of Model 1 were subdivided into two factors. The Q1-Q4, Q11 and Q13 were attributed to the factor "Attitudes Personal" while Q9, Q12 and Q14-Q16 were assigned to a factor labeled "Attitudes Patient-healthcare provider". In Model 2, the items loaded significantly on their respective factors (Knowledge, Attitudes-Personal, and Attitudes Patient-healthcare provider). The model fit indicators improved but did not reach acceptable fit (Table 2). The exploration of the modification statistics indicated that the specification of the model could be improved by correlating the residuals of some items inside the factors. Thus, Model 3 included the structure of Model 2 and the correlation of the residuals Q3-Q4 ($r_{Q14\text{-}Q15} = 0.76$, $p < 0.001$) and Q14-Q16 ($r_{Q14\text{-}Q16} = 0.34$, and $r_{Q15\text{-}Q16} = 0.35$, both $p < 0.001$). Although the χ^2 Difference Test indicated a significant reduction in the magnitude of χ^2 in Model 3 and better fit statistics than Model 2 (Table 2), Model 3 needed to be better specified (according to fixed statistics). A further analysis based on item content and modification statistics suggested a new model (Model 4) with a cross-load of item Q13 on the two Attitude factors (i.e., Personal and Patient-healthcare provider). This change was perfectly adequate since item Q13 includes information of both Attitude factors (i.e., *"If I believe that I need a tranquilizer and the doctor did not prescribe it, I will get it at the pharmacy without a prescription"*).

Model 4 was the final model selected with the best specification of the current study data. In particular, the χ^2 Difference Test indicated a significant reduction on the magnitude of χ^2 with respect to Model 3, and the model fit indicators were acceptable (CFI = 0.93, TLI = 0.92, RSMEA = 0.054, SRMR = 0.05) (Fig. 2 and Tables 2 and 3). Comparing with the rest of models, Model 4 had also the lowest AIC, BIC and aBICR (Table 2). At item level, all the items loaded significantly on their respective factors (Table 3). At factor level, "Knowledge" and "Attitude Personal" were negatively related ($r = -0.60$, $p < 0.0001$), and "Attitude-Personal" and "Attitudes Patient-healthcare provider" were positively related ($r = 0.24$, $p < 0.038$).

3.5. Questionnaire and item acceptability

A total of 836 participants (95 %) accepted to answer the questionnaire and returned it completed, revealing a high acceptability by the population. Fourty-three approached individuals did not agree to participate.

The proportion of unanswered questions ranged between 1 % and 4 %, indicating an acceptable item non-response rate.

3.6. Questionnaire overall reliability

Using data collected from 836 attendants of primary care clinics, the reliability assessment showed that the three factors of the Knowledge and Attitudes construct are reliable: Knowledge (Cronbach's alpha = 0.65), Attitude Personal (Cronbach's alpha = 0.72), and Attitude Patient-healthcare provider (Cronbach's alpha = 0.65).

4. Discussion

In this study, we assessed the validity of the first KAP questionnaire aimed at measuring the level of *knowledge* and identifying *attiudes* related to *practices* of tranquilizers misuse.

The results of the validation tests of the questionnaire demonstrated its face and content validity, reproducibility, reliability, construct validity and acceptability. The test-retest *reliability* assessment of the Knowledge and Attitude items of the questionnaire showed that all the 16 items can generate reproducible measurements. The *construct validity* showed that the theoretical distribution of all items adequately fits the model, as reflected by the fit indicators and by the standardized estimates of factor loadings (Brown, 2006). The structure of the data suggested three differentiated dimensions: Knowledge, Personal Attitudes and Attitudes towards patient-healthcare provider. Although both attitude dimensions were significantly related, their structures are distinct.

Similarly, previous validation studies that used KAP questionnaires to assess the compliance of medications (i.e., antibiotics) indicated two different components for attitudes towards the use of medications (Mallah et al., 2020a). In this regard, our results are in line with previous research that underlined the importance of the patient-healthcare provider's trust in achieving an adequate therapeutic compliance (Brown et al., 2016; Chandra et al., 2018). In addition, in line with previous studies (Allum et al., 2008; ul Haq et al., 2012), the latent structure of our data presented a strong relation between the "Knowledge" and "Personal Attitude" dimensions. Previous reports suggested an existing association between the two dimensions in the specific context of self-medication and misuse of medicines (Mallah et al., 2020a,b). Fi-

Table 2
Test differences and fit indicators for the four tested models.

	χ^2	df	p	$\Delta\chi^2$	Δdf	CFI	TLI	RSMEA (90% CI)	SRMR	AIC	BIC	aBIC
Model 1	1939.22	103	<.001			0.47	0.39	0.146 (0.140, 0.152)	0.13	63,586	63,818	63,662
Model 2	613.21	101	<.001	1326.01	1	0.85	0.83	0.078 (0.072, 0.084)	0.07	62,264	62,505	62,343
Model 3	400.25	97	<.001	212.96[1]	4	0.91	0.89	0.061 (0.055, 0.067)	0.06	62,059	62,319	62,145
Model 4	332.59	96	<.001	67.66[1]	1	0.93	0.92	0.054 (0.048, 0.061)	0.05	61,994	62,258	62,081

[df] = Degree of freedom; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index; RSMEA = Root Mean Square Error Approximation; CI = Confidence Interval SRMR = Standardized Root Mean Square Residual; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; aBIC = Sample-size adjusted Bayesian (BIC).
Model 1 included two factors: Knowledge and Attitudes.
Model 2 encompassed three factors: Knowledge, Attitude personal and Attitudes patient-healthcare provider.
Model 3 consisted of the three factors and residuals of similar items were correlated.
Model 4 also comprised the three factors, with correlation of residuals between similar items and cross loading of item q13.
[1]$\chi 2$ Difference Test is significant at $p < 0.001$.

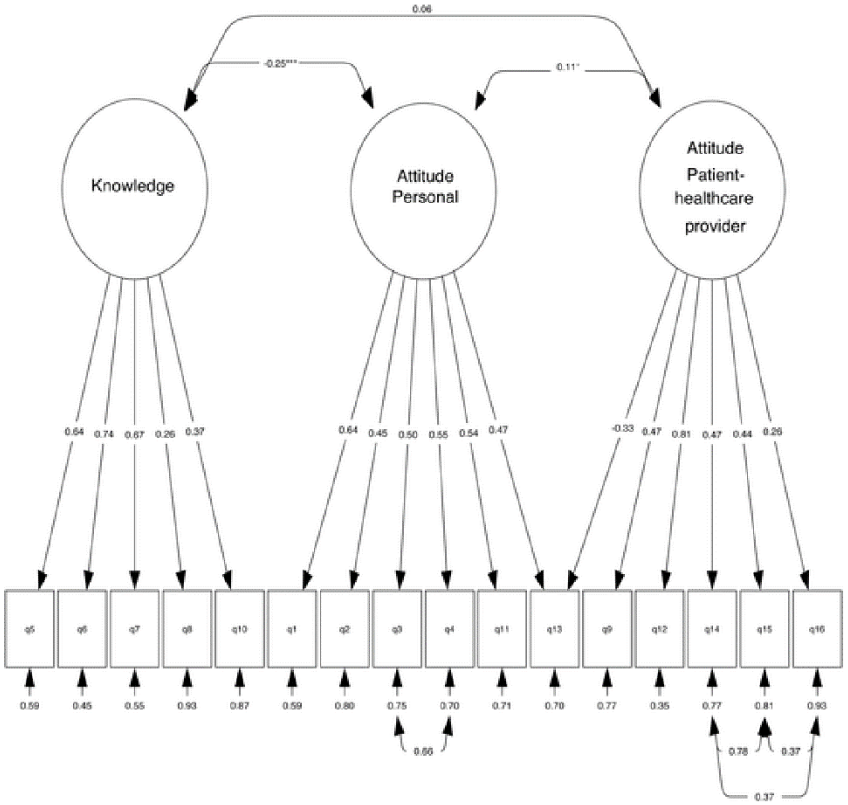

Fig. 2. Confirmatory Factorial Analysis model of the Knowledge and Attitudes construct of the questionnaire. The model includes three factors (Knowledge, Attitude-personal and Attitude patients-healthcare provider) that are represented with their corresponding items, the standardized loading of these items and their residuals. The correlation between an item and its corresponding factor(s) is represented by a single headed arrow. The correlation between factors is indicated by double-sided arrows. The asterisks represent the level of significance: *** and * correspond to p-values < 0.0001 and < 0.01, respectively.

nally, the absence of a significant correlation between the dimensions "Knowledge" and "Attitude Patient-healthcare provider" confirms that the items included in these factors measure distinct and unrelated variables.

In addition to the questionnaire's latent structure, at item level, the best fitted structure model included a cross-load of item q13 "If I believe that I need a tranquilizer and the doctor did not prescribe it, I will get it at the pharmacy without a prescription" on the two attitude factors (i.e., personal and patient-healthcare provider). This could be explained by the fact that the patient's tendency to use tranquilizers without a prescription is due to both the patient's personal attitude towards the drug and to the patient's low degree of confidence in the

Table 3
Standard loading estimates of the Knowledge and Attitudes items on their respective factors.

Item	Loading estimate	Standard Error	P-value	Standard loading estimate
Knowledge				
Q5. Tranquilizers reduce people's control over what they do	1.32	0.07	<0.0001	0.64
Q6. People taking tranquilizers are at increased risk of traffic accidents	1.31	0.06	<0.0001	0.74
Q7. Psychotropic drugs (such as tranquilizers) may affect children's learning abilities when prescribed to them	1.15	0.06	<0.0001	0.67
Q8. If I feel side effects during a course of treatment of tranquilizers, I should stop taking it as soon as possible	0.57	0.08	<0.0001	0.26
Q10. If tranquilizers are consumed in excess, they won't work when they are really needed	0.65	0.06	<0.0001	0.37
Attitude Personal				
Q1. I would agree to take tranquilizers in order to sleep better	1.38	0.08	<0.0001	0.64
Q2. If I feel better after a few days, I will keep taking my tranquilizers even after completing the prescribed course of treatment	0.71	0.06	<0.0001	0.45
Q3. I would take tranquilizers in order to enjoy myself with my family	0.96	0.06	<0.0001	0.50
Q4. I would agree to take tranquilizers when I feel down and sad in order to work better	1.10	0.06	<0.0001	0.55
Q11. I prefer to keep tranquilizers at home in case there is a need for them later	1.20	0.08	<0.0001	0.54
Q13. If I believe that I need a tranquilizer and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	0.66	0.06	<0.0001	0.47
Attitudes patient-healthcare provider				
Q9. I would take the tranquilizers according to the doctor's instructions	0.88	0.08	<0.0001	0.48
Q12. I will trust the doctor's decision if s/he decides to prescribe or not prescribe tranquilizers	1.60	0.13	<0.0001	0.81
Q13. If I believe that I need a tranquilizer and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	−0.55	0.07	<0.0001	−0.33
Q14. I think that doctors often explain clearly to the patients the reasons for prescribing or not prescribing tranquilizers	1.03	0.06	<0.0001	0.48
Q15. I think that doctors often explain clearly to the patients the instructions for the use of tranquilizers	0.92	0.06	<0.0001	0.44
Q16. I think that, when dispensing tranquilizers, the pharmacists tell the customers about the importance of correct therapeutic compliance/adherence	0.61	0.08	<0.0001	0.26

treating physician. In addition, the best fitted model included items that shared information which was not included in the latent factor (i.e., correlated residuals). For example, the correlated residuals of items q3 and q4 might indicate that both items included the use of tranquilizers as mood regulation (i.e., q3- "… in order to enjoy myself…", q4- "…when I feel down and sad …"). Similarly, the correlation of the residuals between items q14 to q16 might be explained by the fact that these items measured the role of the health professional in explaining the motives for prescribing tranquilizers or not, and in elucidating the importance of the correct use of these drugs (i.e., q14 and q15 "Doctors often explain…", and q16 "…the pharmacists tell the customers…"). Item loadings on more than one factor and correlated errors between items are expected findings in questionnaires with multidimensional construct (Kline, 2015).

Our questionnaire has many strengths; first, it was directed to users and non-users of tranquilizers as the Knowledge and Attitudes items were designed to be completed by both groups of participants, allowing therefore to having data of a comparison group, a fundamental issue in epidemiological studies; second, the questionnaire established a specific time limit for the exposure to tranquilizers (last two months), an essential parameter to control for the risk of recall bias. Specifying the duration of the last exposure to tranquilizers also permits external validation of the results and better comparison between findings from different studies; third, the questionnaire was designed to uncover all possible aspects of misuse of tranquilizers (e.g., use without medical prescription, storing/sharing leftovers, shortening the course of treatment, or changing the timing or dosage), allowing therefore a more exhaustive ascertainment of the misuse; fourth, providing a straightforward and comprehensive choice of answers decreased the possibility of leaving a question unanswered. Indeed, the high participation and response rates obtained in our study reveal that the questionnaire is highly accepted by the general population. Some conditions that were considered during the questionnaire development have contributed to these high participation and response rates. These conditions include the length of the questionnaire, which was optimal (8–10 min), the clarity and simplicity of the questions, and the presentation of the questionnaire by an academic institution (Burchell and Marsh, 1992; Edwards et al., 2002; Revilla and Ochoa, 2017; Peer Research Center, 2021).

This questionnaire has some limitations. First, we were not able to assess the concurrent validity due to the absence of previously validated instruments, or *gold standard*, to which we could compare our instrument. Second, the study was limited to the Spanish population. Thus, this instrument would benefit from an adaptation process, beyond that of a simple translation, in different populations and settings.

The availability of a validated questionnaire is of outmost importance to epidemiologic studies that aim to identify psychosocial determinants related to the misuse of tranquilizers, as the use of non-validated questionnaires represents a source of measurement error. Our questionnaire was translated, and pilot tested in three additional languages: English, Arabic and French. After minor adaptations in the demographic questions, the questionnaire was successfully administered to the general population of a developing country (data not shown).

Our questionnaire may prove useful in settings that are different from the one where it was developed.

We believe that we have provided a useful tool to encourage future research initiatives to understand better the psychosocial determinants of tranquilizer misuse and to design awareness and prevention programs. Tranquilizer misuse is an internationally growing public health concern that has affected both developing and developed countries, and the presence of a validated instrument will help launching relevant epidemiological studies.

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None declared

Author contributions

NM carried out the literature review, designed the questionnaire, collected, analyzed, and interpreted the data, and conceived and wrote the manuscript. RR-C participated in data analysis. AF and BT supervised the questionnaire design. BT supervised data analysis and interpretation. All authors reviewed and revised the manuscript and counted responsible for its content.

Data availability

The datasets generated and used in the analyses undertaken in this study are available in the data repository FigShare at the following weblink:

https://figshare.com/s/ccc709e6cf66609e7f5d

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Uncited references

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Declaration of Competing Interest

All authors have no conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2021.108730.

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PLOS ONE

RESEARCH ARTICLE

Association of knowledge and beliefs with the misuse of antibiotics in parents: A study in Beirut (Lebanon)

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Abstract

Background

Antibiotic resistance is a major public health concern. It has been associated with factors such as uncontrolled consumption, lack of knowledge, beliefs, and sociodemographic characteristics. Lebanon is characterized by high levels of antibiotic misuse, as almost half of the population self-medicates with antibiotics and over 30% of the antibiotics are dispensed without prescription. To-date, no studies determined adequately the association between knowledge, beliefs and antibiotic misuse in Lebanon.

Objective

To assess the association between level of knowledge and beliefs about antibiotics, and antibiotic misuse in Lebanon.

Methods

We conducted a cross-sectional study among 1,421 parents of schoolchildren using an anonymous self-administered Knowledge, Attitude and Practices questionnaire. The participants´ level of agreement with each item of knowledge and beliefs was measured using a Likert-type (0–10) scale. Misuse practices in the last month were detected through a series of questions aimed at determining the level of compliance with physicians´ instructions in terms of dosage and duration. Data were analyzed using logistic regression.

