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Improving Adverse Drug Reaction Reporting in Portuguese Health Professional: case-control studies and cluster-randomized trial

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Informan:

Que el trabajo titulado "**Improving Adverse Drug Reaction Reporting in Portuguese Health Professional: case-control studies and cluster-randomized trial"** que presenta la Licenciada en Ciencias Farmacéuticas y Mestre en Ciencias e Ingeniaría Alimentar Dra. Maria Teresa Ferreira Herdeiro para optar al grado de Doctora, fue realizado bajo nuestra dirección, y que estando concluido autorizamos su presentación con el fin de que pueda ser juzgado por el tribunal correspondiente.

Y para que así conste, firmamos el presente informe, en Santiago de Compostela, a Julio de 2005.

Adolfo Figueiras Guzmán Jorge Junqueira Polónia Juan Jesus Gestal Otero

To my husband Paulo, for his love and comprehension.

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Abbreviations

ABBREVIATION	MEANING
ADR	Adverse Drug Reaction
US	United States
UK	United Kingdom
WHO	World Health Organization
FDA	Food and Drug Administration
INFARMED	National Institute of Pharmacy and Medicine
CPMP	Committee for Proprietary Medicinal Products
EMEA	European Agency for Evaluation of Medicinal Products
PhVWP	Pharmacovigilance Working Party
VIGIMED	Restricted e-mail distribution list of set up to stimulate discussion and facilitate rapid exchange of information between representatives of National Centres participating in WHO International Drug Monitoring Program
MEDLINE	Comprehensive Source of Life Sciences and Biomedical Bibliographic Information
OR	Odds Ratio
CI 95%	Confidence interval 95%
RR	Relative rate
RF	Report Form

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RESUMEN EN CASTELLANO

INTRODUCCIÓN

Las reacciones adversas a medicamentos (RAM) es un importante y persistente problema de Salud Pública en términos de morbi-mortalidad y de costes. En un estudio realizado en los Estados Unidos (EE.UU.) se estimó que más de 100.000 personas mueren cada año a consecuencia de las RAM, y que más de 2 millones sufren importantes efectos secundarios, situándose entre la cuarta y la sexta causa de muerte en los EE.UU. En un estudio realizado en el Reino Unido mostró que uno de cada 16 admisiones hospitalarias son causadas por RAM. El coste exacto atribuible a las reacciones adversas no esta bien determinado, es sabido que aumentan de forma importante el tiempo de estancia y los costes sanitarios.

La información sobre la seguridad de un medicamento cuando sale al mercado es limitada. Algunas reacciones adversas de baja incidencia o que ocurren a largo plazo son difíciles de detectar en las fases de investigación clínica precomercialización, debido a que a menudo los ensayos precomercialización tienen bajo poder estadístico para detectar RAM y tiene cortos periodos de seguimiento. En los últimos años se han producido un número significativo de retiradas del mercado de nuevas moléculas después de ser aprobadas por las autoridades sanitarias. Estas retiradas se han producido después de haber provocado importantes problemas de salud pública. Por ejemplo, se ha estimado que el *rofecoxib* ha provocado 100.000 ataques cardiacos e infartos en EE.UU. antes de su retirada, la tercera parte de ellos fatales. Varios autores relacionan estos casos con el papel que las compañías farmacéuticas tienen en la farmacovigilancia de sus propios productos (en EE.UU. entorno al 90% de las notificaciones de RAM provienen de las compañías farmacéuticas). Se ha demostrado que la información de farmacovigilancia proporcionada por los laboratorios a las autoridades sanitarias puede ser enviada tarde o no ser notificada total o parcialmente.

Los sistemas de notificación espontánea permiten a los profesionales de salud notificar directamente a las autoridades sanitarias, y son componentes básicos de la vigilancia post-comercialización de los riesgo inducidos por los medicamentos. Los sistemas de notificación espontánea de RAM por los profesionales sanitarios es la fuente más efectiva para la detección de RAM, y fueron diseñadas para la rápida detección de RAM raras o inesperadas, para a partir de ellas generar hipótesis a poner a prueba en siguientes estudios. Sin embargo, la baja tasa de notificación –se estima que solo se notifica un 10% de las RAM que se producen– limita en gran medida las ventajas de este método de farmacovigilancia.

En Portugal la notificación espontánea de RAM a través de la "tarjeta amarilla" inicialmente dirigida a médicos se inició en 1992. Los farmacéuticos fueron incorporados al sistema en 1995, notificando en colaboración con los médicos hasta 1997, como en otros países. Desde entonces pueden enviar directamente sus notificaciones. La tasa de notificación en Portugal en 2001 fue de 134 notificaciones/millón de habitantes. De las 1342 notificaciones recibidas en el Instituto Nacional da Farmacia y do Medicamento, 837 fueron notificaciones directas de los profesionales sanitarios. El número de notificaciones disminuyo en 2002 (126 notificaciones /millón habitantes) y en 2003 (110 notificaciones /millón habitantes). Comparando Portugal con otros países, las notificaciones por millón de habitantes provenientes de médicos son de 71,51 frente a 138,7 de España, 290,9 de Francia, 288,1 del Reino Unido o 374,0 de Suecia que tienen una tasa de notificación más elevada; pero por otro lado, países como EE.UU. (69.65), Canadá (53,7), Alemania (36,9), Italia (16,1) y Grecia (28,0) tienen tasas de notificación inferiores a las de Portugal en 2001. Para farmacéuticos es difícil realizar comparaciones porque las notificaciones provenientes de los farmacéuticos aun no son contabilizadas en algunos países, aunque hay importantes referencias al importante papel que desempeñan en la monitorización de RAM por su buena relación con el paciente antes y durante el curso del tratamiento. También pueden jugar un importante papel en la monitorización de RAM en hospitales y son los únicos profesionales en contacto con los medicamentos OTC y medicamentos de herbolario.

A pesar de que la infranotificación es la principal limitación de los sistemas de notificación de RAM en todos

los países, las razones para ello aun no están claras. Factores como la dificultad de percibir la importancia de la contribución individual al conjunto del conocimiento de la seguridad del medicamento, la falta de certeza en el diagnóstico de una RAM, falta de tiempo, falta de interés, falta de tarjetas amarillas, y miedo a consecuencias legales han sido descritos como potenciales causas de la infranotificación. Inman propuso en 1976 algunas actitudes como potenciales causas de la infranotificación en médicos, y aunque varios estudios buscaron la relación con estas actitudes, la mayoría de los estudios no encontraron asociación y si lo hicieron fue solo en una, dos o tres actitudes. En contraste con la atención dada a los médicos sobre las rezones de no notificar, ente los farmacéuticos no han sido estudiados. Que nosotros conozcamos, no hay estudios que valoren la influencia ejercida por varios de estos factores (conocimientos, actitudes, profesionales y características personales) en la notificación de los farmacéuticos. Nosotros solo hemos localizado tres estudios que describen las opiniones y actitudes de los farmacéuticos hacia la notificación de RAM, sin embargo no las relacionaba con su mayor o menor probabilidad de notificar.

Cuando revisamos la literatura sobre posibles intervenciones para mejorar la notificación entre los profesionales sanitarios, nosotros solo encontramos cuatro artículos que desarrollen una intervención educativa con el propósito de mejorar la notificación de RAM en médicos, y ninguno de ellos es un ensayo controlado aleatorio. Para los farmacéuticos nosotros solo encontramos dos artículos relacionados con este asunto. Todo esto subraya la falta de evidencia de calidad en la efectividad de intervenciones en esta área.

Para evaluar si una intervención educativa podía disminuir la infranotificación se puso en marcha en Portugal un estudio en dos fases. En la fase I se identificaron los conocimientos y actitudes de los médicos y de los farmacéuticos asociados a la infranotificación. En la fase II se diseñó una intervención educativa diseñada específicamente a partir de estos conocimientos y actitudes, y fue evaluada su efectividad mediante un ensayo controlado aleatorio por *clusters*.

OBJETIVOS

1. Identificar los factores sociodemográficos y personales relacionados con la infranotificación de RAM en los profesionales de salud (los médicos y los farmacéuticos).
2. Identificar los conocimientos y las actitudes de los profesionales de salud (los médicos y los farmacéuticos) relacionados con la notificación de RAM.
3. Valorar si una intervención educativa diseñada para modificar los conocimientos y actitudes –identificadas como asociadas a la infranotificación en el segundo objetivo– aumenta la cantidad y la calidad (relevancia) de la notificación espontánea de RAM en los profesionales de salud (los médicos y los farmacéuticos).
4. Valorar la duración del efecto de la intervención educativa en calidad y cantidad, en médicos y farmacéuticos.
5. Valorar si administrar una tarjeta amarilla/morada durante la intervención aumenta la probabilidad de notificación espontánea de RAM.

MÉTODOS

El estudio se llevo a cabo en la región Norte de Portugal tiene una extensión aproximada de 20.000 Km^2, y 3.7 millones de habitantes (aproximadamente el 50% en la zona metropolitana de Oporto), con el 14% de ellos de más de 65 años. En la región norte hay 25 hospitales y 104 centros de salud. De los 25 hospitales, 15 de ellos son hospitales de referencia (hospitales que cubren un área geográfica determinada), 5 son específicos (p. ej. oncológico, materno-infantiles que abarcan la población de varios hospitales de referencia), y 5 son de pequeño tamaño.

Estudios de casos y controles

Se realizaron dos estudios de casos y controles, uno para médicos y otro para farmacéuticos. Para los médicos, la población estaba definida por los profesionales que trabajaban en el Sistema Nacional de Salud. Los casos eran los 88 profesionales que notificaron al menos una RAM al centro regional de Farmacovigilancia desde enero de 2001 hasta el inicio del estudio a finales de 2002. Los 771 controles eran una muestra de los médicos que nunca habían notificado ninguna tarjeta amarilla.

Entre los farmacéuticos, los casos eran los 34 profesionales que habían notificado alguna tarjeta morada al centro de farmacovigilancia y los controles eran una muestra de 280 profesionales que no habían notificado ninguna tarjeta morada.

La recogida de datos se basó usando un cuestionario autoadministrado. Los conocimientos y actitudes acerca de la notificación espontánea de RAM estaban basados en "los siete pecados capitales" de Inman. El grado de acuerdo con cada una de las cuestiones incluidas en el cuestionario fue medida mediante una escala analógica visual horizontal continua y no numerada de aproximadamente 8 cm. Las respuestas se cuantificaron de cero a 10 con una precisión de 0.5.

Se utilizó regresión logística para determinar el Odds Ratio ajustado asociado al cambio en la exposición correspondiente al rango intercuartílico de cada actitud (IqOR).

Ensayo controlado aleatorio por clusters

La población de nuestro estudio esta compuesta por todos los médicos y farmacéuticos menores de 71 anos que trabajaban en el Sistema Nacional de Salud de la región Norte de Portugal. Se excluyeron del estudio los médicos sin actividad clínica (labores administrativas, genética, histocompatibilidad), los que trabajaban en centros de toxicodependencias, los que trabajaban en el centro regional de farmacovigilancia o en aquellos servicios que tenían un programa específico de notificación voluntaria de RAM. También fueron excluidos del estudio los médicos que desarrollaban sus actividades en hospitales específicos.

Diseño del estudio

Se ha llevado a cabo un ensayo controlado aleatorio con dos años y medio de seguimiento. Con el fin de eliminar la cross-contaminación entre los dos grupos de estudio (intervención y control), las unidades de asignación no fueron médicos o farmacéuticos, sino *spatial-clusters*. Cada *spatial-cluster* estaba constituido por todos los médicos y farmacéuticos que trabajaban en los hospitales, en los centros de salud y en las farmacias comunitarias de la zona geográfica. Los clusters tenían el tamaño mínimo que permitía minimizar la contaminación entre atención hospitalaria, primaria y farmacias. Así, cada *spatial-cluster* estaba formado por un hospital de referencia junto con los centros de salud, otros posibles hospitales de su zona de influencia, y las farmacias comunitarias. Se formaron 15 *spatial-clusters*, de los que fueron excluidos los hospitales específicos ya que, al tener como zona de influencia a toda la región, aumentaban el riesgo de contaminación.

La mayoría de los ensayos aleatorios por clusters distribuyen aproximadamente el mismo número de cluster al grupo de intervención y al de control. Este es el distribución mas eficiente desde el punto de vista estadístico, pero puede no ser la mas eficiente económicamente. Cuando la intervención bajo evaluación tiene una diferencia importante de coste respecto a la del grupo control puede ser más económicamente eficiente distribuir aleatoriamente menos clusters al grupo de intervención que al de control. Nosotros distribuimos los 15 clusters mediante *unequal randomization* con una proporción aproximada de 1:4 para los grupos de intervención: control. La distribución se realizó mediante un procedimiento informático, quedando 4 clusters asignados al grupo de intervención y 11 al de control.

Clusters del grupo de intervención

Según la clasificación de Grimshaw et al, se realizó una intervención múltiple compuesta por visitas externas, mas recordatorio, mas una tarjeta amarilla /morada. El diseño de la intervención educativa se realizó a partir de los resultados de los estudios de casos y controles en los que se encontró que en los médicos la notificación estaba fuertemente asociada a varias actitudes (*complacency, insecurity, diffidence, indifference, y ignorance*) propuestas por Inman como determinantes de la notificación. En los farmacéuticos se encontró que estaban asociadas a tres (*complacency, diffidence, y ignorance*).

Se diseñó un material didáctico interactivo que incidía, en primer lugar, sobre la importancia de las RAM en términos de morbilidad, mortalidad y de costes. Luego se justificaban las limitaciones de los ensayos clínicos para la detección de RAM, y se explicaban las ventajas del sistema de notificación voluntaria y que la infranotificación era su principal limitación. En tercer lugar se incidían en mensajes para modificar las actitudes de *complacenc, insecurity, diffidence, indifference, ignorance*. En cuarto lugar se incidía en que solo necesita de cinco minutos para rellenar la tarjeta amarilla/morada. Finalmente se explicaban los mecanismos para notificar en Portugal (teléfono, fax, web, o tarjeta amarilla /morada). También se elaboró un díptico de color amarillo o morado con los principales mensajes de la presentación.

Antes de las visitas se enviaba una carta a los directores de cada uno de los centro de salud, directores técnicos de farmacia y a los directores clínicos de los hospitales seleccionados explicando los objetivos del estudio y pedirle su consentimiento para participar en el ensayo. La intervención fue aprobada por la comisión de docencia de cada hospital y fue incluida como edu-

cación médica continuada de cada centro. La intervención fue realizada por uno de los investigadores (MTH) que participó en el diseño y preparación de la intervención. La intervención se realizó entre marzo y julio de 2004 y duraba entorno a una hora, con aproximadamente 30 minutos de presentación y otros 30 minutos de coloquio. Los grupos estaban formados entre 10 y 20 médicos, mientras que para los farmacéuticos los grupos estaban constituidos generalmente por entre 1 y 5 profesionales. Al final de la presentación se daba un díptico a cada médico o farmacéutico. Con el fin de evaluar la influencia de proporcionar la tarjeta amarilla/morada sobre la notificación, a un grupo de médicos y farmacéuticos (seleccionados de forma no aleatoria) no se facilitó la tarjeta amarilla/morada a cinco centros de salud, diez farmacias comunitarias, un servicio de farmacia hospitalaria y a tres servicios hospitalarios del grupo de intervención (aproximadamente 10% del grupo de intervención). La tarjeta amarilla/morada no fue facilitada a ningún medico o farmacéutico que no asistió a la intervención.

Clusters del grupo de control

Los médicos y farmacéuticos de los clusters del grupo control no recibieron la intervención pero, al igual que los del grupo de intervención, si recibieron la información y la formación usual proporcionada por el centro regional de farmacovigilancia de la región norte de Portugal.

Seguimiento y fuentes de datos.

Se realizó un seguimiento de 30 meses entre enero de 2003 y junio de 2005 ambos inclusive. Durante este seguimiento para cada médico o farmacéutico y en cada mes de seguimiento se generaron las siguientes variables dependientes: (1) número de notificaciones de RAM totales; (2) graves; (3) imputación de causalidad, definitiva o probable; (4) inesperadas; y (5) de medicamentos con menos de cinco años en el mercado. Todos estos datos y la clasificación de las RAM provenían del centro Regional de Farmacovigilancia del Norte de Portugal. Las variables independientes características de los médicos estudiados (edad, sexo, especialidad y lugar de trabajo) fueron obtenidos a partir de los registros de personal del SNS portugués. Para los farmacéuticos (edad, sexo y lugar de trabajo) fueron obtenidos a partir de los registros de la asociación de farmacéuticos hospitalarios y de la asociación nacional de farmacias.