Results

277 participants (16%) acknowledged using antibiotics in the previous month, 41% of whom showed at least one misuse behavior. Misconceptions and beliefs about antibiotics substantially increased the odds of their misuse. For instance, participants who believed that antibiotics were effective in treating viruses, cold, or sore throat infections were twice as likely to misuse antibiotics [Adjusted Interquartile Odds Ratio (aIqOR): 2.08 (95%CI: 1.32, 3.19), aIqOR: 1.81 (95%CI: 1.41, 2.29), aIqOR: 2.19 (95%CI: 1.61, 2.93), respectively]. Parents

who usually keep antibiotics at home antibiotics for future use were more likely to misuse antibiotics [aIqOR: 2.44 (95%CI: 1.68, 3.46)].

Conclusions

Our findings indicate that the low level of knowledge and the existence of erroneous beliefs about antibiotics are associated with increased odds of antibiotic misuse. Key elements including rationale prescription and control of dispensing should be addressed when designing educational campaigns against antibiotic misuse.

Introduction

Antibiotic resistance is a growing global public health concern, with heavy economic and social burdens. Antibiotic-resistant bacteria cause 700,000 deaths per year worldwide, and it is predicted that resistance will be more lethal than cancer by 2050. [1] The misuse of antibiotics through excessive medical prescriptions and self-medication is an extremely important cause of antibiotic resistance. Indeed, the global consumption of antibiotics increased by 65% between 2000 and 2015, and this steadily increasing trend is mainly observed in low- and middle-income countries. [2] The majority of these antibiotics are consumed outside hospitals, and self-medication with antibiotics is common practice worldwide, except in northern Europe and North America where it is strictly regulated. [3] To prevent further expansion of antibiotic resistance, regional and global action plans were initiated and were mainly based on improving awareness tools that took into consideration critical criteria such as demographic characteristics of consumers, as well as their level of knowledge and beliefs with regard to antibiotic misuse. [4–8]

Population mobility is another important factor contributing to the globalization of the antibiotic resistance threat, as international travelers disseminate resistant bacteria across geographical boundaries. [3, 9–10] In that regard, Lebanon is a country with high immigration rate which has been receiving millions of refugees, mainly from neighboring Arab countries where antibiotic misuse is also very frequent. [11] Antibiotic use and dispensing without medical prescription are frequent in Lebanon. [12–15] Consequently, it is of utmost importance to implement measures that would improve the rational use of antibiotics in the country. Therefore, in the current study, we aimed at determining, through measures of association, the relation between the level of knowledge and beliefs about antibiotics and different aspects of antibiotic misuse in Lebanon. This could prove useful in designing educational campaigns oriented to enhance the awareness towards antibiotics and their rationale use.

Materials and methods

Study setting

A complete list of all private and public schools in the Beirut area was compiled and an invitation to participate in our study was sent to each school's administration. 11 schools accepted our invitation and the parents of schoolchildren attending those schools were enrolled in this study and were provided with a printed copy of the questionnaire.

Our study was authorized by the Lebanese Ministry of Education and Higher Education and approved by the Institutional Review Board at the American University of Science and Technology (AUST-IRB-20180202-01).

Sample size calculation

We calculated the sample size based on the following assumptions: alpha = 0.05, power: 0.8, ratio exposed/non exposed: 2, Odds Ratio to be detected: 2. With these assumptions, the needed number of respondents was 1052 subjects.

Data collection

Schools were contacted by telephone or electronic mail, or were visited, in order to explain the study purpose and obtain the approval of schools' directors to circulate the questionnaire among the community of parents. Before delivering it to parents, the questionnaire was reviewed by the board at every school, and parents were informed about the study objectives and the expected delivery date of the questionnaire by the director's office.

As the questionnaire was anonymous, a written informed consent was neither necessary nor reasonable as it would have defeated the objective of anonymity. We therefore placed the following statement in the first page of the questionnaire (S1 File): "By sending this questionnaire back to us with your answers, you are giving your consent to participate in this study." In the introduction of the questionnaire, we also stated: "You will NOT be asked about your name, address or any other information that reveals your identity. In addition, the answers received from all participants will be pooled into an anonymized database, where all given information will be kept confidential and will be eliminated at the end of the study."

The questionnaire was then delivered to the parents in the main two languages of instruction used at the school (Arabic and English, or Arabic and French). A questionnaire was delivered to every household in a sealed envelope given to only one child of the family attending the school. Only one of the parents (either the mother or the father) was requested to answer the questionnaire. The parents were also notified about the questionnaire delivery in the same day in order to assure that they received the questionnaire. An extensive follow up was conducted to maximize the response rate. Questionnaires were collected five days after they were provided to parents.

Data were collected at different time points: November 2018 and January 2019. The corresponding dataset is available in the data repository FigShare https://doi.org/10.6084/m9.figshare.9929897.v1

Measures

We selected relevant items from published questionnaires that preferably underwent a validation process previously. [5, 16–19] In addition, to identify the most frequent misuse practices, as well as the knowledge and beliefs factors that might be related to these practices, three focus group sessions were held with a total of 18 parents of schoolchildren of different demographic characteristics. Health professionals were excluded from the focus groups. The items were then selected, tailored whenever required for better comprehension and/or better suitability for the Lebanese population, and new questions were developed and added. Subsequently, experts in pharmacology, psychology, epidemiology and professionals with experience in the design of Knowledge, Attitude and Practice (KAP) questionnaires reviewed the face and content validity of the questionnaire in order to ensure that the items designed tackled all aspects of antibiotic misuse in Lebanon. Syntax of questions was altered accordingly.

Using antibiotics without medical prescription, shortening the duration of treatment with antibiotics, saving or sharing leftover antibiotics, skipping a dose of antibiotics or changing the prescribed dose were considered as practices of antibiotic misuse.

The level of agreement with the knowledge and beliefs statements was measured using a scale of zero (total disagreement) to 10 (total agreement). For the items assessing attitude to

antibiotics and demographic characteristics, respondents were given a set of possible answers to choose from. The questionnaire was initially written in English then translated forward and backward by bilingual researchers into Arabic and French languages. The questionnaire was designed using Remark Office OMR software (Remark Office OMR 2014, version 9.2.0.20) to allow for automated optical reading of the data, thereby minimizing errors during data entry. The English version of the questionnaire is available as an online supplement (S1 File). Subsequently, a pilot testing of the questionnaires was conducted on 20 parents to identify any comprehension-related issues and adjust the syntax accordingly.

Statistical analysis

To assess the reproducibility of the instrument, the questionnaire was administered to 60 subjects on two occasions, with a four-week interval. The intraclass correlation coefficients (ICCs) with their 95% CI and the weighted kappa indexes were calculated for variables with 0–10 scale outcomes and for nominal variables, respectively. Items showing an ICC value or weighted kappa index ≥ 0.4 were considered acceptable and retained in the final questionnaire.

In this study, six different outcomes were used to assess the misuse of antibiotics. The first outcome assessed antibiotic use without medical prescription and was determined by asking the following question "Q20. Who prescribed or recommended the use of antibiotics to you?". The second outcome addressed the shortening of antibiotic therapy and was assessed through the question "Q21. The last time you had to take antibiotics; did you complete the course of treatment?". The third outcome assessed whether unused antibiotics were saved or shared, using the question "Q22. What did you do with the antibiotics that were left unused?". The fourth outcome assessed whether in case of a missed dose, the subsequent one was doubled or taken when remembered. The question used was "Q24. What did you do when you skipped a dose of your antibiotics?". The fifth outcome assessed whether the parent modified the dose without medical advice and whether it was an increase or a decrease in the dose. We used two questions: "Q25. The last time you had to take antibiotics, did you change the dose on your own (without medical advice)" and "Q26. What did you do when you changed your dose of antibiotics on your own (without medical advice)?". In the sixth outcome, the occurrence of any of the previously mentioned five misuse behaviors was evaluated.

The independent variables consisted of each item of knowledge, attitude or behavior included in the questionnaire. Covariates included age, sex, financial status, educational level, area of residence, alcohol consumption, access to medical care facilities, and frequency of telephone medical consultation.

Associations between independent variables and misuse of antibiotics were modeled using multiple logistic regression. Potential confounders were introduced consecutively into the model, and those that modified the value of the adjusted odds ratio by at least 10% were retained in the final model. Only individuals with complete data on the variables included in the model were analyzed. Finally, the adjusted interquartile odds ratio (aIqOR) were calculated to measure the effect of the exposure change from the 25th to the 75th percentile.

Results

Out of 4,460 questionnaires distributed, a total of 1,460 (32.7%) were answered by the parents. 39 questionnaires were excluded as they were incompletely answered. We observed that these 39 excluded subjects had very low educational level (unschooled or primary education). The demographic characteristics of the parents included in the analysis are indicated in Table 1.

In our study population, 64.1% of the participants did not always consult the doctor when they were sick; 8.9% of them due to financial reasons and 34.3% because of a lack of time.

Table 1. Participants' demographic characteristics.

	Characteristic	Total (N = 1421)	Any Misuse in the last month (N = 94)
Gender			
	Male	276 (19.4%)	22 (23.4%)
	Female	1092 (76.8%)	69 (73.4%)
	Missing	53 (3.7%)	3 (3.2%)
Age			
	<38 years	355 (25.0%)	37 (39.4%)
	39–42 years	227 (16.0%)	14 (14.9%)
	43–47 years	313 (22.0%)	13 (13.8%)
	> = 48 years	259 (18.2%)	14 (14.9%)
	Missing	267 (18.8%)	16 (17.0%)
Marital status			
	Married	1327 (93.4%)	87 (92.6%)
	Other	74 (5.2%)	6 (6.4%)
	Missing	20 (1.4%)	1 (1.1%)
Educational level			
	Until high school	252 (17.7%)	31 (33.0%)
	University	1157 (81.4%)	62 (66.0%)
	Missing	12 (0.8%)	1 (1.0%)
Spouse educational level			
	Until high school	313 (22.0%)	36 (38.3%)
	University	1028 (72.3%)	53 (56.4%)
	Missing	80 (5.6%)	5 (5.3%)
Number of family members			
	2–4	555 (39.1%)	36 (38.3%)
	5–6	715 (50.3%)	50 (53.2%)
	>6	129 (9.1%)	6 (6.4%)
	Missing	22 (1.5%)	2 (2.1%)
Family income			
	<500$	21 (1.5%)	2 (2.1%)
	500$ - 1499$	260 (18.3%)	34 (36.2%)
	1500–2500$	223 (15.7%)	17 (18.1%)
	>2500$	808 (56.9%)	36 (38.3%)
	Missing	109 (7.7%)	5 (5.3%)
Consulting a doctor			
	Rarely or never	155 (10.9%)	8 (8.5%)
	Sometimes	756 (53.2%)	63 (67.0%)
	Always	493 (34.7%)	22 (23.4%)
	Missing	17 (1.2%)	1 (1.1%)
Reasons for not always consulting a doctor			
	No need	390 (27.4%)	24 (25.5%)
	Fear	29 (2.0%)	2 (2.1%)
	No money	127 (8.9%)	20 (21.3%)
	No time	321 (22.6%)	26 (27.7%)
	Long waiting time	166 (11.7%)	15 (16%)
	No near clinic	53 (3.7%)	4 (4.3%)
Ever received medical consultation over the phone			
	No	491 (34.6%)	30 (31.9%)

(*Continued*)

Table 1. (Continued)

	Characteristic	Total (N = 1421)	Any Misuse in the last month (N = 94)
	Yes	892 (62.8%)	62 (66%)
	Missing	38 (2.7%)	2 (2.1%)

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More than 60% of the respondents tended to consult the doctor over the phone and 27% believed that there was no need for always visiting the doctor.

Patterns of antibiotic misuse

In the month preceding the study, 277 (16%) parents had used antibiotics and 94 (41.4%) of them had shown at least one misuse behavior. The most frequent misuse behaviors consisted in using antibiotics without medical prescription (22.5%), keeping antibiotic leftovers for future use or sharing them with other individuals (22%), and doubling the dose of antibiotics or taking it when remembered, in case a dose was skipped (10.6%). The associations between the items of knowledge and beliefs with each pattern of misuse of antibiotics were calculated after adjusting for gender and age. These variables were kept in the final model due to their biologic relevance and their known potential for confounding in epidemiologic studies. These associations are presented below.

Misconceptions and misbeliefs about the function of antibiotics is associated with their misuse

Parents who thought that antibiotics were effective against viruses were twice as likely to present any of the antibiotic misuse behaviors [aIqOR: 2.08 (95% CI: 1.32, 3.19)] (Table 2). This misconception was strongly associated with using antibiotics without medical prescription [aIqOR: 2.83 (95% CI: 1.61, 5.33)], shortening the course of treatment [aIqOR: 2.66 (95% CI: 1.07, 6.27)], and modifying the dose without medical advice [aIqOR: 5.94 (95% CI: 1.23, 28.04)] (Table 3).

Parents who thought antibiotics treat colds were at substantially higher odds of any misuse behavior [aIqOR: 1.81 (95% CI: 1.41, 2.29)] (Table 2). Specifically, they were more prone to use antibiotics without prescription [aIqOR: 2.29 (95% CI: 1.69, 3.22)], stop taking antibiotics as soon as they felt better [aIqOR: 2.36 (95% CI: 1.52, 3.73)], double the subsequent dose of antibiotics or postpone their intake when forgotten [aIqOR: 1.94 (95% CI: 1.26, 3.13)], store unused antibiotics or share them with other individuals [aIqOR: 2.22 (95% CI: 1.57, 3.04)], and modify doses without medical advice [aIqOR: 4.42 (95% CI: 2.14, 9.38)] (Table 3).

The odds of misusing antibiotics were more than twice higher among parents who usually take antibiotics when they suffer from a sore throat [aIqOR: 2.19 (95% CI: 1.61, 2.93)] (Table 2). These parents were three times as likely to self-prescribe antibiotics [aIqOR: 3.30 (95% CI: 2.29, 5.00)]. Moreover, they were more susceptible to shortening the course of treatment [aIqOR: 2.19 (95% CI: 1.22, 3.86)], changing the prescribed dose of antibiotics [aIqOR: 4.01 (95% CI: 1.69, 9.54)], and saving the unused antibiotics or sharing them with someone [aIqOR: 2.10 (95% CI: 1.40, 3.05)] (Table 3).

Storage of leftover antibiotics and self-prescription are related to antibiotic misuse

Participants who usually keep antibiotics at home for future use were more than twice as likely to misuse antibiotics [aIqOR: 2.44 (95% CI: 1.68, 3.46)] (Table 2). They were even at higher odds of using antibiotics without medical prescription [aIqOR: 3.64 (95% CI: 2.19, 6.05)], and

Table 2. Association of knowledge and attitudes with any misuse of antibiotics in 1392 parents of schoolchildren.

Knowledge or attitude statements	Percentile of responses			No misuse (N)	Any Misuse (N)	aIqOR* (95% CI)
	25%	50%	75%			
Antibiotics are effective against viruses	0	4	7	1171	86	2.08 (1.32, 3.19)
Each type of infection needs a different antibiotic	8	10	10	1174	87	1.17 (0.94, 1.44)
Antibiotics can kill the bacteria that normally live on the skin and in the gut	5	8	10	1138	85	1.16 (0.77, 1.61)
If antibiotics are consumed in excess, they won't work when they are really needed	8	10	10	1168	85	0.96 (0.81, 1.14)
When I get a cold, I take antibiotics to help me feel better faster	0	0	4	1187	88	1.81 (1.41, 2.29)
I expect my doctor to prescribe antibiotics if I suffer from common cold or flu symptoms	0	5	9	1180	88	1.42 (0.91, 2.36)
When I have a sore throat, I prefer to use an antibiotic	0	0	5	1187	88	2.19 (1.61, 2.93)
If I feel side effects during a course of treatment of antibiotics, I should stop taking them as soon as possible	5	9	10	1170	86	1.40 (0.95, 2.01)
It is good to be able to get antibiotics from relatives or friends without having to see a medical doctor	0	0	0	1186	88	1.00 (1.00, 1.00)
I take the antibiotics according to the doctor's instructions	10	10	10	1186	86	1.00 (1.00, 1.00)
I prefer to keep antibiotics at home in case there is a need for them later	0	2	6	1181	86	2.44 (1.68, 3.46)
I trust the doctor's decision if s/he decides to prescribe or not prescribe antibiotics	8	9	10	1183	87	0.88 (0.76, 1.04)
If I believe that I need an antibiotic and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	0	0	2	1180	87	1.51 (1.35, 1.72)
Doctors often explain clearly to the patient the reasons for prescribing or not prescribing antibiotics	5	7	9	1180	86	0.75 (0.57, 1.00)
Doctors often explain clearly to the patient the instructions for the use of antibiotics	5	8	10	1179	86	0.66 (0.47, 0.90)
When you buy antibiotics, the pharmacist tells you about the importance of correct therapeutic compliance/adherence	3	6	9	1181	87	1.27 (0.83, 1.87)

(*): adjusted for gender and age

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modifying the dose of antibiotics without any prior medical advice [aIqOR: 5.05 (95% CI: 1.59, 16.78)] (Table 3).

Similar results were obtained for subjects who tends to buy antibiotics without medical prescription when they believe that they need a drug-based treatment that the physician did not prescribe (Tables 2 and 3).

Patient-physician adequate communication is associated with a lower frequency of antibiotic misuse

Parents who believed that the physician explained clearly the motives for prescribing or not prescribing antibiotics were less likely to use antibiotics without medical prescription [aIqOR: 0.63 (95% CI: 0.43, 0.92)] (Table 3). The pattern was similar when parents believed that the physician explained clearly the instructions of use of antibiotics. These parents were less likely to misuse antibiotics in general [aIqOR: 0.66 (95% CI: 0.47, 0.90)] and to self-medicate with antibiotics [aIqOR: 0.59 (95% CI: 0.37, 0.90)] (Tables 2 and 3).

Table 3. Association of knowledge and attitudes with the different aspects of antibiotic´s misuse in parents of schoolchildren.

Knowledge or attitude statements	Unprescribed use (N = 1,361)		Shortened treatment (N = 1,376)		Changed dose (N = 1,293)		Improper action when skipping a dose (N = 1,295)		Storing or sharing leftovers (N = 1,298)	
	Events №	alqOR* (95%CI)	Events №	alqOR* (95%CI)	Events №	alqOR* (95%CI)	Events №	alqOR* (95%CI)	Events №	alqOR* (95%CI)
Antibiotics are effective against viruses	47	2.83 (1.61, 5.33)	23	2.66 (1.07, 6.27)	10	5.94 (1.23, 28.04)	24	1.71 (0.75, 3.58)	46	1.71 (1.00, 3.19)
Each type of infection needs a different antibiotic	49	1.17 (0.86, 1.59)	23	1.28 (0.77, 2.07)	11	0.77 (0.52, 1.17)	24	1.14 (0.76, 1.77)	46	1.06 (0.81, 1.42)
Antibiotics can kill the bacteria that normally live on the skin and in the gut	49	0.86 (0.53, 1.40)	22	0.86 (0.73, 1.76)	11	0.70 (0.25, 1.84)	24	1.16 (0.56, 2.49)	45	1.40 (0.82, 2.49)
If antibiotics are consumed in excess, they won't work when they are really needed	45	0.94 (0.76, 1.17)	21	0.86 (0.64, 1.17)	9	0.72 (0.50, 1.04)	22	1.08 (0.72, 1.59)	43	0.98 (0.76, 1.21)
When I get a cold, I take antibiotics to help me feel better faster	49	2.29 (1.69, 3.22)	23	2.36 (1.52, 3.73)	11	4.42 (2.14, 9.38)	24	1.94 (1.26, 3.13)	46	2.22 (1.57, 3.04)
I expect my doctor to prescribe antibiotics if I suffer from common cold or flu symptoms	49	1.42 (0.76, 2.77)	23	3.52 (1.30, 10.60)	11	1.20 (0.29, 4.79)	24	1.20 (0.52, 3.00)	47	1.42 (0.76, 2.77)
When I have a sore throat, I prefer to use an antibiotic	49	3.30 (2.29, 5.00)	23	2.19 (1.22, 3.86)	11	4.01 (1.69, 9.54)	24	1.34 (0.73, 2.39)	47	2.10 (1.40, 3.05)
If I feel side effects during a course of treatment of antibiotics, I should stop taking them as soon as possible	47	2.49 (1.28, 4.83)	23	2.70 (1.00, 7.59)	10	1.28 (0.42, 3.86)	24	1.05 (0.56, 2.10)	46	1.16 (0.70, 1.84)
It is good to be able to get antibiotics from relatives or friends without having to see a medical doctor	49	1.00 (1.00, 1.00)	23	1.00 (1.00, 1.00)	11	1.00 (1.00, 1.00)	24	1.00 (1.00, 1.00)	47	1.00 (1.00, 1.00)
I take the antibiotics according to the doctor's instructions	47	1.00 (1.00, 1.00)	23	1.00 (1.00, 1.00)	10	1.00 (1.00, 1.00)	24	1.00 (1.00, 1.00)	50	1.00 (1.00, 1.00)
I prefer to keep antibiotics at home in case there is a need for them later	47	3.64 (2.19, 6.05)	23	2.08 (1.06, 4.00)	10	5.05 (1.59, 16.78)	24	1.06 (0.53, 2.08)	46	3.30 (1.97, 5.29)
I trust the doctor's decision if s/he decides to prescribe or not prescribe antibiotics	48	0.86 (0.71, 1.08)	23	0.83 (0.61, 1.12)	11	0.59 (0.41, 0.85)	24	0.89 (0.71, 1.37)	47	0.88 (0.71, 1.10)
If I believe that I need an antibiotic and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	48	1.64 (1.39, 1.90)	23	1.49 (1.19, 1.88)	11	1.64 (1.21, 2.25)	24	1.51 1.21, 1.88)	47	1.54 (1.32, 1.82)
Doctors often explain clearly to the patient the reasons for prescribing or not prescribing antibiotics	47	0.63 (0.43, 0.92)	23	0.66 (0.39, 1.13)	11	0.60 (0.27, 1.26)	23	1.22 (0.69, 2.22)	46	0.89 (0.60, 1.36)
Doctors often explain clearly to the patient the instructions for the use of antibiotics	47	0.59 (0.37, 0.90)	23	0.59 (0.31, 1.16)	11	0.44 (0.17, 1.10)	23	0.77 (0.39, 1.54)	46	0.62 (0.39, 1.00)
When you buy antibiotics, the pharmacist tells you about the importance of correct therapeutic compliance/adherence	48	2.44 (1.27, 4.61)	23	1.50 (0.65, 3.46)	11	3.81 (0.89, 16.16)	24	1.27 (0.57, 2.84)	47	1.42 (0.78, 2.57)

(*): adjusted for gender and age

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Discussion

This study is the first to quantitatively assess the relation between the level of knowledge and beliefs, and the misuse of antibiotics in Lebanon, using measures of association. We showed that the misuse of antibiotics in Lebanon is strongly associated with the level of knowledge and the beliefs of the population. Furthermore, preference for storing antibiotic leftovers was identified as an attitude leading to antibiotic misuse. In contrast, trusting the physician´s decision, believing that the physician explained clearly the motives for prescribing or not prescribing antibiotics, and believing that the pharmacist explained clearly the instructions of use of

antibiotics and their correct therapeutic compliance, were associated with a lower frequency of misuse.

Our findings have important implications. They confirm that the prevalence of antibiotic misuse remains high in the country, since 41% of the participants who took antibiotics in the month prior to the survey showed at least one misuse practice. Previous studies had shown that 22% to 51% of the Lebanese self-medicated themselves with antibiotics. [12, 13] Furthermore, our results indicate that self-prescription and saving antibiotic leftovers were the most frequent misuse behaviors among the Lebanese community. Our results also suggest that there was over-prescription by physicians, poor therapeutic compliance, and ease of access to antibiotics in Lebanon. Previous studies showed that, in Lebanon, more than half of the antibiotics were inadequately prescribed in terms of motives for prescription, appropriateness of the type of antibiotics, dosage and duration [14], and that more than one-third of these drugs were dispensed without medical prescription. [15, 20]

To date, the determinants of inappropriate antibiotic prescription have not been evaluated in Lebanon specifically. However, inappropriate antibiotic prescription practices have been widely reported, including in developed countries. [21, 22] In general, the main reason for improper antibiotic prescription seems to be the excessive complacency with the patients' demands. [17] On the other side, pharmacists in Lebanon claim that the main motive for dispensing antibiotics without medical prescription is the patients´ inability to afford a visit to the doctor. This could be a consequence of the lack of social security coverage for around 52% of the Lebanese people. [23] We also showed that more than half of the study population does not always visit the doctor in case of sickness. These figures are alarming, especially with the increasing number of pharmacies and the continuous trust of the Lebanese parents in receiving antibiotics prescribed by a pharmacist. [24] A considerable concern is the pharmacists' belief that some antibiotics are harmless, and their will to retain customers by delivering antibiotics without any medical prescription to increase their economic benefit. [20] In our study, parents showed considerable misunderstanding of the role of antibiotics. In fact, half of the parents thought that antibiotics cured viral infections and 75% expected to receive an antibiotic prescription when they suffered from common cold and preferred to keep antibiotics at home in case of future need. These misconceptions could have favored the misuse of antibiotics. Our findings are in line with other regional and international studies that reported an association between misconceptions about antibiotics and their misuse. [25–28]

The present study has its strengths and limitations. To our knowledge, it is the largest study that was ever conducted in the country on this topic though we cannot disregard the fact that only one-third of the parents answered the questionnaire, which may have increased the possibility of response bias. However, as observed in some studies, non-respondents are more likely to have poorer socio-economical levels and health profiles than the respondents. [29, 30] Therefore, they are more susceptible to misuse antibiotics. Our results would then have been more extreme with a higher response rate.

Previous studies in similar settings in Lebanon have mainly relied on convenience sampling. [12, 13] Our study population cannot be considered as a representative sample of the population of Beirut, however this should not alter our results since measures of association (OR) are independent of representativeness. [31] In addition, restricting the assessment to antibiotic use in the month that preceded the administration of the questionnaire, represented a short recall period and thus decreased the risk of recall bias.

Another potential limitation of our study is its cross-sectional design. Theoretically, this design does not allow inferring causal effects as the outcome (misuse of antibiotics) may have preceded the exposure (knowledge on antibiotics). However, in KAP studies, this is unlikely to occur as knowledge and beliefs, in general, are formed long before the misuse practices.

Finally, we cannot ignore the possibility of overestimating the statistical significance due to multiple comparisons.

Since patients´ demands and perceptions strongly contribute to inappropriate prescription and use, as well as to antibiotic dispensing without medical prescription, we believe that interventions aiming at promoting proper use of antibiotics should include public awareness, implementation of regulations regarding the sale of antibiotics without medical prescription, the dispensing of exact quantities as indicated in the medical prescription, as well as enforcing laws for antibiotic prescription according to international clinical guidelines. In this regard, it has been shown that modern communication methods such as social media platforms and web-based initiatives proved useful in improving the knowledge of the population on antibiotic medication. [32]

Conclusion

In the present study we identified the factors (knowledge and beliefs of the population) that are associated with the behavior towards antibiotics. Our results could prove useful for countries that share a similar situation of antibiotics´ improper use. We showed that there is a need for educational campaigns that improve the awareness of the population towards the proper use of antibiotics and the consequences of their misuse. Future studies assessing country-specific determinants of antibiotic misuse, such as country wealth and healthcare system factors would be useful for the implementation of comprehensive multilevel interventional programs aimed at limiting the spread of antibiotic resistance.

Supporting information

S1 File. Questionnaire applied to collect data about the knowledge, attitudes and practices towards antibiotics in Lebanon.
(PDF)

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ORIGINAL RESEARCH ARTICLE

Comparison of Longitudinal and Cross-Sectional Approaches in Studies About Knowledge, Attitude, and Practices Related to Antibiotic Misuse

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Abstract

Introduction Cross-sectional studies on the association between knowledge, attitudes, and practices of antibiotic misuse are abundant. Conversely, longitudinal studies are unavailable.

Objective The objective of this study was to compare findings from cross-sectional and longitudinal data analyses of the same study on knowledge and attitudes related to practices of antibiotic misuse in the general adult population.

Methods A validated knowledge, attitudes, and practices questionnaire was self-administered at baseline and participants were followed up bimonthly. Logistic regression was used on baseline data to compute adjusted odds ratios in the cross-sectional data analysis. In the longitudinal approach, Poisson regression and generalized linear mixed models were used to estimate adjusted incidence rate ratios and adjusted odds ratios, respectively.

Results Seven hundred and forty-seven adults completed the baseline and the follow-up questionnaires. In the cross-sectional analysis, 78 participants misused antibiotics and strong associations were observed between agreement with various knowledge and attitudes statements and antibiotic misuse practices, with odds ratios between 1.94 and 5.66. In the longitudinal data analysis using Poisson regression, 46 events of antibiotic misuse were detected. No associations were observed between knowledge, attitudes, and misuse practices, except for two statements about the preference of storing antibiotics [adjusted incidence rate ratio: 2.33 (95% confidence interval 1.20–4.54)] and taking antibiotics when getting a cold [adjusted incidence rate ratio: 2.28 (95% confidence interval 1.24–4.21)]. The magnitude of these associations was lower than that observed in the cross-sectional analysis. Findings of the generalized linear mixed-model analysis were similar to those yielded by Poisson regression.

Conclusions The cross-sectional and the longitudinal approaches yield divergent results in our setting. Risk of bias in both analyses should be scrutinized.

1 Introduction

Antibiotic resistance remains among the ten biggest threats to global public health. The World Health Organization has placed a recent urgent call to avert a health crisis from antibiotic resistance [1, 2]. The rise in resistant bacterial infections has threatened the progress in healthcare worldwide, overwhelmed healthcare systems, and imposed huge economic and social burdens [1–4].

The international antibiotic resistance problem is driven by local factors but aided by globalization [5, 6]. Antibiotic resistance is mainly caused by inappropriate prescription by prescribers, and by self-medication and incompliance with the treatment regimen by patients [7].

To defeat antibiotic resistance, the World Health Organization proposed specific measures in its global-related action plan in which it advocated for increased awareness and proper antibiotic use [8]. Numerous epidemiologic studies based on knowledge, attitudes, and practice (KAP) questionnaires on antibiotics have been carried out worldwide. These KAP studies relied on the cross-sectional design because of its rapidity and low cost. However, cross-sectional designs are less adapted to infer causal relations than follow-up

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Key Points

Cross-sectional and longitudinal analyses of the association of knowledge and attitudes with practices of antibiotic misuse yield divergent results, even when using data from the same study

In the cross-sectional analysis, strong associations were observed between agreement with several knowledge and attitudes statements and antibiotic misuse practices, while only a few associations of lower magnitude were observed when using longitudinal approaches

Important sources of bias should be considered while designing a knowledge and attitudes with practices-based study and interpreting the related findings

studies [9]. To-date, follow-up studies on this subject remain unavailable.