Análisis estadístico

Todo el análisis estadístico se realizó por intención de tratar; por se motivo los sujetos que, aunque fuesen asignados al grupo de intervención no la recibieron fueron incluidos también en el análisis como pertenecientes al grupo de intervención. La inclusión de todos los sujetos en el análisis estadístico elimina cualquier sesgo de selección por la no asistencia de los médicos a la intervención.

Para el análisis estadístico se utilizaron modelos lineales mixtos con *penalized quasi-likelihood*. Para elaborar los modelos, nosotros tomamos como variable dependiente el número de notificaciones (totales, graves, definidas o probables, inesperadas, y medicamentos nuevos) de cada mes, el término independiente como efecto aleatorio, y la distribución aleatoria de los *spatial-cluster* como efecto cluster. Los modelos se ajustaron por aquellas variables sociodemográficas y personales por las que en las que los grupos pudiesen quedar desequilibradas después de la distribución al azar.

Para medir el efecto de la intervención, se creo una variable indicadora dicotómica. Esta variable –llamada *periodo*– toma valores 0 para el periodo basal y 1 para los meses entre la intervención y el final del seguimiento. El efecto de la intervención fue evaluado a través de la interacción entre la variable grupo (1 para grupo de intervención, y 0 para el grupo control) y la variable periodo. Para el análisis de la duración del efecto, se construyó otra variable indicadora con cinco categorías (valor 0 para el periodo basal, 1 para el primer cuatrimestre después de la intervención, y 2, 3, 4 para los siguientes). El efecto de la intervención en cada cuatrimestre se evaluó a través de de la interacción entre esta variable indicadora y la variable grupo. Todos los análisis se realizaron utilizando software S-Plus. Los resultados se expresan en RR y sus intervalos de confianza al 95%, que nos indican las veces que aumenta la exposición la probabilidad de notificar.

RESULTADOS

Estudios de casos y controles

Un total de 397 cuestionarios fueron recibidos de 731 médicos elegibles (54.3%). Los médicos que trabajaban en atención primaria tienen una mayor probabilidad de notificar que los que trabajan en medio hospitalario, y los médicos generales o los de especialidades médicas tienen mayor probabilidad de notificar que los de especialidades quirúrgicas o médico-quirúrgicas. Las actitudes respecto a las RAM están fuertemente asociadas a la probabilidad de notificar.

Así, una disminución de una magnitud de un intercuartil de las siguientes actitudes aumenta la probabilidad de notificar en un: (a) 87% (p<0.05) para la *complacency* (creer que las reacciones adversas realmente serias ya están bien documentadas cuando el medicamento sale al mercado), (b) 109% (p<0.01) para la *insecurity* (creer que prácticamente imposible determinar cuando un medicamento es responsable de una reacción adversa en particular), (c) 143% (p<0.001) para *diffidence* (creer que solo se debería notificar una reacción adversa si se esta seguro de que esta relacionada con el consumo de un determinado medicamento), (d) 220% (p<0.001) para *indifference* (considerar que un caso de un médico individual no puede aportar mucho conocimiento al conocimiento médico), y (e) 71% (p<0.05) para *ignorance* (cree que solo es necesario notificar RAM serias o inesperadas).

Para farmacéuticos la tasa de respuesta fue del 86.8%. La probabilidad de notificar fue mayor en los farmacéuticos hospitalarios que en los comunitarios (OR=20.0; 95CI: 3.3-125.0, p<0.001). Las actitudes hacia las RAM están fuertemente asociadas con la probabilidad de notificar. Así, una disminución equivalente al rango intercuartílico disminuye en cada una de las siguientes actitudes en: (a) 223% (IC95%: 51% a 595%, p<0.05) para la *complacency* (creer que las reacciones adversas realmente serias ya están bien documentadas cuando el medicamento sale al mercado); (b) 240% (IC95%: 89% a 508%) para *diffidence* (creer que solo se debería notificar una reacción adversa si se esta seguro de que esta relacionada con el consumo de un determinado medicamento), (c) 316% (IC95%: 44% a 1104%, p=0.010) para *ignorance* (cree que solo es necesario notificar RAM serias o inesperadas).

Estudio controlado aleatorio por clusters

Del total de 6950 médicos iniciales, fueron excluidos del ensayo 40 médicos por desarrollar tareas administrativas y en centros de genética y histocompatibilidad, 24 por trabajar en centros de toxicodependencias, 3 por estar en centro de farmacovigilancia e protocolo y 432 por trabajar en hospitales específicos. Finalmente fueron influidos en el análisis 6451 médicos, de los cuales 1388 pertenecían al grupo de intervención y 5063 pertenecían al grupo de control. De los sujetos del grupo de intervención asistieron a la intervenciones 655 (47.2%). La tarjeta amarilla no fue facilitada a 184 médicos (13.3%) del grupo de intervención. La mediana del periodo se seguimiento fue de 13 meses para el periodo post-intervención. Del total de 1451 farmacéuticos se excluyeron 2 por ser miembros del centro regional de farmacovigilancia. Además, 16 farmacéuticos trabajaban en hospitales específicos también fueron excluidos. Finalmente, 1433 farmacéuticos fueron incluidos, 342 en el grupo de intervención, y 1091 al grupo control. La tarjeta morada no fue administrada a 46 farmacéuticos. El número de farmacéuticos del grupo de intervención que realmente recibieron la intervención fueron 276 (80.7%).

Respeto a las características básales del grupo de intervención y de control para los médicos, se observa que la distribución por sexos y por edad es similar, pero hay una menor proporción de médicos generales y de médicos que trabajan en atención primaria en los clusters el grupo de intervención. Cuando comparamos los valores básales de las notificaciones los médicos del grupo intervención tenían un promedio de notificación global, de RAM graves, con causalidad definitiva o probable inferior a la del grupo control, mientras que tienen unos valores similares en medicamentos nuevos. Los farmacéuticos, el grupo de intervención tiene un promedio de RAM graves, con causalidad definitiva o probable inferior a la del grupo control, mientras que tienen unos valores ligeramente superior para la notificación global y para las inesperadas. Todas estas posibles diferencias en los valores básales entre grupos no sesgan los resultados porque Poisson-GLMM ajusta por estas diferencias básales.

Las tasas de notificación de los médicos por el total de RAM y por tipos de RAM, en cada uno de los periodos de estudio, ajustada por los valores básales y por especialidad y lugar de trabajo, se observa que la intervención incrementa la tasa de notificaciones total en 10 veces (RR=9.65; p<0.001) a lo largo del periodo post-intervención. El efecto de la intervención en la tasa de notificación ajustados por los valores básales y por el lugar de trabajo de los farmacéuticos incrementa la tasa de notificación en 5-veces (RR=5.87; p=0.001) durante el periodo pos-intervención.

Al analizar la evolución mensual de la tasa de notificación por 1000 médicos-mes en el grupo de intervención y en el de control, se muestra que la tasa de notificación en el grupo de intervención se incrementa bruscamente cuando se inicia la intervención (en el primer cuatrimestre la notificación se aumenta en mas 20 veces (RR=23.3; p<0.001), y posteriormente decrece, pero se mantiene una tasa de notificación entre 4.7 y 6.6 veces superior –y estadísticamente significativas– a la del control en el segundo, tercer y cuarto cuatrimestre. Al estudiar la evolución mensual de la tasa de notificación por 1000 farmacéuticos-mes en el grupo de intervención y en el de control, se observa que cuando empieza la intervención, en los primeros cuatro meses

la tasa de notificación se incrementa en mas de 20 veces (RR=20.2; p<0.0001) y luego disminuye, pero se mantienen entorno a 3 veces mas que el grupo control en el segundo y tercer cuatrimestre. En el cuarto cuatrimestre la intervención incrementa en casi tres veces la notificación pero no es estadísticamente significativa (RR=2.77; p= 0.354).

El efecto de la intervención sobre la notificación de reacciones adversa graves, inesperadas, con causalidad definida o probable, y sobre los medicamentos nuevos en médicos, se observa que la intervención multiplica por seis veces (RR=6.1, p=0.001) la tasa de notificación de RAM graves, por 8 veces (RR=8.5, p<0.001) la tasa de notificación de RAM con causalidad definida o probable, en 32 veces (RR=32.6, p<0.001) la tasa de notificación de RAM inesperadas, y en 8 veces la tasa (RR=8.2, p=0.002) de notificación de RAM de medicamentos nuevos. En farmacéuticos se muestra que la intervención multiplica por 10 veces (RR=9.8; p=0.002) la tasa de notificación de RAM graves, por 8 veces (RR=8.7; p=0.002) la tasa de notificación de RAM con causalidad definida o probable, en 4 veces (RR=4.4; p=0.04) la tasa de notificación de RAM inesperadas, y en 9 veces (RR=9.3; p<0.001) la tasa de notificación de RAM de medicamentos nuevos.