Available cross-sectional studies differ in their definition of the timing of the last antibiotic use. While some studies explored the association of knowledge and attitude with antibiotic misuse practices in the past 2 weeks [10], or in the last month [11, 12]; others assessed this association over the past year [13]. Time differences are crucial in drawing correct conclusions as patients' level of knowledge and attitudes might change over time. Furthermore, none of the previously conducted KAP studies about antibiotic use by adults applied a questionnaire that underwent a thorough validation process [14], which leaves room for measurement error. Therefore, using a fully validated questionnaire, we aimed in the present study to compare the results of the cross-sectional approach data gathered at baseline to those of the longitudinal approach in the same cohort study assessing the relationship between knowledge, personal attitudes towards antibiotics, and the patient-healthcare provider relationship and misuse practices of antibiotics.

2 Materials and Methods

2.1 Study Setting

We carried out a cohort study in the general population. Participants consisted of adults (aged ≥ 18 years) accompanying a next-of-kin to medical consultations in primary care settings of the University Hospital of Santiago de Compostela, the administrative capital of the Spanish Autonomous Region of Galicia, a city of 80,000 inhabitants with a university of 25,000 students. Participants were recruited between January and December 2019. Spain is among the European countries with the highest level of antibiotic consumption in primary care [15], and it continues to endure inappropriate prescribing of antibiotics and dispensing without medical prescription, though it is an unlawful action [16].

2.2 Sample Size Calculation

Sample size was calculated as follows: for a two-sided alpha level of 0.05, a statistical power of 80%, a ratio unexposed/exposed of 7, and an odds ratio (OR) of 2 to be detected, the necessary sample size was 686 subjects.

2.3 Measures

Participants completed a self-administered questionnaire that was provided in Galician, the native language of the participants. The questionnaire was developed and validated previously [17]. It was designed to study the association of knowledge and attitudes with practices of antibiotic misuse. The questionnaire consists of three domains: 1. Knowledge and Attitudes (Q1–Q16): explores what the participants know about antibiotics (e.g., whether they are effective to treat cold symptoms or viral infections) and determines their attitudes towards the use of antibiotics (e.g., whether they prefer to use antibiotics to treat sore throat infections) as well as towards healthcare providers with respect to antibiotic prescription (e.g., whether they agree with their doctors when they refrain to prescribe antibiotics); 2. Practice (Q17–Q27): investigates the source of antibiotics (whether they are obtained through medical prescription or from another source such as family or friends) and the patient's compliance with physician's instructions in terms of timing, dosage, and duration; 3. Demographic Characteristics (Q28–Q34): examine general attributes such as sex, age, educational level, family size, and frequency of medical consultancy in case of sickness. The knowledge and attitudes statements were answered using a 0–10 Likert scale that represents the participant's level of agreement with the corresponding statements. Questions in the practice and demographics blocks were answered by selecting from a series of answers. The English version of the questionnaire is available as Electronic Supplementary Material (ESM).

Participants who completed the baseline questionnaire were then followed up by phone every 2 months for 1 year to inquire about their exposure to antibiotics in the past 2 months. Individuals who reported using antibiotics in the past 2 months (Q17) were asked the questions corresponding to the practice block of the questionnaire to determine the occurrence of misuse (Q19–Q24). Participants who did not answer any follow-up questionnaire were excluded from the study. We attempted to reach out to the participants in at least four occasions before proceeding to their exclusion.

2.4 Outcome

The outcome of this study was the occurrence of any of the following practices of misuse of antibiotics: self-medicating with antibiotics/use without prescription (Q19), shortening the course of treatment (Q20), storing or sharing antibiotic leftover (Q21), not adhering to the physician's instructions with respect to the timing and the dosage, i.e., skipping doses (Q22), doubling the dose when the participant forgets to take a previous dose or taking it when remembered (Q23), or modifying the prescribed dose without medical consultation (Q24).

2.5 Exposure

The exposure was the level of knowledge and the attitude towards antibiotics and healthcare provider. Each item of the 16 knowledge and attitude statements (Q1–Q16) served as an independent variable that was analyzed separately.

2.6 Statistical Analysis

We undertook two different approaches. The first analysis was based on cross-sectional data obtained from the baseline questionnaire and collected at the first contact with the subjects of the cohort study, while the second analysis made use of the data collected during the follow-up of these subjects.

2.6.1 Cross-Sectional Data Analysis

Data collected from the baseline questionnaire were analyzed using multiple logistic regression models. We estimated adjusted ORs (aORs) along with their 95% confidence intervals (CIs).

2.6.2 Cohort Data Analysis

2.6.2.1 Person-Time Approach Using Poisson Regression A person-time value is registered for each participant since their recruitment in the study until the occurrence of the first antibiotic misuse practice, drop-out, loss to follow-up, or completion of the study, whichever happened first. We applied Poisson regression models to estimate adjusted incidence rate ratios (aIRRs) of antibiotic misuse and their 95% CIs.

2.6.2.2 Longitudinal Approach by GLMM We estimated aORs of antibiotic misuse practices and their 95% CIs using generalized linear mixed models (GLMM) [18]. The GLMM analysis allows the consideration of repeated observations during the follow-up stages for the same subject. Taking into consideration that the outcome (misuse of antibiotics) is a binary variable, GLMM models were fitted with the binomial family.

The OR and IRR estimates were adjusted for sex and age. In addition, we tested the effect of other potentially confounding variables (educational level, family size, employment, consulting the doctor in case of sickness, and receiving a medical prescription over the phone) using the change-in-estimate method [19]. We selected those variables that showed a p-value < 0.2 in the univariate analysis and introduced them successively in the multivariate model. Variables that modified the OR IRR estimates of the main exposure by 10% or more were retained in the final model. Only individuals with complete data in the variables included in the model were considered. In our analyses, we checked the distribution of the levels of agreement reported by the participants on each of the 16 knowledge and attitude statements, and then estimated the aORs or aIRRs per level of independent variable. The group that corresponded to the highest level of knowledge or to the most adequate attitude was used as a reference category in both approaches.

2.6.3 Sensitivity Analysis

To assess the effect of attrition due to loss to follow-up, we carried out two sensitivity analyses. In the first analysis, we used Multiple Imputations by Chained Equations with 20 imputed data sets. We followed Rubin's rules for the combination of results across the 20 imputed datasets [20, 21]. We used the imputed data to re-estimate aIRRs and their 95% CIs using Poisson regression models.

In the second analysis, we recalculated the originally estimated aIRRs and their 95% CIs under two extreme assumptions. In the first scenario, we supposed that all individuals who were lost to follow-up had misused antibiotics, i.e., had presented the outcome of interest, while in the second scenario, we assumed that no participant lost to follow-up presented the outcome. Poisson regression models were applied in both scenarios. Analyses were carried out using STATA Version 12 (Stata Statistical Software: Release 12; StataCorp LP; College Station, TX, USA), and lme4 package of R Statistical Software (Version 4.0.1).

3 Results

Out of 890 approached individuals, 847 accepted to participate in the study and completed the baseline questionnaire, of whom 115 reported using antibiotics. The general demographic characteristics of these 847 individuals are available in the ESM. Forty-three contacted individuals refused to enrol in the study because of a lack of time.

One hundred (11.81%) participants were lost to follow-up (ESM). The motives of dropout from the study were a lack

of time to answer the follow-up questions because of work or family duties ($n = 76$) and incorrect phone number ($n = 24$).

Seven hundred and forty-seven adults completed at least one follow-up assessment and were included in the analysis. Most of these participants were female ($n = 560$, 75.0%), employed ($n = 561$, 75.1%), with higher education level ($n = 462$, 61.8%), and living in a family of four or fewer members ($n = 609$, 81.5%). Almost half of the participants declared not always visiting the doctor in the case of illness ($n = 381$, 51.0%) and 40.0% ($n = 299$) reported ever receiving medical consultation over the phone (Table 1).

The comparison of the level of agreement on knowledge and attitude statements between individuals who abandoned the study and those who completed the follow-up did not show any notable difference. In addition, no difference was observed between the two groups regarding the misuse practices of antibiotics.

3.1 Cross-Sectional Data Analysis

In the cross-sectional data analysis, 78 individuals showed at least one practice of antibiotic misuse. Strong associations were observed between a low level of knowledge and certain attitudes with practices of misuse of antibiotics (Table 2).

Individuals with a high level of agreement on quitting a course of antibiotics early if they feel better are at a substantially higher odds of misusing antibiotics than those who completely disagree on shortening the course of treatment [aOR: 4.44 (95% CI 2.69–7.32)] (Table 2). Participants who do not totally disagree with the statement "It is good to be able to get antibiotics from relatives or friends without having to see a medical doctor" are five times more likely to misuse antibiotics than those who totally disagree with this statement [aOR: 5.12 (95% CI 2.83–9.26)] (Table 2).

The likelihood of antibiotic misuse by individuals with a high level of agreement on using antibiotics in

Table 1 General characteristic of individuals who participated in the study

Characteristic	Total ($N = 747$)	Cross-sectional study ($N = 747$) Misuse		Cohort study ($N = 747$) Misuse	
		No ($n = 669$)	Yes ($n = 78$)	No ($n = 701$)	Yes ($n = 46$)
Sex, n (%)					
Male	187 (25)	164 (24.5)	23 (29.5)	173 (24.7)	14 (30.4)
Female	560 (75)	505 (75.5)	55 (70.5)	528 (75.3)	32 (69.6)
Missing	0	0	0	0	0
Age, years, n (%)					
< 35	131 (17.5)	114 (17)	17 (21.8)	122 (17.4)	9 (19.6)
36–45	373 (49.9)	345 (51.6)	28 (35.9)	347 (49.5)	26 (56.5)
≥ 46	243 (32.5)	210 (31.4)	33 (42.3)	232 (33.1)	11 (23.9)
Missing	0	0	0	0	0
Educational level, n (%)					
Until high school	258 (34.5)	228 (34.1)	30 (38.5)	433 (61.8)	17 (37)
University	462 (61.8)	418 (62.5)	44 (56.4)	241 (34.4)	29 (63)
Missing	27 (3.6)	23 (3.4)	4 (5.1)	27 (3.9)	0
Family size, n (%)					
≤ 4	609 (81.5)	543 (81.2)	66 (84.6)	569 (81.2)	40 (87)
> 4	111 (14.9)	102 (15.2)	9 (11.5)	105 (15)	6 (13)
Missing	27 (3.6)	24 (3.6)	3 (3.8)	27 (3.9)	0
Consulting a doctor, n (%)					
Not always	381 (51)	337 (50.4)	44 (56.4)	353 (50.4)	28 (60.9)
Always	338 (45.2)	307 (45.9)	31 (39.7)	320 (45.6)	18 (39.1)
Missing	28 (3.7)	25 (3.7)	3 (3.8)	28 (4)	0
Phone medical consultation, *n* (%) No	419 (56.1)	378 (56.5)	41 (52.6)	388 (55.3)	31 (67.4)
Yes	299 (40)	265 (39.6)	34 (43.6)	284 (40.5)	15 (32.6)
Missing	29 (3.4)	26 (3.9)	3 (3.8)	29 (4.1)	0
Employment status, n (%)					
Employed	561 (75.1)	502 (75)	16 (20.5)	524 (74.8)	9 (19.6)
Unemployed	160 (21.4)	144 (21.5)	59 (75.6)	151 (21.5)	37 (80.4)
Missing	26 (3.5)	23 (3.4)	3 (3.8)	26 (3.7)	0

Table 2 Associations of knowledge and attitudes with practices of antibiotic misuse assessed by cohort and cross-sectional approaches

Item	Level of agreement	Cohort study ($N = 747$) Poisson analysis				Cohort study ($N = 1442$) GLMM analysis				Cross-sectional study ($N = 747$)			
		Misuse		aIRR (95% CI)		Misuse		aOR (95% CI)		Misuse		aOR (95% CI)	
		No	Yes			No	Yes			No	Yes		
Q1. Antibiotics are effective against viruses													
	0	319	17	1		634	18	1		305	31	1	
	1–2	32	1	0.55 (0.72–4.15)		69	1	0.50 (0.06–3.82)		29	4	1.20 (0.39–3.67)	
	3–8	230	17	1.44 (0.73–2.83)		438	17	1.34 (0.68–2.63)		221	26	1.16 (0.66–2.02)	
	9–10	111	11	1.69 (0.79–3.64)		230	14	1.99 (0.96–4.09)		106	16	1.56 (0.81–2.98)	
Q2. When I get a cold, I take antibiotics to help me feel better faster													
	0	492	25	1		962	28	1		475	42	1	
	1–2	55	3	0.96 (0.29–3.18)		114	3	0.86 (0.57–2.49)		53	5	1.11 (0.42–2.94)	
	3–10	151	18	2.28 (1.24–4.21)		306	19	2.04 (0.27–1.60)		139	30	2.48 (1.48–4.15)	
Q3. If I feel better after a few days, I sometimes stop taking my antibiotics before completing the course of treatment													
	0	504	30	1		989	32	1		501	33	1	
	1	22	0	NA		44	0	NA		20	2	1.45 (0.32–6.53)	
	2–10	169	16	1.52 (0.82–2.81)		345	18	1.55 (0.85–2.83)		143	42	4.44 (2.69–7.32)	
Q4. I expect my doctor to prescribe antibiotics if I suffer from common cold or flu symptoms													
	0	329	18	1		630	21	1		315	32	1	
	1–2	41	2	0.84 (0.19–3.62)		86	2	0.66 (0.15–2.89)		41	2	0.46 (0.11–2.02)	
	3–10	327	26	1.39 (0.76–2.54)		665	27	1.21 (0.68–2.16)		310	43	1.39 (0.85–2.26)	
Q5. It is good to be able to get antibiotics from relatives or friends without having to see a medical doctor													
	0	636	42	1		1267	46	1		622	56	1	
	1–10	62	4	1.03 (0.37–2.88)		116	4	0.93 (0.33–2.64)		45	21	5.12 (2.83–9.26)	
Q6. When I have a sore throat, I prefer to use an antibiotic													
	0	480	35	1		971	37	1		476	39	1	
	1–2	58	0	NA		105	0	NA		52	6	1.34 (0.54–3.35)	
	3–10	158	11	0.97 (0.48–1.93)		308	13	1.07 (0.55–2.06)		138	31	2.68 (1.60–4.49)	
Q7. Each type of infection needs a different antibiotic													
	0–5	191	12	0.87 (0.44–1.75)		379	14	0.98 (0.38–1.7)		181	22	1.17 (0.66–2.08)	
	6–8	168	9	0.76 (0.35–1.64)		330	10	0.80 (0.38–1.7)		155	22	1.34 (0.75–2.39)	
	9–10	335	24	1		663	25	1		326	33	1	

Table 2 (continued)