DISCUSIÓN

Discusión del método

La principal limitación de los estudios de casos y controles tanto de médicos y farmacéuticos es la diferente porcentaje de respuesta entre los casos y los controles. Sin embargo, es razonable pensar que los controles que participaron son probablemente los más motivados. Si aun así, nosotros observamos diferencias entre las actitudes/conocimientos los casos y los controles, es razonable suponer que estas diferencias serían aun mayores si los casos se comparasen con todos los controles, incluidos los no respondedores. La tasa de respuesta global en farmacéuticos se puede considerar como muy buena (86,8%) mientras que en médicos (54.3%), no es muy alta, pero es razonablemente buena especialmente si lo comparamos con otros estudios realizados en la Unión Europea por *European Pharmacovigilance Research Group*, en el que la tasa de respuesta obtenida en Portugal fue del 37.0%.

El ensayo controlado aleatorio por cluster presenta varias fortalezas y limitaciones. Utilizar un grupo control permite eliminar otros potenciales fuentes de sesgos como variaciones estaciónales o "brotes" de notificaciones. Nuestro ensayo al ser aleatorio, evita potenciales sesgos de selección y al realizar la distribución por cluster disminuye el riesgo de contaminación entre grupos, pero aumenta el riesgo de que los grupos queden desequilibrados por valores básales, sobre todo cuado el número de clusters es pequeño como es el caso de nuestro ensayo. Nosotros eliminamos este efecto ajustando en el análisis estadístico por las variables que han quedado desequilibradas tras la randomización y por los valores básales de las variables dependientes y comparando los cambios antes y después dentro del grupo de intervención con la del control. Otra posible limitación es el bajo porcentaje de participación en el grupo de intervención (aunque es cifra parecida a la de otros estudios con sesiones en grupo). Para evitar que el porcentaje de participación produzca un sesgo de selección (posiblemente los médicos que asistieron son los más motivados), se realizó el análisis estadístico por "intención de tratar" Este enfoque infraestima la eficacia de la intervención, pero proporciona una medida mas cercana a su efectividad.

Discusión de resultados

Estudios de casos y controles

Nosotros resultados indican que las actitudes e conocimientos dos médicos e farmacéuticos son un factor determinante en infranotificación de RAM. Desde 1976, cuando Inman propuso los "siete pecado capitales" como a principal razón de la infranotificación, varios estudios intentaron valorar estas relaciones. Este es el primer estudio que encuentra una fuerte asociación entre las actitudes y conocimientos relacionados con los "siete pecados capitas" y la subnotificación para los médicos e farmacéuticos. Además, nuestros resultados sugieren que el tipo de especialidad médica y el local de trabajo (hospital versus centros de salud) ejercen influencia en la notificación de los médicos. La probabilidad de notificar es mas baja en las especialidades quirúrgicas y médico-quirúrgicas. Por otro lado, los médicos que trabajan en el hospital notifican siete veces menos que los médicos que trabajan en centros de salud. Estos resultados son similares a otros realizados en España, Alemania, EE.UU. y Reino Unido. Para los farmacéuticos la situación es diametralmente opuesta a la de los médicos: los farmacéuticos hospitalarios tienen una probabilidad de notificar mas elevada que la de los farmacéuticos comunitarios.

Nosotros encontramos que los farmacéuticos y médicos portugueses no sienten la necesidad de una recompensa económica por algo que sienten que tienen

la responsabilidad profesional de realizar, y que no compromete su responsabilidad legal. Estos resultados están en línea de otros estudios realizados en Europa pero son diferentes a otros realizados en EE.UU. Otro factor propuesto fue la ambición de publicar, pero no parece un motivo importante entre los médicos e farmacéuticos portugueses, ya que una búsqueda en el Medline, apenas hay estudios sobre la notificación.

Para médicos, nuestro estudio es el primero en encontrar una asociación entre la probabilidad de notificar y todas las 5 razones propuestas por Inman (*complacency, insecurity, diffidence, indifference* y *ignorance*) en contraste con otros estudios que encontraron apenas una, dos, tres o cuatro de estas razones relacionadas con a notificación. Este es el primer estudio que analiza a relación entre as actitudes e conocimientos de los farmacéuticos y la notificación (*complacency, diffidence* y *ignorance*). Los otros estudios realizados sobre el mismo tema apenas describen las opiniones de los farmacéuticos acerca das RAM. Consideramos que las discrepancias entre nuestro estudio y otros publicados se deben a la utilización de una escala analógica visual. Esta escala es capaz de detectar pequeñas, pero relevantes, diferencias en las actitudes y conocimientos de los médicos e farmacéuticos que no es posible captarlas cuando se usa una escala tipo categórica con 3 ó 4 categorías. Así, gracias a esta escala, detectamos una fuerte asociación entre las actitudes y la notificación. De acuerdo con nuestros datos, para los médicos, potenciales cambios equivalentes al intervalo interquartílico puede llevar asociado un aumento da probabilidad de notificar de un 100% para actitudes como *insecurity, diffidence* y *indifference* y un 50% para *complacency*, y *ignorance*. Para los farmacéuticos estas alteraciones del grado de acuerdo aumentaría la probabilidad de notificar RAM en 240 % para a, *diffidence*, un 223% para la *complacency*, y un 316% para a *ignorance*.

Estudio controlado aleatorio por clusters

En este gran ensayo controlado por clusters los médicos multiplican por más de 9 veces la tasa de notificaciones durante el año siguiente a haber recibido una intervención educativa de una hora de duración. Este efecto es máximo –20 veces– en los cuatro primeros meses, y se mantiene en 5 veces incluso trascurrido mas de un año desde la intervención. En farmacéuticos el incremento ha sido menor, pero muy importante: más de 5 veces. El efecto también es máximo en los cuatro meses con magnitudes muy parecidas a la de los médicos, y también se mantiene en el tiempo (a excepción de que a partir de un año de seguimiento existe un efecto –casi tres veces– pero no estadísticamente significativo). La intervención produce una mejora en la relevancia de las notificaciones incrementando la notificación de reacciones graves, inesperadas, de medicamentos nuevos y de imputación de causalidad elevada, tanto para médicos como para farmacéuticos. Los resultados de este ensayo pueden tener una gran importancia tanto desde el punto de vista educacional, como desde el punto de vista de la salud pública, ya que indican que estrategias educativas pueden contribuir a mejorar de una forma muy importante la vigilancia de las RAMs.

La magnitud del efecto encontrada en nuestro ensayo pocas veces se ha observado en la alteración de rendimiento de los profesionales sanitarios. Las revisiones sobre la eficacia de intervenciones para mejorar el rendimiento profesional ya consideran como "moderadamente importantes" mejoras del 20%, mientas que en nuestro ensayo las mejoras están en el orden del 900%, para los médicos y de 500% para los farmacéuticos y esta mejora no es solo a corto plazo, sino que se mantiene durante más de un año. Los factores que pueden explicar el efecto de una intervención en los cambios de los profesionales son múltiples: el objetivo de la intervención, el tipo de intervención (p. ej. material impreso o formación '*face to face*'), numero de intervención, el organismo patrocinador de la intervención, la ausencia de barreras o la existencia de incentivos, el grado de interactividad de las intervenciones, o su diseño a partir de las lagunas o fallos detectadas en los profesionales sanitarios.

Posiblemente uno de los factores que pueda explicar una magnitud de efecto tan importante se debe el objetivo de nuestra intervención. Las intervenciones educativas dirigidas a mejorar el rendimiento de los profesionales sanitarios como mejorar la prescripción, a optimizar la utilización de test diagnósticos, chocan con múltiples barreras como la presión o motivación de los pacientes, la influencia de la industria farmacéutica, o trabas administrativas como la falta de tiempo. Por el contrario, el objetivo de nuestra intervención apenas tiene barreras: las posibles (falta tiempo y de tarjeta) fueron específicamente tratadas durante la intervención. La ausencia de barreras en este objetivo podría explicar también las elevadas magnitudes de efecto que encontraron otros autores sobre el mismo tema. En nuestro ensayo las únicas co-intervenciones eran un díptico informativo y una tarjeta. Nosotros creemos que la tarjeta se puede entenderse como una co-intervención que puede actuar como factor facilitador o como de recuerdo y que, por su bajo coste, debe-

ría acompañar a cualquier intervención educativa para mejorar la notificación.