Item	Level of agreement	Cohort study ($N = 747$) Poisson analysis			Cohort study ($N = 1442$) GLMM analysis			Cross-sectional study ($N = 747$)		
		Misuse		aIRR (95% CI)	Misuse		aOR (95% CI)	Misuse		aOR (95% CI)
		No	Yes		No	Yes		No	Yes	
Q8. If I feel side effects during a course of treatment of antibiotics, I should stop taking them as soon as possible										
	0–4	179	12	1	331	13	1	168	23	1
	5	174	9	0.69 (0.19–1.65)	351	11	0.75 (0.33–1.71)	170	13	0.58 (0.28–1.19)
	6–10	342	25	0.99 (0.49–1.98)	697	26	0.91 (0.46–1.81)	326	41	0.90 (0.52–1.56)
Q9. I take the antibiotics according to the doctor's instructions										
	0–6	21	4	3.02 (1.04–8.70)	47	4	2.65 (0.89–7.93)	19	6	2.88 (1.09–7.60)
	7–9	129	6	0.69 (0.29–1.65)	248	6	0.62 (0.26–1.49)	115	20	1.70 (0.97–2.99)
	10	542	36	1	1077	40	1	527	51	1
Q10. If antibiotics are consumed in excess, they will not work when they are really needed										
	1–9	217	15	0.96 (0.51–1.80)	406	15	0.92 (0.49–1.73)	197	35	1.94 (1.19–3.18)
	10	471	31	1	916	35	1	462	40	1
Q11. I prefer to keep antibiotics at home in case there is a need for them later										
	0	423	23	1	828	24	1	423	23	1
	1–5	156	9	1.01 (0.47–2.19)	319	9	0.94 (0.43–2.04)	141	24	2.99 (1.63–5.49)
	6–10	112	14	2.33 (1.20–4.54)	224	17	2.64 (1.39–5.02)	96	30	5.66 (3.14–10.22)
Q12. I trust the doctor's decision if s/he decides to prescribe or not prescribe antibiotics										
	0–8	176	14	1.18 (0.63–2.24)	333	14	1.19 (0.63–2.25)	167	23	1.33 (0.79–2.26)
	9–10	504	31	1	987	33	1	483	52	1
Q13. If I believe that I need an antibiotic and the doctor did not prescribe it, I will get it at the pharmacy without a prescription										
	0	574	37	1	1139	38	1	558	53	1
	1–10	116	9	1.27 (0.61–2.64)	232	12	1.57 (0.81–3.07)	101	24	2.47 (1.45–4.20)
Q14. Doctors often explain clearly to the patient the reasons for prescribing or not prescribing antibiotics										
	0–5	310	15	0.74 (0.33–1.65)	619	15	0.64 (0.3–1.39)	291	34	1.12 (0.59–2.13)
	6	58	4	1.15 (0.36–3.67)	103	3	0.76 (0.21–2.75)	54	8	1.46 (0.58–3.66)
	7–9	167	16	1.50 (0.68–3.31)	335	19	1.57 (0.21–2.75)	163	20	1.18 (0.58–2.41)
	10	153	10	1	308	12	1	148	15	1

Table 2 (continued)

Item	Level of agreement	Cohort study ($N = 747$) Poisson analysis				Cohort study ($N = 1442$) GLMM analysis				Cross-sectional study ($N = 747$)			
		Misuse		aIRR (95% CI)		Misuse		aOR (95% CI)		Misuse		aOR (95% CI)	
		No	Yes			No	Yes			No	Yes		
Q15. Doctors often explain clearly to the patient the instructions for the use of antibiotics													
	0–5	200	12	0.73 (0.36–1.48)		399	13	0.74 (0.37–1.48)		185	27	1.27 (0.72–2.23)	
	6–8	226	12	0.70 (0.34–1.41)		426	13	0.72 (0.36–1.43)		217	21	0.87 (0.48–1.57)	
	9–10	260	22	1		528	24	1		254	28	1	
Q16. When you buy antibiotics, the pharmacist tells you about the importance of correct therapeutic compliance/adherence													
	0–3	199	11	0.76 (0.33–1.75)		395	12	0.66 (0.3–1.46)		186	24	1.02 (0.53–1.99)	
	4–6	153	12	1.03 (0.45–2.36)		305	13	0.9 (0.41–1.98)		147	18	0.99 (0.49–2.03)	
	7–9	186	12	0.915 (0.40–2.08)		367	11	0.68 (0.3–1.52)		180	18	0.79 (0.39–1.60)	
	10	153	11	1		302	14	1		147	17	1	

Misuse is defined as the occurrence of any of the practices assessed in questions 19 to **24** of the questionnaire

CI confidence interval, *aIRR* incidence rate ratio adjusted by age and gender; *N* number of participants, *aOR* odds ratio adjusted by age and gender

the case of common cold symptoms [aOR: 2.48 (95% CI 1.48–4.15)] or sore throat infections [OR: 2.68 (95% CI 1.60–4.49)] is almost three times higher than that of individuals who totally refuse to use antibiotics for these health conditions. Subjects who agree on storing antibiotics at home for a future need show a higher OR of antibiotic misuse [aOR: 5.66 (95% CI 3.14–10.22)] (Table 2). Finally, individuals who do not believe that excessive consumption of antibiotics makes them ineffective, as well as those who accept getting antibiotics from the pharmacy without a prescription, are at a higher odds of misusing these drugs [aOR: 1.94 (95% CI 1.19–3.18) and aOR: 2.47 (95% CI 1.45–4.20), respectively] (Table 2). Similarly, subjects who state they do not usually follow doctor's instructions are at a higher odds of antibiotic misuse [aOR: 2.88 (95% CI 1.09–7.60)] (Table 2).

3.2 Cohort Data Analysis

3.2.1 Person-Time Approach Using Poisson Regression

During follow-up, 46 individuals presented with at least one practice of antibiotic misuse. Only three of the 16 knowledge and attitude statements were associated with misuse of antibiotics. These three statements correspond to individuals who prefer to store antibiotics at home for a future need [$aIRR_{6-10}$: 2.33 (95% CI 1.20–4.54)], might take antibiotics when they get a cold [$aIRR_{3-10}$: 2.28 (95% CI 1.24–4.21)], and do not usually follow doctor's instructions [aIRR: 3.02 (95% CI 1.04–8.70)] (Table 2).

3.2.2 Longitudinal Approach Using GLMM

Fifty observations of misuse of antibiotics were obtained for the GLMM analysis from the follow-up data. No association was observed between the knowledge and attitude statements and misuse practices of antibiotics, except for the statement about the preference of keeping antibiotics at home for future need [aOR_{6-10}: 2.64 (1.39–5.02)] (Table 2).

3.3 Sensitivity Analysis

Multiple Imputations by Chained Equations analysis revealed that there was no substantial difference between aIRRs calculated from the observed data and those computed from imputed data, and that knowledge and attitudes were not associated with misuse practices of antibiotics (Table 3). Similar results were also obtained from the two sensitivity analyses under extreme conditions (Table 4).

Table 3 IRRs and 95% CI of misuse practices of antibiotics after imputation of missing data (MICE procedure)

Item	Imputed aIRR (95% CI)
Q1. Antibiotics are effective against viruses	
0	1
1–2	0.93 (0.63–1.36)
3–8	1.06 (0.84–1.33)
9–10	0.97 (0.74–1.28)
Q2. When I get a cold, I take antibiotics to help me feel better faster	
0	1
1–2	1.07 (0.78–1.48)
3–10	0.96 (0.69–1.32)
Q3. If I feel better after a few days, I sometimes stop taking my antibiotics before completing the course of treatment	
0	1
1	0.92 (0.59–1.43)
2–10	0.93 (0.66–1.30)
Q4. I expect my doctor to prescribe antibiotics if I suffer from common cold or flu symptoms	
0	1
1–2	0.96 (0.62–1.51)
3–10	0.96 (0.80–1.17)
Q5. It is good to be able to get antibiotics from relatives or friends without having to see a medical doctor	
0	1
1–10	0.91 (0.39–2.15)
Q6. When I have a sore throat, I prefer to use an antibiotic	
0	1
1–2	1.05 (0.75–1.46)
3–10	0.99 (0.77–1.26)
Q7. Each type of infection needs a different antibiotic	
0–5	1.11 (0.89–1.39)
6–8	1.02 (0.83–1.25)
9–10	1
Q8. If I feel side effects during a course of treatment of antibiotics, I should stop taking them as soon as possible	
0–4	1
5	0.92 (0.73–1.17)
6–10	1.01 (0.80–1.27)
Q9. I take the antibiotics according to the doctor's instructions	
0–6	0.77 (0.42–1.42)
7–9	1.03 (0.84–1.26)
10	1
Q10. If antibiotics are consumed in excess, they will not work when they are really needed	
1–9	0.94 (0.76–1.17)
10	1
Q11. I prefer to keep antibiotics at home in case there is a need for them later	
0	1
1–5	0.98 (0.78–1.23)
6–10	0.93 (0.70–1.24)
Q12. I trust the doctor's decision if s/he decides to prescribe or not prescribe antibiotics	
0–8	0.90 (0.72–1.12)
9–10	1
Q13. If I believe that I need an antibiotic and the doctor did not prescribe it, I will get it at the pharmacy without a prescription	
0	1
1–10	1.01 (0.69–1.48)

Table 3 (continued)

Item	Imputed aIRR (95% CI)
Q14. Doctors often explain clearly to the patient the reasons for prescribing or not prescribing antibiotics	
0–5	
8	0.99 (0.77–1.27)
7–9	1.05 (0.76–1.45)
10	1.04 (0.82–1.31)
Q15. Doctors often explain clearly to the patient the instructions for the use of antibiotics	1
1–5	
6–8	1.05 (0.82–1.35)
9–10	1.04 (0.84–1.29)
Q16. When you buy antibiotics, the pharmacist tells you about the importance of correct therapeutic compliance/ adherence	1
0–3	
4–6	0.99 (0.77–1.30)
7–9	1.10 (0.86–1.40)
10	1.10 (0.88–1.38)
	1

aIRR incidence rate ratio adjusted by age and sex, *CI* confidence interval, *MICE* Multiple Imputations by Chained Equations

Misuse is defined as the occurrence of any of the practices assessed in questions 19–24 of the questionnaire

4 Discussion

All published KAP studies on the misuse of antibiotics used a cross-sectional design. To the best of our knowledge, no cohort study has been carried out so far.

A meta-analysis of the knowledge and attitudes about antibiotics and antibiotic resistance in the general population worldwide reported a lack of knowledge with more than one-third of the population not knowing that antibiotics treat bacterial infections, more than half of the studied individuals did not recognize that antibiotics do not treat viral infections, more than one-fourth of the people were not aware that misuse of antibiotics leads to antibiotic resistance, and almost half of the population seize their antibiotic treatment once improvement was noticed [22]. In 2018, only 25% of the European population answered correctly to all knowledge questions about antibiotics in the Eurobarometer survey, with the highest average number of correct answers being given by Finnish and Swedish individuals and the lowest average by Latvian and Romanian citizens [23].

In our study, we compared the results concerning the association of knowledge and attitudes with practices of antibiotic misuse obtained through a cross-sectional analysis at baseline, with those obtained in the follow-up of the same population. In the cross-sectional data analysis of our study, we found that poor knowledge and several attitudes increase the odds of antibiotic misuse substantially. Conversely, only three items were associated with antibiotic misuse in the Poisson regression-based longitudinal analysis and only one in the GLMM analysis.

Differences in results from cross-sectional and longitudinal data analyses have been widely described in the literature [24–28]. Although cross-sectional studies are often deemed misleading and unreliable because of methodological limitations [9, 29, 30], including their incapability to infer causal relationships and their inability to analyze the data over time, in the particular setting of KAP studies, potential biases should be scrutinized in both analyses.

As exposure and outcome are measured at the same time, simultaneity bias represents a concern in the cross-sectional approach. Indeed, misuse of antibiotics may be simultaneous to acquisition of erroneous knowledge or incorrect attitude.

Furthermore, in the cross-sectional approach, the measure of association of interest is the prevalence OR. It may be erroneously understood as a "proxy" for relative risk, or an IRR. Prevalence is a function of incidence rate *and* duration of the outcome. Cross-sectional analyses and longitudinal analyses assess concepts that are not equivalent [31].

Knowledge, attitudes, and practice-related cohort studies and their associated longitudinal analyses are not free from the risk of bias. Indeed, individuals with a low level of knowledge are expected to participate less often in research studies and may therefore introduce selection bias [32, 33]. They are then expected to abandon follow-up more frequently than subjects with a higher level of knowledge. However, this was not the case in our study, as the level of knowledge and attitudes was similar between individuals who dropped out after completing the baseline questionnaire and those who completed the follow-up.

Table 4 IRRs and 95% CI from the two sensitivity analyses of the longitudinal data

Item	Lost individuals considered as non cases ($N = 847$)			Lost individuals considered as cases ($N = 847$)		
	Misuse		aIRR (95% CI)	Misuse		aIRR (95% CI)
	No	Yes		No	Yes	
Q1. Antibiotics are effective against viruses						
0	354	17	1	15	356	1
1–2	46	3	1.45 (0.42–5.00)	3	46	1.02 (0.74–1.39)
3–8	256	15	1.25 (0.62–2.51)	9	262	1.10 (0.93–1.29)
9–10	135	11	1.70 (0.79–3.65)	7	139	1.08 (0.88–1.32)
Q2. When I get a cold, I take antibiotics to help me feel better faster						
0	553	25	1	24	554	1
1–2	66	3	0.95 (0.29–3.15)	1	68	1.02 (0.79–1.32)
3–10	179	18	2.19 (1.19–4.04)	9	188	1.12 (0.94–1.33)
Q3. If I feel better after a few days, I sometimes stop taking my antibiotics before completing the course of treatment						
0	570	30	1	23	577	1
1	40	1	0.45 (0.62–3.33)	2	39	0.97 (0.70–1.35)
2–10	185	15	1.64 (0.87–3.09)	9	191	1.08 (0.91–1.28)
Q4. I expect my doctor to prescribe antibiotics if I suffer from common cold or flu symptoms						
0	375	18	1	15	378	1
1–2	47	2	0.86 (0.20–3.72)	2	47	1.00 (0.73–1.35)
3–10	374	26	1.43 (0.78–2.62)	17	383	1.00 (0.96–1.15)
Q5. It is good to be able to get antibiotics from relatives or friends without having to see a medical doctor						
0	725	42	1	33	734	1
1–10	73	4	0.94 (0.34–2.63)	1	76	1.14 (0.90–1.46)
Q6. When I have a sore throat, I prefer to use an antibiotic						
0	540	35	1	24	551	1
1–2	67	0	N.A.	2	65	1.07 (0.82–1.40)
3–10	188	11	0.90 (0.46–1.80)	8	191	1.12 (0.94–1.33)
Q7. Each type of infection needs a different antibiotic						
0–5	220	12	0.86 (0.43–1.72)	6	226	1.04 (0.88–1.23)
6–8	190	9	0.76 (0.35–1.64)	10	189	0.99 (0.83–1.19)
9–10	383	24	1	18	389	1
Q8. If I feel side effects during a course of treatment of antibiotics, I should stop taking them as soon as possible						
0–4	311	16	1	16	311	1
5	96	8	1.58 (0.68–3.69)	5	99	0.90 (0.72–1.14)
6–10	376	21	1.06 (0.55–2.04)	13	384	0.99 (0.85–1.15)
Q9. I take the antibiotics according to the doctor's instructions						
0–6	24	4	3.07 (1.08–8.72)	3	25	0.99 (0.66–1.48)
7–9	149	6	0.66 (0.28–1.57)	6	149	1.03 (0.86–1.24)
10	615	36	1	25	626	1
Q10. If antibiotics are consumed in excess, they will not work when they are really needed						
1–9	254	15	1.00 (0.53–1.86)	14	255	0.99 (0.85–1.15)
10	530	31	1	20	541	1
Q11. I prefer to keep antibiotics at home in case there is a need for them later						
0	479	23	1	19	483	1
1–5	177	9	1.02 (0.47–2.21)	7	179	1.01 (0.85–1.21)

Table 4 (continued)

Item	Lost individuals considered as non cases ($N = 847$)			Lost individuals considered as cases ($N = 847$)		
	Misuse		aIRR (95% CI)	Misuse		aIRR (95% CI)
	No	Yes		No	Yes	
6–10	131	14	2.39 (1.25–4.65)	8	137	1.09 (0.90–1.33)
Q12. I trust the doctor's decision if s/he decides to prescribe or not prescribe antibiotics						
0–8	207	14	1.27 (0.67–2.40)	13	208	0.97 (0.83–1.15)
9–10	569	31	1	21	579	1
Q13. If I believe that I need an antibiotic and the doctor did not prescribe it, I will get it at the pharmacy without a prescription						
0	652	37	1	30	659	1
1–10	134	9	1.23 (0.59–2.56)	4	139	1.10 (0.92–1.33)
Q14. Doctors often explain clearly to the patient the reasons for prescribing or not prescribing antibiotics						
0–5	356	15	0.70 (0.32–1.57)	17	354	0.99 (0.83–1.20)
6	63	4	1.09 (0.34–3.50)	2	65	1.06 (0.79–1.42)
7–9	192	16	1.47 (0.66–3.24)	6	202	1.03 (0.84–1.27)
10	172	10	1	9	173	1
Q15. Doctors often explain clearly to the patient the instructions for the use of antibiotics						
0–5	226	12	0.73 (0.36–1.48)	8	230	0.96 (0.81–1.14)
6–8	248	12	0.68 (0.34–1.37)	8	252	0.97 (0.82–1.15)
9–10	307	22	1	16	313	1
Q16. When you buy antibiotics, the pharmacist tells you about the importance of correct therapeutic compliance/adherence						
0–3	220	11	0.77 (0.33–1.78)	13	218	0.96 (0.83–1.24)
4–6	182	12	0.99 (0.43–2.62)	6	188	1.03 (0.84–1.28)
7–9	212	12	0.88 (0.39–2.01)	6	218	1.01 (0.83–1.24)
10	173	11	1	9	175	1

aIRR incidence rate ratio adjusted by age and sex, *CI* confidence interval, *N.A.* not applicable

Misuse is defined as the occurrence of any of the practices assessed in questions 19–24 of the questionnaire

Bias due to loss to follow-up could be a concern in the cohort study [34]. One-tenth of the participants who left the study before the first follow-up had showed at least one misuse practice of antibiotics at baseline. Consequently, it is likely that this selective attrition reduced the number of misuse events in the cohort approach but not in the cross-sectional approach. This might have produced estimates with wider confidence intervals in the longitudinal approach than in the cross-sectional approach.

The absence of association between knowledge and attitudes and the misuse practices of antibiotics in the longitudinal approach could be stemmed from a change in exposure status during the follow-up period after having received an educational intervention [35]. Indeed, we are aware that nationwide campaigns to enhance the prudent use of antibiotics was launched simultaneously with our study [36, 37], which could have led some participants to modify their behavior towards antibiotics during follow-up.

Interview-based studies like ours are also subject to observation bias, known as the "Hawthorne effect" [38], by which participants might improve their behavior when they are participating in a research study. Closely related to the Hawthorne effect is the "social desirability bias" [39], by which some participants tend to provide socially accepted answers, and under-rate their negative practices regarding antibiotics. Though the socially accepted responses might be present in both cross-sectional and longitudinal approaches, it is likely that the effect of this bias is higher in the phone-based follow-up than during self-completion of the baseline questionnaire of the cross-sectional approach.

We conclude from this comparative study that both approaches, cross-sectional and longitudinal, are not free from bias in KAP studies. Knowledge, attitudes, and practice researchers should be aware that assessment of time-varying variables such as knowledge and attitudes, generally measured at baseline in cohort studies, may be subject to bias and

may eventually lead to incorrect conclusions if the measurement of such variables is not carried out de novo during the follow-up. However, these researchers should be aware that the underlying parameter in the cross-sectional approach is the prevalence of the outcome, not the incidence, and that both measures are not forcedly exchangeable. Results from both approaches should be carefully scrutinized to obtain sound conclusions in KAP studies.

Regulations about the dispensing of antibiotics should be enforced and additional control should be exerted to prevent the supply of antibiotics without prescription, especially in vulnerable settings such as rural regions, and when pressure by patients exists. Patients should be trained and empowered in the control of frequent diseases such as upper respiratory infections and urinary infections, to address the issue of the unnecessary use of antibiotics.

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Conflict of interest Narmeen Mallah, Adolfo Figueiras, and Bahi Takkouche have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval The study was approved by the Ethics Committee of the University of Santiago de Compostela (R00002, No. 2019/179), and authorized by the Spanish Agency for Medication and Healthcare Products (AEMPS, Reference AFG-ANT-2018-01).

Consent to participate A written consent form was obtained from the participants before their enrollment in the study and the data were anonymized prior to analysis.

Consent for publication Not applicable.

Availability of data and material The data generated and analyzed in this study are available in the data repository FigShare and can be accessed through the following link: https://figshare.com/s/590c03dc14194b47cfda (reserved https://doi.org/10.6084/m9.figshare.13187732).

Code availability Not applicable.

Authors contributions NM carried out the literature review, formulated the research idea, collected, analyzed, and interpreted the data, and conceived and wrote the manuscript. NM, AF, and BT designed the study. AF and BT supervised the data analyses and interpretation. All authors reviewed and revised the manuscript and are responsible for its content.

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Asunto: Your submission: KK-21-1458R1

Ref.: Ms. No. KK-21-1458R1
Association of Knowledge and Attitudes with Practices of Misuse of Tranquilizers: A Cohort Study in Spain
Drug and Alcohol Dependence

Dear Dr. Takkouche,

I am pleased to inform you that your submission to Drug and Alcohol Dependence has now addressed all of the issues that were raised in the review process. Thank you for your careful responses to the questions raised by the reviewers and myself. Congratulations again on this interesting and important paper.

The manuscript is being forwarded to the Central Editorial Office with my recommendation that it be published. If there are no further changes that need your attention, the manuscript will promptly be sent on to Elsevier Science Ireland, Ltd. where it will be prepared for publication. You will be alerted by email about the availability of page proofs and about any other actions needed from you. Please respond to such emails as quickly as you can to avoid delays in the appearance of your paper in the journal. After you receive communication from Elsevier, you will be able to follow the status of your paper on the Internet by logging on and registering with the Elsevier (http://www.elsevier.com/authors) which provides additional services, such as Contents Direct that sends to you the tables of contents of your selected journals.

We appreciate and value your contribution to Drug and Alcohol Dependence. We regularly invite authors of recently published manuscript to participate in the peer review process. If you were not already part of the journal's reviewer pool, you have now been added to it. We look forward to your continued participation in our journal, and we hope you will consider us again for future submissions.

Thank you for submitting your work to this journal.

With kind regards,

Kyle M. Kampman, MD
Associate Editor
Drug and Alcohol Dependence

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SYSTEMATIC REVIEW

Prenatal Exposure to Macrolides and Risk of Congenital Malformations: A Meta-Analysis

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Abstract

Introduction Macrolides are widely used during pregnancy; however, their fetal safety remains uncertain. We performed a meta-analysis to assess the relation between prenatal exposure to macrolides and occurrence of congenital malformations.

Methods We searched MEDLINE, EMBASE, and other databases until June 12, 2019. We assessed the quality of the studies and checked for heterogeneity and publication bias. We performed three different analyses and compared the effect of macrolides with each of the following unexposed populations: Group 1: babies unexposed to any medicine before birth, Group 2: babies exposed to non-macrolide antibiotics/non-teratogens, and Group 3: mixed population of the first and second comparators.

Results A weak association between macrolides and congenital malformation of any type was observed when macrolides were compared with the mixed population ($OR_{group\ 3}$ 1.06 [95% CI 1.01–1.10]). Subgroup analysis showed that this weak association is restricted to fetus exposure in the first trimester of pregnancy (OR 1.06 [95% CI 1.01–1.11]) and to cohort studies (OR 1.07 [95% CI 1.02–1.13]). Digestive system malformations were found to be slightly associated with prenatal exposure to macrolides ($OR_{group\ 3}$ 1.14 [95% CI 1.02–1.26]). The musculoskeletal system was also found to be potentially affected ($OR_{group\ 2}$ 1.21 [95% CI 1.08–1.35] and $OR_{group\ 3}$ 1.15 [95% CI 1.05–1.26]). European studies showed a slightly stronger association than American studies in these two comparisons.

Conclusions Our study suggests a weak association between prenatal use of macrolides and congenital malformations, limited to exposure in early pregnancy, and musculoskeletal and digestive systems. In addition to studies with a larger control of confounding, risk–benefit research is needed to determine the usefulness of macrolides during pregnancy.

Key Points

Macrolides are widely used during pregnancy; however, knowledge about their fetal safety is uncertain.

This meta-analysis shows that macrolide intake during pregnancy is associated with a weak increase in the odds of congenital abnormalities, limited to some subgroups.

These findings along with additional assessment of the risks and benefits of macrolides are crucial to determine their usefulness during pregnancy.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40264-019-00884-5) contains supplementary material, which is available to authorized users.

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1 Introduction

Congenital abnormalities are malformations of organs or body parts during organogenesis, which mainly take place in the first trimester of pregnancy [1, 2]. Some malformations may also occur in the second and third trimesters of pregnancy as the tissues and organs continue to develop [2].

Birth defects are the leading risk factor for infant mortality worldwide [1, 3–5]. However, the causes of the occurrence of these defects are not well determined [1]. According to the Global Report on Birth Defects, the proportion of malformations due to genetic factors is small compared with the proportion of abnormalities due to exposure to teratogenic intra-uterine factors such as certain medicines [6]. It is remarkable that 97.7% of the drugs approved by the US FDA between 2000 and 2010 have 'undetermined' teratogenic risk in human pregnancy [7]. Antibiotics are frequently prescribed during pregnancy, mainly to treat urinary infections. Indeed, around one-fourth of pregnant women receive antibiotics during pregnancy, comprising 80% of all prescriptions [8]. Some antibiotics used for this purpose were found to harm fetal formation [9].

Macrolides are among the most consumed antibacterial medicines [10–12]. The major types of macrolides include erythromycin, azithromycin, clarithromycin, and roxithromycin. Data about the association between prenatal exposure to macrolides and birth defects are inconclusive [9, 13–16]. For instance, when used in early pregnancy, erythromycin was associated with anencephaly, transverse limb deficiency, pyloric stenosis, and other congenital malformations, [9, 13] while no relation was found between clarithromycin and the risk of fetal malformations [16].

Except for a meta-analysis aimed at assessing general adverse child outcomes, which included a limited number of original studies, no comprehensive review has been carried out on this topic so far [17]. Therefore, to determine if there is an effect of prenatal exposure to macrolides on congenital abnormalities and to study whether this effect varies according to the type of macrolide and to the exposure pregnancy term, we carried out a systematic review and meta-analysis.

2 Methods

2.1 Information Sources and Search Strategy

We retrieved published studies on the use of macrolide antibiotics during pregnancy and the development of congenital malformations by searching MEDLINE from 1966 until June 12, 2019. To identify the relevant articles, we used the following syntax: (macrolide* OR erythromycin OR roxithromycin OR clarithromycin OR azithromycin OR macrolide [MeSH Terms]) AND ((birth defect*) OR (congenital) OR "congenital abnormalities" [MeSH Terms] OR fetal OR fetus). The search was exclusive to studies involving humans. Our search was not limited to any language of publication.

We excluded cross-sectional studies from our search due to the impossibility of this design to infer any causal effect. We also conducted a search using the following terms as free-text words: birth defects, congenital malformation, congenital abnormalities, pregnancy, macrolides, cohort, case–control and incidence. We adopted similar strategies to search EMBASE from 1980 until 2019; the five regional bibliographic databases of the World Health Organization (WHO)—African Index Medicus (AIM), Latin American and Caribbean Health Science Literature Database (LILACS), Index Medicus for the Eastern Mediterranean Region (IMEMR), Index Medicus for South-East Asia Region (IMSEAR), Western Pacific Region Index Medicus (WPRIM); as well as the Open Access Thesis and Dissertations (OATD). We also searched for abstracts of scientific meetings using the Conference Proceedings Citation Index from inception in 1990 until June 2019. Finally, we manually examined the references of all obtained articles as well as those of related systematic reviews. All searches were carried out independently by two epidemiologists (N. M. and B. T.) and the results were merged.

We registered the review protocol of this study in the International Prospective Register of Systematic Reviews (PROSPERO) (Reference: CRD42017055131) [18].

2.2 Eligibility Criteria and Study Selection

We included studies that fulfilled the following eligibility criteria: (1) reporting original data from randomized clinical trials, case–control or cohort studies; (2) examining the association between prenatal exposure to macrolides and the development of congenital malformation; (3) providing estimates of relative risk (RR) or odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) or presenting enough data to calculate them. Due to their limitation in inferring causal relationships, cross-sectional studies were excluded. We restricted our analysis to congenital malformations in live births only. We excluded articles on drugs that could be assimilated to macrolides such as ivermectin, nystatin, and natamycin and limited our study to true macrolides. We also excluded studies that investigated the postnatal maternal and/or infant exposure to macrolides. Duplicate studies were detected by identifying the study population. Only the most updated study was included in

the meta-analysis. In addition, for publications about different macrolides that were carried out by the same investigator in the same population, we calculated the pooled RRs or ORs of these different publications and presented them as a single study. When effect measures of maternal exposure to different types of macrolides and/or during distinct terms of pregnancy were reported in the same study, we analyzed each outcome separately.

2.3 Data Extraction

We scanned the titles and abstracts of the collected articles in order to exclude the irrelevant ones, and subsequently reviewed the full texts of the remaining articles to check their eligibility. We recorded the following information from the eligible studies: (1) study name and source; (2) publication year; (3) study design (cohort study and case–control study); (4) study period; (5) sample size (number of cases and controls for case–control studies, or number of cases and cohort size for cohort studies); (6) type of control (unexposed to any drug, exposed to non-macrolide antibiotics or to non-teratogens, or a mixture of the unexposed and non-macrolide exposed fetuses), (7) study country; (8) ascertainment of macrolide exposure; (9) exposure dose; (10) exposure period; (11) effect measures and 95% CI; (12) adjustment, matching, and restriction variables; (13) percentage of drop-outs in cohort studies; (14) response rate in case–control studies; (15) type of macrolide; and (16) use of individual or a mixture of macrolides.

2.4 Quality Assessment

We assessed the quality of the studies by using a seven-point scale extracted from the Newcastle–Ottawa scale according to the requirements of this meta-analysis [19]. We assessed the following criteria:

- Macrolide exposure ascertainment: based on a clinical history or any other documented proof (1 point), else (0 points).
- Confounding assessment: results adjusted for maternal age and urinary tract infections (2 points, 1 point each), else (0 points).
- Exposure description: reported duration (1 point) and determined dose (1 point), else (0 points).

To assess methodological issues that were not common to cohort studies and case–control studies, we used the following criteria:

- Drop-out rate or losses to follow up in cohort studies: < 20% (2 points), 20–40% (1 point), and > 40% or not explained (0 points)
- Participation rate in case–control studies: > 80% (1 point), < 80%, or not reported (0 points).

We carried out a pooled analysis on studies scoring > 4 points and compared the results with those of studies with a lower quality score.

Both data extraction process and quality rating were independently performed by two epidemiologists [N. M. and H. T.] and discrepancies were resolved through discussion with a third party [B. T.].

2.5 Data Synthesis

We extracted the adjusted ORs and their 95% CIs from the studies included in our meta-analysis. We used the crude ORs if no adjusted estimate was provided, or computed them from the data provided by the authors. Subsequently, we weighted the log RRs and log ORs for cohort and case–control studies, respectively, by the inverse of their variance to obtain a pooled OR and its 95% CI. ORs were considered unbiased estimates of the RR [20].

We carried out three different analyses according to the characteristics of the unexposed population. In the first approach, we included all studies that used fetuses unexposed to any drug as a comparator (comparison group 1). The second approach encompassed studies that compared the effect of parental exposure to macrolides with exposure to non-macrolides or nonteratogenic drugs (comparison group 2). The third analysis involved the combination of the studies of the two approaches described above (comparison group 3).

We presented both fixed and random effects pooled estimates. We checked for heterogeneity using DerSimonian and Laird's Q test. We quantified the heterogeneity by calculating the proportion of the total variance due to between-study variance (Ri) [21]. Large values (> 0.75) of Ri indicate large amount of heterogeneity, values between 0.4 and 0.75 suggest a moderate amount, while small values (< 0.4) indicate low heterogeneity. Subsequently, we restricted the analysis to subgroups defined by study characteristics such as adjustment factors, exposure period, anatomical location of congenital malformations, and study design. Prior to data analysis, we contacted the authors in order to know whether abstracts retrieved in our search were published later as a full paper and to have more information about the comparison group used in the studies [14, 16, 22–25]. We repeated the same analysis for the three categories of comparison populations.