Otro factor que puede influir en la efectividad de la intervención es la el diseño de la intervención. Las revisiones sobre el tema indican que cuanto más interactivos sean los materiales y las presentaciones más efectivas son. Nuestra intervención fueron diseñada para ser lo más interactiva posible tanto la exposición, discusión y el díptico. Otro punto que puede explicar la efectividad de nuestra intervención es que fue diseñada expresamente a partir de las lagunas de formación detectadas en la fase I de nuestro ensayo. Ello permite elaborar mensajes específicos y concretos, y por tanto más efectivos. Además estos mensajes eran dados por un organismo patrocinador académico e independiente (*"academia detail"*), lo que se ha asociado a una mayor efectividad de la intervención.

Se podría argumentar que la magnitud del efecto encontrado se debe a la baja tasa de notificación de partida en Portugal, lo que haría que estos resultados no fuesen aplicables a otros entornos. Si consideramos la tasa de notificación total, las cifras de notificación en Portugal son unas de las más bajas. Sin embargo, cuando comparamos solo las notificaciones directas de médicos observamos que la tasa de notificación en Portugal es superior a la de países como Alemania, Italia, Grecia, EE.UU. o Canadá, lo que indicaría que, en lo que a tasa de notificaciones se refiere, numerosos los entornos se podrían beneficiar de una intervención como la de nuestro ensayo.

Una de las posibles limitaciones de las intervenciones educativas es que su efecto puede ser limitado en el tiempo. Sobre esto hay muy pocos estudios sobre la duración de los efectos de la educación médica continuada en la práctica. Los estudios existentes indican que el efecto de la educación médica continuada disminuye con el tiempo, pero que se puede mantener entre nueve meses y dos años. Nuestros datos indican que existe un efecto máximo a corto plazo, y que existe efecto menor –pero muy importante– mantenido en el tiempo hasta más allá de un año.

No tenemos datos a largo plazo, pero creemos que para mantener el interés de los médicos y farmacéuticos por el sistema, podría ser de interés realizar intervenciones repetidas y regulares. Nuestros datos muestran que podría ser suficiente realizar estas intervenciones anuales.

Los resultados de nuestro estudio indican que la infranotificación de RAM puede reducirse cambiando ciertas actitudes de los profesionales sanitarios, mediante estrategias educativas elaboradas a partir de las necesidades de formación de los profesionales. Así, intervenciones educativas de menos de una hora de duración ha llevado a importantes incrementos en la notificación resultados indican que los médicos y farmacéuticos responden bien y de forma prolongada a visitas formativas para mejorar la notificación de RAM.

En el momento en que las recientes casos de retiradas de medicamentos ha conducido a una importante crisis en la monitorización de la seguridad de los medicamentos, nuestros resultados pueden ser de gran relevancia: una de las medidas puede ser potenciar los métodos en de farmacovigilancia independientes de los laboratorios como la notificación directa de los médicos, que se ha mostrado muy exitoso en la identificación de nuevas RAM a pesar de la gran infranotificación existente. Nuestros resultados indican que los médicos responden bien y de forma prolongada a breves visitas formativas para aumentar la notificación. Si estos resultados pueden ser replicados a lo largo del tiempo en otros entornos, podría indicar que los numerosos países podrían mejorar sustancialmente en cantidad y relevancia la notificación de RAMs mediante estrategias educativas diseñadas a partir de las necesidades de formación de los médicos. Ello permitiría aumentar el protagonismo a los profesionales sanitarios en la farmacovigilancia y detectar de forma mas tempana y fiable las RAMs, lo que supondría una importante mejora de la monitorización de la seguridad de medicamentos.

1 INTRODUCTION

Adverse Drug Reaction (ADR) is a persistent and important public health problem in terms of morbidity, mortality, and cost. [1-6] In a study performed in the United States (US) it was estimated that more than 100 000 people die every year as a consequence of ADR and more than 2 million suffer serious after-effects, and some researcher's place fatal ADR between the fourth and sixth leading causes of death in the US. [7,8] A study carried out in the United Kingdom (UK) demonstrated that one in 16 admissions to a hospital is caused by ADR.[9] The exact costs attributable to adverse drug reactions are not well known, it has been suggested however, that ADR can prolong hospital stays and add to healthcare expenditure.[10]

Drug safety information at the time when a drug is licensed is limited.[11,12] Some adverse events of low incidence or those occurring a long time after administration are difficult to detect during the clinical research phases prior to commercialization, due to the fact that premarketing trials are often underpowered to detect ADR and have limited follow-up.[12-14] An significant number of withdrawals of new molecules introduced to the market after being approved by competent health authorities has been observed in the last few years. This withdrawal has been carried out after public health problems were observed. For example, it has been estimated that the Vioxx® (*rofecoxib*) molecule has provoked 100 000 heart attacks and strokes in US, a third of them fatal, before the market withdrawal.[15] Several authors[16,17] relate these cases to the role that pharmaceutical companies have in the pharmacovigilance of their own products (in US about 90% of ADR report provided by pharmaceutical companies).[18] It has been demonstrated that pharmacovigilance information provided by companies to health authorities might be sent late or non-reporting of case reports or failure to report any ADR at all may occur.[12,17]

Spontaneous ADR reporting systems empower health professionals to report directly to National Health Authorities and are the basic components for comprehensive post-marketing surveillance of drug-induced risks. The spontaneous ADR systems by health professionals is the most effective source for ADR detection and are primarily designed for rapid detection of uncommon or unexpected ADR, thereby creating hypotheses to be tested in subsequent studies.[19-21] Nevertheless, low spontaneous reporting rates greatly limit the advantages of-

fered by this surveillance method.[22-24] Indeed, it is estimated between 10 and 50% of serious adverse reactions are reported. [25-29]

In Portugal, the spontaneous report of ADR, through the "Yellow Form" initially use by physicians, started in 1992. Pharmacists were incorporated into the system in 1995, and proceeded to report in collaboration with physicians until 1997, as in other countries,[30] after that they submitted their reports directly. Thus, the report ratio is rather low in Portugal and in 2001 was 134 reports/million habitants.[31] Of the 1342 reports received in National Institute of Pharmacy and Medicine, just 837 were directly from health professionals.[30] The number of reports decreased in 2002 (126 reports/million habitants) and in 2003 (110 reports/million habitants), in Portugal.

Comparing physician reports/million habitants in Portugal (71.51) with other countries, it were observed that Spain (138.70), France (290.94), UK (288.09) and Sweden (373.97) had report ratios higher than Portugal but on the other hand, countries as US (69.65), Canada (53.75), Germany (36.87), Italy (16.13) and Greece (27.96) had report ratios lower than that in Portugal, these data are all from 2001.[30] Concerning reporting by pharmacists, it is difficult to compare because the reports from pharmacists are not considered in some countries yet, although is important referring that pharmacists are a vital link with the patient before and during a course of drug therapy, they could play an important role in monitoring adverse events in hospitals and are the only professionals in contact with over-the-counter[32-34] and herbal medicines.[35]

Despite the fact that under-reporting is the principal limitation of ADR reporting systems in all countries, the reasons for that are not clear. Factors such as failing to perceive the importance of the individual contribution to the overall knowledge of drug treatment safety, lack of certainty about the diagnosis of a particular ADR, lack of time, lack of interest, lack of report forms, and fear of involvement in litigation have been described as potential causes of under-reporting behaviour.[36-40] Inman[37] first proposed some attitudes in 1976 as potential causes of ADR under-reporting in physicians and, even though various other studies have looked at these relationships,[41-45] the majority of studies have either failed to find an association or found only one, two or three attitudes associated.[43-45] In contrast to the attention given to medical practitioners the reasons for under-reporting among pharmacists have not been studied. To our knowledge, there are no studies that have assessed the influence exerted by the various factors (knowledge-attitudes, professional and personal characteristics)

on pharmacists reporting. We have only managed to locate three studies[46-48] that describe opinions and attitudes held by pharmacists vis-à-vis ADR reporting, yet no link was made between such opinions, attitudes and higher or lower likelihood of reporting.

With under-reporting being the major drawback of the spontaneous report of ADR, it is of extreme importance to identify the factors that cause it, in order to improve the system. When reviewing the literature, numerous articles concerning the study of the factors that condition the reporting of ADR could be found concerning physicians but not for pharmacists. Nevertheless, only four articles[21,39,49,50] were found about the assessment of educative intervention with the purpose of developing knowledge and attitudes relating to ADR, with the aim of increasing ADR reports by physicians, however, none of them were controlled randomized trials, for pharmacists we only establish two articles related with this subject,[49,50] but not a controlled randomized trials. All this highlighted the lack of good quality evidence on the effectiveness of intervention in this an area.