2.6 Assessment of Publication Bias

We assessed publication bias visually using funnel plots at first, and then, more formally, using Egger's regression

test [26]. We used the trim-and-fill method to correct for potential publication bias.

We also performed a sensitivity analysis by assuming that the results of case–control studies are the least likely to be published when they show no effect. Accordingly, we recalculated the pooled OR assuming that (1) the case–control studies retrieved in our search represent only half of the studies ever conducted, (2) the unpublished studies found a null association (OR 1) between prenatal exposure to macrolides and congenital malformation, and (3) the unpublished studies found the same prevalence of congenital malformation as the average of the published studies. We re-calculated the pooled OR under these extreme assumptions.

All subgroup analyses, including anatomic location of the malformation, type of macrolides, and pregnancy term, were planned a priori and were identified and published in the protocol registered in PROSPERO.

All analyses were carried out using the software HEpiMA version 2.1.3 [27], and STATA version 12 (Stata Corp, College Station, TX, USA).

3 Results

Out of 2841 publications retrieved initially, 17 cohort studies [14–16, 22–25, 28–37] and 4 case–control studies [9, 11, 38–40] met our inclusion criteria and were included in the meta-analysis (Fig. 1). The data of two case–control studies that encompassed different macrolides but were carried out in the same population were analyzed together and considered as one single study [38, 40]. No clinical trial was retrieved in our search. In these 21 studies, the comparator consisted of fetuses non-exposed to any drug and/or fetuses exposed to non-macrolide antibiotics or non-teratogens before birth. ORs of birth defects after prenatal exposure to macrolides in comparison with fetuses not exposed to any

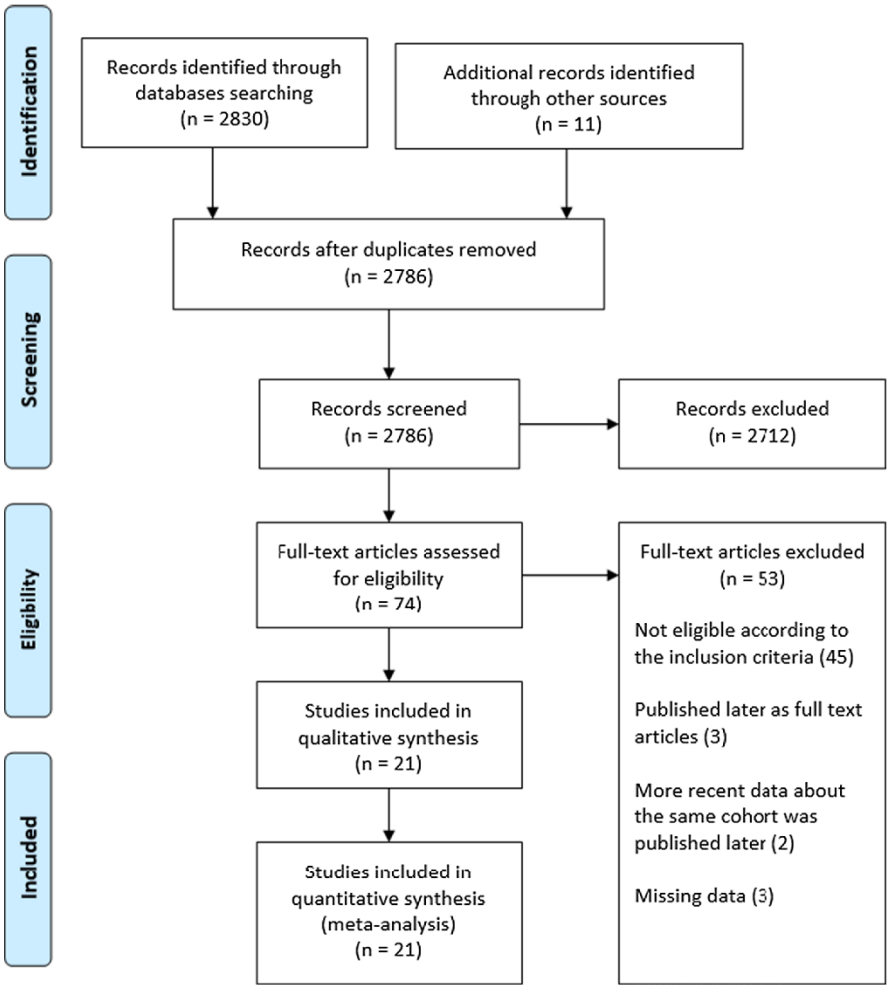

Fig. 1 Flow chart of screening for literature about prenatal exposure to macrolides and congenital malformation

drug (comparison group 1) were obtained from 14 of the 21 included studies; and ORs in reference to prenatal exposure to non-macrolide antibiotics or non-teratogens (comparison group 2) were available in 13 studies.

All case–control studies were population-based and included an average 10,483 cases and 12,937 controls. The 21 studies were mainly concentrated in Europe and North America and were carried out between 1998 and 2017 (Online Resources 2 and 3 [see Electronic Supplementary Material, ESM] and Fig. 2).

The three different analyses yielded similar results (Tables 1, 2, 3). No significant association was observed between prenatal exposure to macrolides and fetal malformation, when the unexposed population was that of fetuses not exposed to any drug ($OR_{group\ 1}$ 1.05 [95% CI 0.99–1.12]) (Table 1). Compared with fetuses exposed to non-macrolides/non-teratogens, the pooled $OR_{group\ 2}$ was 1.06 (95% CI 1.00–1.12) (Table 2). When the unexposed population was composed of fetuses non-exposed to any drug and/or those exposed to non-macrolide antibiotics or non-teratogens, the pooled $OR_{group\ 3}$ of any congenital malformation in babies born to women exposed to macrolides during pregnancy was 1.06 (95% CI 1.01–1.10) (Table 3).

Subgroup analysis in reference to fetuses unexposed to any drug before birth (comparison group 1) did not reveal any significant association between macrolides and birth defects. This lack of association was also observed in most of the subgroups in the other two analyses (comparison groups 2 and 3).

Pooled estimates of cohort studies were only significant when comparison was made in reference to the mixed population of unexposed fetuses (comparison group 3) ($OR_{group\ 3}$ 1.07 [95% CI 1.02–1.13]), while the case–control studies did not show any significant association between macrolides use during pregnancy and congenital malformations.

We did not detect any heterogeneity in the subgroup analysis that compared macrolides exposure with non-exposure to any drug during pregnancy (comparison group 1). When babies prenatally exposed to macrolides were compared with those exposed to non-macrolides/non-teratogenic drugs (comparison group 2) and to the mixed population of unexposed fetuses (comparison group 3), a substantial heterogeneity was detected in the studies assessing malformations in the urogenital system ($Ri_{group\ 2}$ 0.84 and $Ri_{group\ 3}$ 0.81), and nervous systems ($Ri_{group\ 2}$ 0.70 and $Ri_{group\ 3}$ 0.71), as well as in those evaluating the effect of erythromycin ($Ri_{group\ 2}$ 0.84 and $Ri_{group\ 3}$ 0.79). Finally, the studies involving cardiovascular malformations, digestive system malformations, and exposure during the third trimester of pregnancy also harbored a substantial amount of heterogeneity when macrolides were compared with the mixed non-exposure category ($Ri_{group\ 3}$ 0.71, $Ri_{group\ 3}$ 0.44, and $Ri_{group\ 3}$ 0.62, respectively).

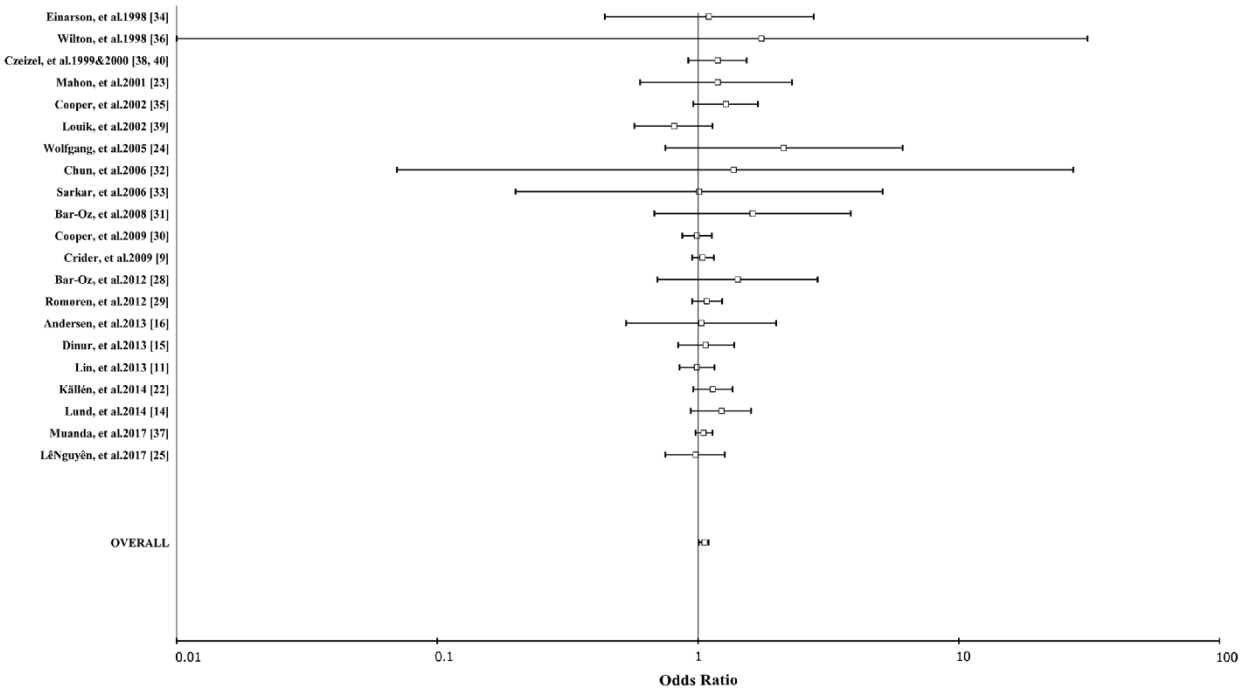

Fig. 2 Study-specific and pooled odds ratios of prenatal exposure to macrolides and congenital malformations

Table 1 Pooled odds ratios (ORs) and 95% confidence intervals (CIs) of macrolides intake and congenital malformations (comparison group 1: fetuses not exposed to any drug)

	Number of studies	OR (95% CI) fixed effects	OR (95% CI) random effects	Ri[a]	*Q* test (*p* value)
Any congenital malformation					
All studies	14	1.05 (0.99–1.12)	1.05 (0.99–1.12)	0.00	0.81
Study design					
Cohort	11	1.07 (0.99–1.15)	1.07 (0.99–1.15)	0.00	0.90
Case–control studies	3	1.02 (0.92–1.14)	1.01 (0.88–1.17)	0.39	0.21
Anatomic location					
Cardiovascular	8	1.03 (0.93–1.14)	1.05 (0.90–1.22)	0.48	0.07
Head and neck	4	1.27 (0.94–1.72)	1.27 (0.94–1.72)	0.00	1.00
Musculoskeletal system	5	1.06 (0.91–1.24)	1.06 (0.85–1.31)	0.33	0.27
Digestive system	8	1.13 (0.97–1.31)	1.12 (0.9–1.33)	0.18	0.30
Urogenital system	5	1.00 (0.80–1.24)	0.98 (0.71–1.35)	0.43	0.17
Nervous system	4	1.14 (0.86–1.52)	1.12 (0.81–1.55)	0.19	0.28
Adjustment					
Full	2	1.04 (0.94–1.15)	1.04 (0.94–1.15)	0.00	0.50
Incomplete	12	1.06 (0.98–1.15)	1.06 (0.98–1.15)	0.00	0.75
Quality score					
≥4	7	1.04 (0.95–1.14)	1.04 (0.95–1.14)	0.00	0.78
<4	7	1.06 (0.98–1.16)	1.06 (0.98–1.16)	0.00	0.56
Macrolide exposure period					
First trimester	11	1.07 (1.00–1.14)	1.07 (1.00–1.14)	0.00	0.93
Third trimester	3	1.00 (0.79–1.28)	1.08 (0.73–1.59)	0.60	0.11
Geographic location					
Europe	6	1.10 (0.98–1.23)	1.10 (0.98–1.23)	0.00	0.71
North America	6	1.03 (0.96–1.12)	1.03 (0.96–1.12)	0.00	0.45
Type of treatment					
Erythromycin	7	1.05 (0.97–1.15)	1.05 (0.97–1.15)	0.00	0.46
Azithromycin	2	1.15 (0.97–1.36)	1.15 (0.97–1.36)	0.00	0.37
Clarithromycin	2	1.10 (0.88–1.38)	1.10 (0.88–1.38)	0.00	0.84
Roxithromycin	2	2.03 (0.75–5.48)	2.03 (0.75–5.48)	0.00	0.79

[a] *Ri* Proportion of total variance due to between-study variance

The quality score of the 21 studies ranged between 1 and 7 points, with a median of 4. In the studies that used fetuses unexposed to any medicine as a comparator, those scoring 4 points or more showed a statistically non-significant pooled OR, similar to that of the studies with lower score ($OR_{group\ 1}$ 1.04 [95% CI 0.95–1.14] vs $OR_{group\ 1}$ 1.06 [95% CI 0.98–1.16]). However, the pooled OR of studies scoring at least 4 points was statistically significant when fetuses exposed to macrolides were compared with fetuses exposed to other antibiotics ($OR_{group\ 2}$ 1.08 [95% CI 1.01–1.15]), or to the mixed population of non-exposed fetuses ($OR_{group\ 3}$ 1.07 [95% CI 1.01–1.13]). This statistical significance was not observed in studies scoring < 4 points ($OR_{group\ 2}$ 1.02 [95% CI 0.92–1.13] and $OR_{group\ 3}$ 1.04 [95% CI 0.97–1.12]).

In a similar fashion, no substantial difference was found between studies with full adjustment and those with incomplete adjustment in the three patterns of analyses.

The magnitude of the association of prenatal exposure to macrolides and congenital malformations slightly varied between geographical regions in the analyses that compared fetuses exposed to macrolides with those exposed to non-macrolides (comparison group 2) and to the mixed unexposed population (comparison group 3). The association is higher in studies carried out in a European population ($OR_{group\ 2}$ 1.15 [95% CI 1.01–1.31] and $OR_{group\ 3}$ 1.12 [95% CI 1.03–1.22]) than in North American studies ($OR_{group\ 2}$ 1.04 [95% CI 0.98–1.11] and $OR_{group\ 3}$ 1.03 [95% CI 0.98–1.09]).