To valuate if an educative intervention could decrease ADR under-reporting a two-phase study was carried out in Portugal. In phase I the knowledge and attitudes related to under-reporting of physicians and pharmacists were identified through a case control study.[51] Phase II was then designed to modify specifically these knowledge and attitudes and was evaluated by a randomized controlled trial cluster.

2 LITERATURE REVIEW

The 20th century bore witness to an unprecedented happening in medical history: a pharmacologic boom where numerous drugs have been discovered and, simultaneously, innovative technical and management systems were developed to allow large scale production and marketing of these drugs.

In the late 1960s world public opinion began to be directed towards ADRs with the "thalidomide disaster" that consisted in thousands of cases of phocomelia in children exposed to that drug during gestation. Since at that time there were no organised systems of drug security monitoring after marketing, it took 4 years (from 1957 to 1961) to identify the teratogenicity of thalidomide when the cases of phocomelia were already several hundreds.

Following the thalidomide occurrences, the 16th World Meeting of the World Health Organization (WHO) met in Geneva in 1963 decided upon the creation of a world monitoring ADR program whose objective was the creation and implementation of detection, registry and evaluation systems of hypothetical ADR. Consequently, ADR effects could be minimised and their occurrence limited. Subsequent to these decisions some European countries created National Pharmacovigilance Centres, the first of all in Netherlands in that same year. Simultaneously, in the US, the Food and Drug Administration (FDA) started to assume a more active role in the security monitoring of drugs. The pharmaceutical industry also started to develop they own pharmacovigilance departments.

Currently, the majority of developed countries have systems for monitoring during the entire life cycle of a drug. It is well know by all that ADR are a serious health public problem with important implications for health care and the economy charges.[20] Although many of the implicated drugs have proved benefits, measures need to be put into place to reduce the burden of ADR and thereby further improve the benefit: risk ratio of the drugs.

A revision of literature shows that ADR are an important cause of hospital admissions, with estimates varying between 5-15%.[52-55] In a largest prospective analysis performed in UK[9] about this subject, the results showed that up to 6.5% of all hospital admissions are related to ADR, the overall fatality was 0.15%. A study performed in Canada[56] with the aims of reviewing and summarizing studies concerning reporting rates of drug-related hospital admissions,

found that ADR accounted for approximately 5% of all admissions. Another study in Europe,[52] performed in internal medicine departments of a university hospitals, found a factor of 8.4% for drug-related hospital admissions. In elderly patients, the hospital admissions are higher (about 19.0%)[8] nevertheless for children the rate of drug-related hospital admissions is lower (between 1.8 and 3.2%) except for cancer patients. [56]

Thus, prevention of unnecessary hospitalisations by ADR might be an important goal in health policy decision-making. Patients who developed adverse effects were hospitalized an average of 0.72 to 5.5 days[57,58] and the excess costs associated with ADR ranged from $US 677 to $US 4685.[6,59-61] The estimates are conservative because they do not include the costs of injuries to patients or malpractice costs. This is important considering the fact that the majority of drugs (nearly 90%) are prescribed outside of hospitals, in the general community, where a large number of ADR can occur with the number of reports representing only a tiny fraction of the supposed total ADR.[54]

According to 1990 study by the US General Accounting Office, 51% of approved drugs have serious adverse effects undetected before approval. Examples of ADR detected after marketing approval was what happened with drugs as cerivastatin, and rofecoxib. This situation created some doubts about the security of drugs and the responsibility of authorities and pharmaceutical companies in this process.[12,29] An article published in 2003 stated that FDA receives approximately 280 000 such reports annually, consolidating them into a large database. Healthcare practitioners and consumers submit few reports (<10%) directly to FDA. Rather, manufacturers receive more than 90% of reports and must report them to the FDA.[18] However, late or non-reporting of cases by drug companies, or failure to report any adverse event at all, are major problems, and there is indeed a conflict of interest in asking industry to monitor its own drugs.[12] The spontaneous reporting system remains the primary and the best method for identifying ADR to newly marketed drugs, and physicians are in the frontline of the FDA post-marketing surveillance program, and their reports make a significant difference.[17] Inadequate reporting of adverse events by health professionals may delay detection of post-marketing adverse drug events.[11]

2.1 Pharmacovigilance

No drug is completely free from adverse effects it is the evaluation of the benefit/risk of each drug that will determine its Marketing Authorisation Holder and its maintenance in the market. The development of a new drug follows a series of tests of efficiency and safety in animal models that are designed to evaluate their properties. This first phase of pre-marketing studies is called pre-clinic tests, after what the clinic tests begin. During phase I of clinic tests, the main objective is the assessment of the molecule security in humans and a limited number of healthy volunteers. Phase II consists of the first tests carried out in patients so that minimum and maximum dosages can be determined. Finally, in phase III, more patients are observed and tests have a longer duration. In this phase it is intended to evaluate the efficiency and safety in patients.[62]

Clinical tests carried out during drug pre-marketing had numerous methodological limitations, mainly the reduced number of individuals exposed to the drug, test duration, exclusion of associated pathologies, and the exclusion of special population groups such as old people, children and pregnant women.[13,63] Therefore, a detailed security assessment of the drug could not be assessed before its commercialisation. In fact, the experimental environment is significantly different from that where the drug will be used after marketing.[62]

Pos-marketing studies, also known as phase IV studies, are intended to solve some of the lack that were left by pre-marketing studies, namely: compared efficiency; effectiveness; other therapeutically uses; small incidence ADR; long treatment consequences and other situations. Pharmacovigilance is the study of drug safety during the pos-marketing phase.[20,63]

According to the WHO definition ADR is any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy. This definition excludes therapeutic failures, intentional and accidental poisoning (ex: overdose), and drug abuse. Also, this does not include adverse events due to errors in drug administration or non-compliance (taking more or less of a drug than the prescribed amount).[7] A serious ADR is defined as any untoward medical occurrence that at any dose: results in death; life-threatening; requires hospital admission or prolongation of stay in hospital; results in persistent or great disability, incapacity, or both; congenital anomaly, birth defect.[28] Several types of ADR can be defined: type A: dose-related (augmented) are those that can be explained by the action mechanism of the drug; type B: non-dose-related (bizarre) are those

that can not be explained by the action mechanism of the drug and that can be explained by hypersensitivity or immunological mechanisms; type C: dose-related and time-related (chronic) are associated with long treatments; type D: time-related (delayed) are associated with carcinogenicity and teratogenicity that occur delayed; type E: withdrawal (end of use) are those that take place after the end of use of the drug such as benzodiazepines; and finally type F: unexpected failure of therapy (failure) inadequate dosage of an oral contraceptive.[64]

2.1.1 Pharmacovigilance in Portugal

In Portugal, the National System of Pharmacovigilance was created in 1992 as a consequence of the adhesion of Portugal to European Union, former European Economic Union. The Decree Law 72/91 that transpose for Portuguese law the European Guidelines in the drug area states in Artº 94 that "Holders of Marketing Authorisation, physicians, technical directors of pharmacies and other health technicians should inform National Institute of Pharmacy and Medicine (INFARMED) the ADR that occur as a consequence of a drug use". The Decree Law 107/92 from 27th of June initially defined the organization of the system. The National System of Pharmacovigilance is integrated net of agents that promote together for the same objective, to ensure a safe use of available marketed drugs.

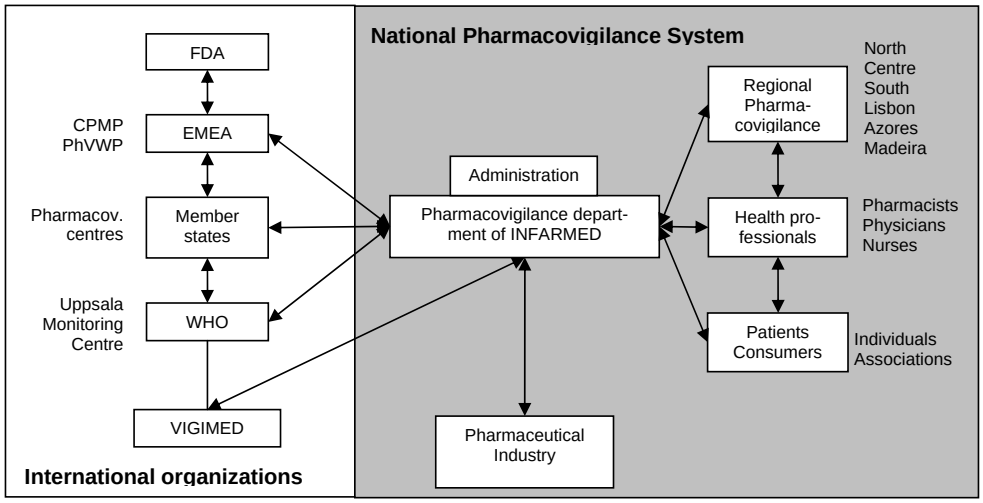

Figure 1. Graphic representation of National System of Pharmacovigilance and the relationship with European System of Evaluation and Supervision of Drugs as well as with other international organisations.