In the subgroups of exposure period, macrolides were exclusively associated with a minimal increase in the

Table 2 Pooled odds ratios (ORs) and 95% confidence intervals (CIs) of macrolides intake and congenital malformations (comparison group 2: fetuses exposed to non-teratogenic drugs/non-macrolides)

	Number of studies	OR (95% CI) fixed effects	OR (95% CI) random effects	Ri[a]	*Q* test (*p* value)
Any congenital malformation					
All studies	13	1.06 (1.00–1.12)	1.06 (1.00–1.12)	0.00	0.88
Study design					
Cohort	11	1.07 (1.00–1.15)	1.07 (1.00–1.15)	0.00	0.86
Case–control studies	2	1.03 (0.93–1.14)	1.03 (0.93–1.14)	0.00	0.36
Anatomic location					
Cardiovascular	7	0.87 (0.81–0.95)	0.93 (0.80–1.07)	0.50	0.10
Head and neck	4	1.08 (0.90–1.29)	1.05 (0.78–1.42)	0.54	0.12
Musculoskeletal system	4	1.21 (1.08–1.35)	1.21 (1.08–1.35)	0.00	0.85
Digestive system	5	1.14 (0.98–1.33)	1.11 (0.90–1.38)	0.44	0.15
Urogenital system	4	0.89 (0.76–1.05)	0.92 (0.60–1.39)	0.84	0.001
Nervous system	4	1.14 (0.92–1.42)	1.05 (0.68–1.62)	0.70	0.03
Adjustment					
Full	2	1.05 (0.96–1.15)	1.05 (0.96–1.15)	0.00	0.48
Incomplete	11	1.07 (0.99–1.15)	1.07 (0.99–1.15)	0.00	0.84
Quality score					
≥4	8	1.08 (1.01–1.15)	1.08 (1.01–1.15)	0.00	0.74
<4	5	1.02 (0.92–1.13)	1.02 (0.92–1.13)	0.00	0.86
Macrolide exposure period					
First trimester	9	1.05 (0.99–1.12)	1.05 (0.99–1.12)	0.00	0.83
Third trimester	2	1.33 (0.99–1.79)	1.33 (0.99–1.79)	0.00	0.34
Geographic location					
Europe	7	1.15 (1.01–1.31)	1.15 (1.01–1.31)	0.00	0.90
North America	6	1.04 (0.98–1.11)	1.04 (0.98–1.11)	0.00	0.81
Type of treatment					
Erythromycin	6	0.92 (0.86–0.99)	0.99 (0.83–1.18)	0.84	0.00
Azithromycin	6	1.08 (0.98–1.19)	1.08 (0.98–1.19)	0.00	0.63
Clarithromycin	4	0.92 (0.82–1.04)	0.92 (0.82–1.04)	0.00	0.95
Roxithromycin	3	1.50 (0.81–2.77)	1.74 (0.69–4.37)	0.53	0.13

[a] *Ri* Proportion of total variance due to between-study variance

odds of congenital malformations ($OR_{group\ 3}$ 1.06 [95% CI 1.01–1.12]) when taken during the first trimester of pregnancy. This significant association was also limited to the analysis that involved the mixed unexposed population (comparison group 3). Exposure during the third trimester did not show any significant increase in the odds when macrolides were compared with any of the three types of unexposed population.

The studies included in this meta-analysis encompass several classes of macrolides, mainly erythromycin, azithromycin, clarithromycin, and roxithromycin. Analyzing the individual effect of each type of macrolides revealed that roxithromycin presents a substantial but statistically non-significant association with fetal malformation when compared with fetuses that were not exposed to any drug ($OR_{group\ 1}$ 2.03 [95% CI 0.75–5.48]), to fetuses exposed to non-macrolides or non-teratogenic antibiotics ($OR_{group\ 2}$ 1.50 [95% CI 0.81–2.77]), and to fetuses of both groups ($OR_{group\ 3}$ 1.63 [95% CI 0.96–2.75]). The other macrolides were not found to be associated with fetal malformations when compared with any of the three unexposed groups.

Stratifying the analysis by anatomical location showed that there is no significant association in relation to prenatal exposure to macrolides and any of the body system malformations when macrolides were compared with fetuses non-exposed to any drug (comparison group 1). Increased odds of the musculoskeletal system malformation were observed when comparison was made with fetuses exposed to non-teratogenic antibiotics ($OR_{group\ 2}$ 1.21 [95% CI 1.08–1.35]) as well as when compared with the mixed population of unexposed fetuses ($OR_{group\ 3}$ 1.15 [95% CI 1.05–1.26]). Digestive system malformations

Table 3 Pooled odds ratios (ORs) and 95% confidence intervals (CIs) of macrolides intake and congenital malformations (comparison group 3: mixed population of unexposed fetuses)

	Number of studies	OR (95% CI) fixed effects	OR (95% CI) random effects	Ri[a]	*Q* test (*p* value)
Any congenital malformation					
All studies	21	1.06 (1.01–1.10)	1.06 (1.01–1.10)	0.00	0.86
Study design					
Cohort	17	1.07 (1.02–1.13)	1.07 (1.02–1.13)	0.00	0.93
Case–control studies	4	1.03 (0.95–1.11)	1.02 (0.94–1.12)	0.14	0.35
Anatomic location					
Cardiovascular	11	0.93 (0.87–0.98)	1.03 (0.89–1.18)	0.71	0.002
Head and neck	5	1.13 (0.96–1.32)	1.12 (0.93–1.35)	0.19	0.31
Musculoskeletal system	6	1.15 (1.05–1.26)	1.15 (1.05–1.26)	0.00	0.40
Digestive system	9	1.14 (1.02–1.26)	1.10 (0.94–1.28)	0.44	0.08
Urogenital system	6	0.93 (0.81–1.05)	0.96 (0.69–1.34)	0.81	0.001
Nervous system	5	1.15 (0.97–1.36)	1.02 (0.72–1.47)	0.71	0.01
Adjustment					
Full	3	1.05 (0.98–1.12)	1.04 (0.97–1.12)	0.00	0.50
Incomplete	18	1.06 (1.00–1.12)	1.06 (1.00–1.12)	0.00	0.84
Quality score					
≥4	12	1.07 (1.01–1.13)	1.07 (1.01–1.13)	0.00	0.78
<4	9	1.04 (0.97–1.12)	1.04 (0.97–1.12)	0.00	0.70
Macrolide exposure period					
First trimester	16	1.06 (1.01–1.11)	1.06 (1.01–1.11)	0.00	0.95
Third trimester	4	1.12 (0.93–1.35)	1.15 (0.85–1.56)	0.62	0.05
Geographic location					
Europe	10	1.12 (1.03–1.22)	1.12 (1.03–1.22)	0.00	0.86
North America	9	1.03 (0.98–1.09)	1.03 (0.98–1.09)	0.00	0.74
Type of treatment					
Erythromycin	9	0.96 (0.91–1.01)	1.00 (0.88–1.14)	0.79	0.00
Azithromycin	6	1.09 (1.00–1.19)	1.09 (1.00–1.19)	0.00	0.73
Clarithromycin	5	0.96 (0.86–1.07)	0.96 (0.86–1.07)	0.00	0.97
Roxithromycin	5	1.63 (0.96–2.75)	1.66 (0.95–2.89)	0.08	0.36

[a] *Ri* Proportion of total variance due to between-study variance

were also associated with a borderline increase in the odds of malformations when macrolides were compared with the mixed unexposed population ($OR_{group\ 3}$ 1.14 [95% CI 1.02–1.26]). Cardiovascular congenital malformations were not associated with prenatal exposure to macrolides when compared with fetuses unexposed to any drug and to the mixed comparison group. However, surprisingly, prenatal exposure to macrolides was associated with decreased odds of cardiovascular birth defects when compared with other antibiotics ($OR_{group\ 2}$ 0.87 [95% CI 0.81–0.95]).

The visual examination of the funnel plot revealed some degree of asymmetry with a larger number of studies that favor the existence of effect (right-hand side of the figure) (Fig. 3). However, this asymmetry was not confirmed by the Egger's regression test (*p* value = 0.074), but the trim-and-fill procedure imputed six studies and suggested a corrected OR of 1.02 (95% CI 1.00–1.04).

Under the assumptions of our sensitivity analysis, there was no increase in the odds of malformations (OR 1.00 [95% CI 0.98–1.03]).

4 Discussion

The etiology of birth defects is not well determined and could be related to various conditions such as prenatal exposure to certain drugs. Therefore, to determine whether prenatal exposure to macrolides exerts an effect on the risk of congenital abnormalities and to study whether this effect varies according to the type of macrolide and to the exposure pregnancy term, we carried out a meta-analysis.

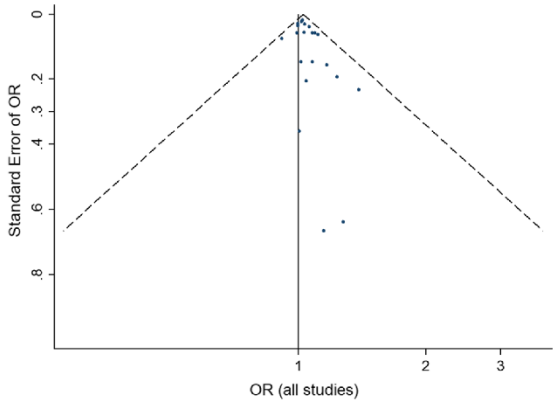

Fig. 3 Funnel plot of prenatal exposure to macrolides and any congenital malformation. *OR* odds ratio

To address any potential bias due to treatment, we carried out three analyses using comparison groups that differ by their exposure to medicines. Globally, our results suggest the existence of a weak association between prenatal use of macrolides and congenital malformations, limited to exposure in early pregnancy, and musculoskeletal and digestive systems. This association was observed only in the analysis that involved mixed exposures in the comparison group.

Our results are in line with a previous report that only found increased odds of digestive system birth defects based on two studies [17]. It was also suggested that erythromycin acts as a motilin agonist, which provokes strong gastric contractions that in turn leads to defects in the digestive system such as hypertrophy in the last trimester of pregnancy [41]. Animal studies revealed that, during the early development of the embryo, the heart is extremely susceptible to drugs that block the cardiac potassium channel (such as macrolides), which leads to bradycardia, arrhythmia, and cardiac arrest, even at concentrations not affecting the maternal heart [42]. In this meta-analysis, we also reported that the musculoskeletal system might be potentially affected by prenatal exposure to macrolides, but to date, there is lack of information that would justify this association. Moreover, we found that macrolides are associated with lower odds of cardiovascular malformations when compared with exposure to other antibiotics. This suggests, surprisingly, that macrolides could be safer than other antibiotics when used during pregnancy. A recent meta-analysis that assessed the cardiovascular safety of macrolides in reference to penicillin did not find any association between macrolides and the risk of arrhythmia or cardiovascular mortality [43].

A specific population-related effect was observed in our meta-analysis, as prenatal exposure to macrolides seems to increase the odds of birth defects in the European population more than in North America. Canfield et al. showed that many congenital anomalies vary across ethnic groups [44]. This difference between the two continents could also be due to variations in the types of infection treated in these countries. In the US, macrolides are among the first-line agents for treating respiratory infections and their prescription is approved in case of infections caused by atypical pathogens, while in Europe, atypical infections are considered less clinically relevant and patients with these infections would probably receive a β-lactam instead of macrolides, especially after the threats of macrolides resistance [45].

Publication bias may have plausibly affected the results of our meta-analysis, causing an overestimation of the effect. Indeed, we detected some asymmetry in the funnel plot and the trim-and-fill procedure imputed not fewer than six potentially unpublished studies, which yielded a corrected OR that favored the absence of effect.

Furthermore, an overestimation of the statistical significance of our results cannot be ruled out due to the fact that multiple comparisons were carried out.

As in any meta-analysis of observational studies, the results should be carefully assessed as to whether they might be biased by residual confounders that were not eliminated by adjustment. It is remarkable that only 3 out of the 21 studies were adjusted for both maternal age and urinary tract infections, factors that were associated with an increased risk of non-chromosomal congenital abnormalities in previous studies and could represent potential confounders [9, 46]. However, it is worth mentioning that the results after restriction of the analysis to the fully adjusted studies did not differ from that of the incompletely adjusted studies.

Misclassification of the outcome is highly improbable to occur for such a diagnosis. Misclassification of exposure to macrolides is also unlikely as it was well documented in more than half (13 out of 21) of the included studies, in which the corresponding data were collected through medical records. In addition, although it is unlikely that recall bias may have affected our results, we recalculated the pooled OR by excluding the studies that assessed exposure using a questionnaire or an interview (and not medical records), and the results remained unaltered. However, exposure to macrolides might be misclassified if some women did not actually take the macrolides that were prescribed.

Due to the absence of data in the original studies, the results of our meta-analysis are limited by the absence of dose–response analysis. In addition, due to unavailability of data, we did not consider malformation outcomes in abortions or stillbirths. Therefore, we cannot rule out a mutagenic effect of macrolides that could have caused abortions or stillbirths.

5 Conclusion

In summary, our meta-analysis showed that the increase in the odds of birth defects among women who consumed macrolides during their pregnancy is very low. However, a harmful effect of macrolides cannot be ruled out, especially for the musculoskeletal and digestive systems. Risk–benefit research is needed to address the question of whether macrolide prescription should be restricted during pregnancy.

Author Contributions Conception and design of the study: BT and ME; Conceptualization of the manuscript and review and synthesis of the literature: NM; Data extraction: NM and HT; Coordination and supervision of data extraction and analysis: BT and AF; All authors made substantial contribution to the interpretation of data, critically reviewed the manuscript, and approved its submission for publication.

Compliance with Ethical Standards

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Conflict of interest Narmeen Mallah, Hamid Reza Tohidinik, Mahyar Etminan, Adolfo Figueiras, and Bahi Takkouche declare that they have no conflict of interest.

Data Sharing All data generated or analyzed during this study are included in this published article and its Supplementary Information File (Online Resource 1, see ESM).

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Annex III. International Mention of PhD Degree

Authorization of the Academic Commission of Doctoral Program in Epidemiology and Public Health for a three-month research stay at Karolinska Institutet, Sweden

PROGRAMA DE DOUTORAMENTO EN
EPIDEMIOLOXÍA E SAÚDE PÚBLICA
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A Comisión Académica do Programa de Doutoramento en Epidemioloxía e Saúde Pública, informou favorablemente a solicitude da estudante Narmeen Mallah para realizar unha estadía de investigación dentro do Programa ERASMUS no Karolinska Institutet, desde a data 1/1/2021 ata 31/3/2021.
Por ser a única solicitante, elévase esta proposta de concesión provisional a definitiva.

En Santiago de Compostela, a 28 de decembro de 2019

O/A Coordinador/a da CAPD

MONTES MARTINEZ AGUSTIN - 76804086W

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Report about three-month research stay from the supervisor at Karolinska Institutet, Sweden

Dept. Global Public Health
Head of Biostatistics Team
Senior Researcher of Biostatistics
Associate Professor of Medical Statistics
Nicola Orsini, PhD
http://ki.se/en/phs/biostatistics-team

Stockholm, March 31, 2021

To Whom It May Concern

This is to certify that Mrs **Narmeen Mallah** ([redacted]) spent a three-month research stay between 01/01/2021 and 31/03/2021, under my supervision at the Department of Global Public Health, Karolinska Institutet.

During her stay, Mrs Mallah learned dose-response meta-analysis techniques that she applied on two studies related to her doctoral thesis. The first study "Income level and antibiotic misuse: a dose-response meta-analysis" has been completed, presented to Equity and Health Policy Research Group at our department, and the corresponding manuscript was prepared for submission. The second study "Education level and antibiotic misuse: a dose-response meta-analysis" is in an advanced stage and the corresponding manuscript will be prepared soon.

Mrs Mallah also actively participated in the regular meetings of the Equity and Health Policy Research Group to which I belong. The overall performance of Mrs Mallah was excellent. She was attentive to detail and consistent in her research activities; very good in oral and written communications; set ambitious goals and managed well her time in order to achieve these goals independently. In addition, Mrs Mallah demonstrated commitment to the research activity, openness to criticisms, and willingness to makes appropriate decisions.

Sincerely,
Nicola Orsini

Report about activities performed during three-month research stay at Karolinska Institutet, Sweden

Karolinska Institutet

2021-03-22

Dnr: <Dnr>
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Department of Global Public Health
Bo Burström, MD PhD
Professor in Social Medicine

Narmeen Mallah

This is to certify that Narmeen Mallah, during her exchange visit at the Department of Global Public Health, Karolinska Institutet, orally presented her research project on Income and antibiotic misuse to our Equity and Health Policy Research Group, on March 22, 2021.

Narmeen's presentation was extremely well prepared, both in terms of its content and the layout, as well as the performance. Narmeen also responded to all questions from the group, showing her deep knowledge both of the methodology and of the results of her study.

It has been our great pleasure to have Narmeen as a visitor to our research group from January through March.

Bo Burström MD, Professor in Social Medicine
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