In Figure 1, a schematic representation of different components of the system and its relation with the European System of Evaluation and Supervision of Drugs as well as with other international organisations can be seen.

Pharmacovigilance Department of INFARMED that together with Regional Units of Pharmacovigilance, created in 1999 through Law 605/99 that defines the standards and regulations coordinate the system. With the creation of Regional Units of Pharmacovigilance, the National System of Pharmacovigilance is no longer a centralised system, similarly with what happens in countries such as Spain or France.

National System of Pharmacovigilance is articulated with the European system of security and drugs control. The Committee for Proprietary Medicinal Products (CPMP) of European Agency for Evaluation of Medicinal Products (EMEA) and the respective Pharmacovigilance group (Pharmacovigilance working party – PhVWP) are the pieces of the system. Portugal contributed with drug information for WHO ADR database. National System of Pharmacovigilance collaborated with restricted e-mail distribution list of set up to stimulate discussion and facilitate rapid exchange of information between representatives of National Centres participating in WHO International Drug Monitoring Program (VIGIMED).

The National System of Pharmacovigilance is essentially based on spontaneous reports of ADR by health professionals. This means that health professionals are the foundation of all the system. The first report form of ADR was created in 1992, inspired by the "yellow card" used by the English system, and was designed for use by physicians. Later, a new form was designed for use by pharmacists. It is important to note that Portugal was one of first European countries that actively engage pharmacists in detection and report of ADR. The pharmaceutical industry is an important piece in the system that has specific obligations defined by legislation, among them the responsibility for constant monitoring of drugs with Marketing Authorisation Holder.

2.2 Pharmacovigilance Methodologies

Pharmacovigilance is an observation and selection process of information about the effect of drugs under the usual practical clinical conditions, searching data regarding drug safety and risk. Two types of report systems could be identified under this assumption: the spontaneous

reporting system and the epidemiologic studies. The spontaneous reporting systems may be systematic and organized systems (for example the Yellow Card or the Prescription Event Monitoring Program) or anecdotic (report in medical journals). Epidemiologic studies require large enough populations or groups that allow data extrapolation such as: (1) intensive monitoring; (2) record-linkage systems; (3) the use of morbidity and mortality databases; and (4) the cohort and case-control studies that allow the certification of the alerts and hypotheses originated by spontaneous report.

Spontaneous reporting of ADR is denominated in many countries according with colour of formulary used to collect data, normally "Yellow Card". This system collects information about general population, all medicines and all types of ADR. Prescription Event Monitoring is a program dedicated essentially to monitoring medicines security, in first years of commercialization. This program is used for a reduced number of medicines and specific patients. The anecdotic report is an anarchic method with many limitations, the main one being the publication of cases where causality between the medicine and the reaction is finding. This situation is difficult to happen in clinical practice and could delay the alert.[62]

Intensive monitoring programs were created to collect intensive and complete data about diagnostic and treatment of hospitalized patients, with this data is possible to build databases and perform incidence and prevalence studies. Record-linkage systems are available only in a reduced number of countries because of the costs and of the organization. This system has some limitations such as the included population, type of data and quality of data. The study of morbidity and mortality databases with information about medicines consumption could be important to establish relation with a particular ADR, normally serious, and the use of medicines. Following the alerts generated about suspicions in security of a medicine it is necessary to test the hypotheses and quantify risk. The cohort and case-control studies are normally used in this situation. These specific studies are based in groups of patients exposed to a specific medicine or patients that have a characteristic ADR, studding the medicines used by the patient.[62]

2.2.1 Spontaneous Report of Adverse Drug Reactions

The main objective of spontaneous report of ADR is to promote the rational use of drugs based on security and efficiency criteria. The base parameters it are: (1) collect, evaluate and divulge information about ADR; (2) identify ADR; (3) analyse and examine a possible existence of a causality drug-ADR; (4) create methodologies for data acquisition; (5) evaluate the

safety profile of marketed drugs; (6) produce technical standards for using drugs; (7) elaborate activities to reduce drug risks; and (8) collect data about drug consumption.

The methodology used in Portugal to evaluate causality is the global introspection. This means that temporal relation, pharmacologic plausibility, base diseases, concomitant situations, concomitant medication, evolution after suspension, effect after re-exposition and quality of information are analysed altogether. Thus, the ADR profile could be defined regarding clinical and laboratorial evidences, severity, intensity and frequency for drugs of the same group, eventual action mechanism, causality nexus, predisposal factors, reversibility, and sequels. This evaluation allows the estimation the degree of probability that might be: definitive, probable, possible, improbable, conditional, and non-classifiable, according to WHO definitions.

Epidemiological vigilance of drugs is based on spontaneous reports of ADR by health professionals, through report forms. This form can be completed in an easy and fast way, and collects the necessary information to evaluate the ADR suspicion. The information collected is that considered as indispensable to obtain causality. All information collected through report forms is confidential.

In Portugal there are report forms specific (Appendix A) for each professional group: yellow for physicians, purple for pharmacists and white for nurses. Essentially, these forms collect all the same type of data but their differentiation is justified by different clinical practices.

The spontaneous report of ADR have numerous advantages such as: (1) simple method that can be implemented in a short period of time; (2) is cost effective; (3) includes all the population and all possible reporters; (4) includes all the drugs in the market during their entire life cycle; (5) doesn't interfere with prescription practice; and (6) might be used as a basis for the design of specific epidemiologic studies. Nevertheless, this advantages come with several disadvantages: (1) low level of participation of health professionals, the under-reporting; (2) it is not possible to calculate the incidences of ADR, because it is not possible to know the number of patients exposed to the suspicious drug neither the exact number of induced reactions; (3) it is quite difficult to detect reactions that has a large latent period as might be the case of carcinogenic and teratogenic reactions, (4) spontaneous report do not reliably detect ADR that represent an increased risk of an adverse event that occurs commonly in popula-

tion not exposed to the drug, and (5) identification of ADR associated with long-term administration of drugs for chronic diseases also remains problematic.[13]

2.2.2 Under-reporting

The spontaneous reporting of ADR is fundamental to the safety surveillance of market medicines. A number of studies have suggested that fewer than 10% of ADR are reported.[21,54]

Even in countries with high reports ratios the usual report ratio is about 10 to 50% of serious ADR.[25] Others studies had been suggested that at most only 14% of all suspected ADR are reported in general practice[65] and reporting from hospitals appears to be worse, even though they presumably see more serious reactions.[66,67] A study carried out in UK hospital shown that only 6.3% of the potential reports cards hospital had been sent to the Authorities.[54]

The European Pharmacovigilance Research Group conducted a series of surveys in European Union countries to assess the attitudes of physicians towards ADR reporting between 1993 and 1994 shown a wide variation in the percentage of physician respondents in each country, who stated that they had "ever" reported an ADR, ranging from 19.4 % in Italy to 74.4 % in France. The national reporting rate (between 1989 and 1993) for each country varied between 44.3 reports/million habitants/year in Italy to 389.7 in France. Portugal participated in this study with a report of 8.6 reports/million habitants/year but the Portuguese system started only in 1992.[68] A study[30] performed with data from 2001, provided from national pharmacovigilance centres permitted observed that some countries as Spain, France, UK and Sweden had spontaneous report ADR ratios from physicians higher than Portugal (71.5 physicians' report/million habitants), nevertheless countries as Italy and Greece had report ratios lower than Portugal. In relation to pharmacists the data were different because we did not had data from Sweden, UK and Greece, nevertheless, Spain and France had values higher than Portugal (19 pharmacists' report/million habitants) but in Italy the report ratio are lower than Portugal, in both situations we talk about directly reports from health professionals.

Pharmacovigilance aims at the detection, assessment and prevention of adverse effects or of any other possible drug-related problems.[20] However, pharmacovigilance has historically been underused by physicians.[39] Physicians are on the frontline of reports programs, and their reports could make the difference, the spontaneous reporting is the most effective and rapidly method for detection new ADR.[17] Under-reporting may delay the detection of impor-

tant ADR. Several studies performed in different environments (US,[36,39,47] Portugal,[51] Spain,[41] Italy,[19] UK,[21,44-46,48] Netherlands,[42] Sweden,[43] European Union,[68]) are stable that the knowledge-attitudes of physicians and pharmacists in respect to the spontaneous ADR report system are inadequate and associated with under-reporting.

It is very important for pharmacovigilance centres understand the reasons of under-reporting and take appropriate measures to increase the spontaneous report.[42] Portugal is one of the countries where under-reporting is the major disadvantage of the system and this is the reason why this study intends to know the reasons that cause it, and act above them to increase report from our health professionals.

2.3 Factors related with ADR report

To simplify the bibliographic revision about factors related with ADR report a theoretical model for the system of spontaneous reporting of ADR was developed and was used as a reference to accomplish a bibliographical revision[36,39,43-45,69,70] of the factors that condition the reporting. The bibliographic revision was done in Comprehensive Source of Life Sciences and Biomedical Bibliographic Information (MEDLINE). We searched these indices from January 1985 to January 2005 and the following search strategies were: (1) report* AND (adverse-drug-reaction* OR adverse-drug-event*) AND (attitud* OR knowled*) AND (pharmacis* OR physician* OR doctor), (2) drug* AND adverse* AND education* AND (medical* OR pharmacist*) AND continuing*. Abstracts and titles were read and the articles selected. Additionally an ascending search based on selected articles.

The proposed theoretical model (Fig.2) distinguishes two major condition types: (1) intrinsic condition, related with the health professional's education, and (2) extrinsic condition that included all those factors associated to the professionals' interaction with their work atmosphere. According to this model[71,72] the theory of habits acquisition in health sciences *knowledge-attitudes-practices* would explain the influence of the health professionals' education and the theory of the *satisfaction of needs*[73,74] would explain the influence of the factors on the work atmosphere. This theoretical model was applied to the prescription of drugs[75] and too the spontaneous reporting of ADR[76].

In this model, the intrinsic conditions such as the medical and pharmacist education and the amount and quality of the sources of information, at the professionals' disposal in their activity, condition their knowledge in what respects the surveillance of medicines and that knowledge generates attitudes on the reporting system, which comes to be reflected in their reporting practices. However, the *knowledge-attitudes-practices* relationship is not univocal (the same knowledge does not lead to the same customs) and therefore it is modified by extrinsic factors[77], whose influence on the reporting can be explained by the theory of the *satisfaction of needs*.[78] Thus, in the process of reception of information professionals can develop mechanisms of *selective perception* capable of isolating them from information that they received *a priori*. Therefore, when it is possible to generate in the professional certain attitudes about spontaneous reporting, these can be in contradiction with his practices, as a result of extrinsic factors such as his daily relationship with patient, administration and pharmaceutical companies. According to the model of *satisfaction of needs*, professionals will feel the need to keep a harmonious relationship with their work environment, thus adapting, consciously or unconsciously, their practices of drug surveillance to the demands, in many cases opposed to these three elements.

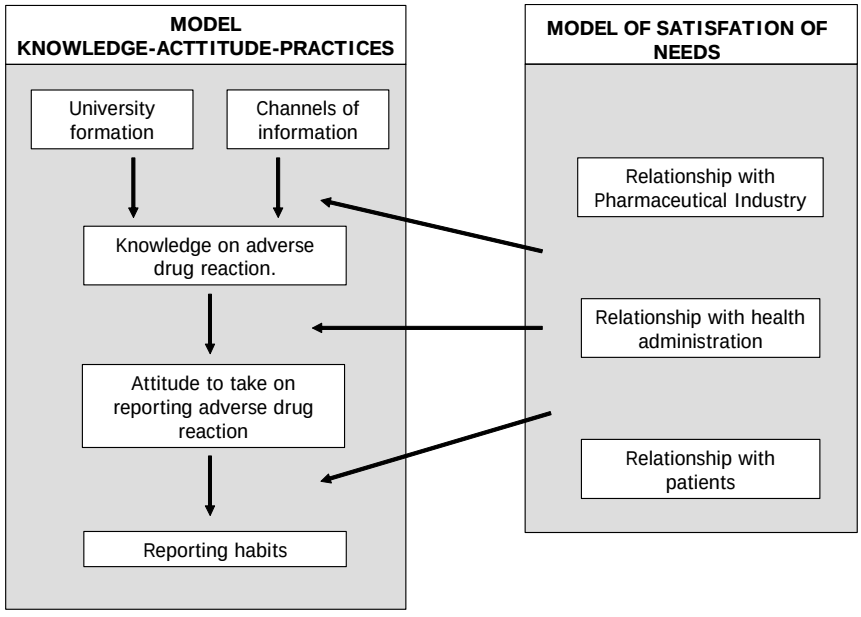

Figure 2. Mixed theoretical model of the factors that condition the health professionals' attitudes in the reporting of ADR to medicines.

2.3.1 Intrinsic condition

According to the *knowledge-attitudes-practices* model, the medical and pharmacist background together with the sources of information at the disposal of the health professionals in their activity, generate knowledge and attitudes on the system of spontaneous reporting of adverse reactions to medicines, which condition the reporting practices.

The knowledge acquired during university studies gives the future professional important information. However, this varies in a significant way among the various countries, and in the same country among different universities.[79,83] Studies carried out in the US[84] and UK[85,86] seem to demonstrate some dissatisfaction on the part of medical students with the time available for the teaching of pharmacology and therapeutics and they propose important changes in the undergraduate teaching curriculum, such as prescribing for the elderly, management of overdose, and adverse drug events. Other studies performed with pharmacy students demonstrated that educational activities like identification of potential ADR, changes in drug therapy regimens, have a positive influence on patient care.[87-89] According to some studies[90,91] the knowledge, attitude and practices of both undergraduates and prescribes were comparable but they need further improvement, thus suggesting the need for suitable changes in the undergraduate teaching curriculum; furthermore, prescribes also need periodic reinforcement regarding ADR monitoring.

The topic of continuing education is considered by some authors[39,92-96] to be extremely important in providing up-to-date information and knowledge to physicians and pharmacists. According to them there exists a direct relationship between the intensity of the educational intervention and the number of processes that present positive results. There are many different types of intervention that can be used to promote behavioural change among healthcare professionals and the implementation of research findings.[97,98] Disentangling the effects of intervention from the influence of contextual factors is difficult when interpreting the results of individual studies of behavioural change. Nevertheless, systematic reviews of rigorous studies[99-102] provide the best evidence of the effectiveness of different strategies for promoting behavioural change: (1) passive dissemination of information that is generally ineffective; (2) didactic sessions as conferences that has little direct impact on improving professional practice; and (3) methods such as systematic practice-based interventions and outreach visits used by continuing medical education providers that are more effective. Interactive continuing medical education sessions that enhance participant activity and provide the opportunity

to practice skills can effect change in professional practice and, on occasion health care outcomes. A study performed in Spain[103] demonstrate that a larger personalization of the session make them more efficient, although an study realized in Indonesia[104] to evaluate the efficacy of different methods of interventions to improve the appropriate use of drugs for acute diarrhoea, showed that the small group face-to-face intervention did not appear to offer greater impacts over large seminars in improving the appropriate use of drugs.

According to the *knowledge-attitudes-practices* model, the university education and specialization are probably the main conditions of the health professionals' reporting, as well as the sources of information at the professional's disposal in daily work. During their professional life they come across numerous medicines, new therapeutic indications, and at the same time new adverse reactions are being discovered, all of which forces them to keep up-to-date.[90,92,93,105-107]

Based on the origin of the sources information that a physicians and pharmacists use we can distinguish: (1) independent sources, mainly scientific journals and books; (2) institutional sources, pharmacological guides, surveillance bulletins, report procedures; and (3) commercial sources, mainly medical and pharmaceutical information people and publicity from the pharmaceutical companies. In a study[108] performed in Drug Information Centres in Italy, was verified that 90% of these Centres produce newsletters and/or bulletins and are involved in research projects, regarding the question-answer service, requests are mainly concerned with clinical comparative efficacy, therapeutic use, adverse effects, and the most frequent users are physicians followed by pharmacists. The most frequently used information sources are: books (Martindale), journals (ADR bulletin) and databases (MEDLINE). Drug information services in hospitals are very important for health professionals. A study describes a higher use of hospital-pharmacy-based online by physicians and pharmacists, when information about drugs is available on time and in comprehensive way.[109]

Scientific journals are probably, the independent sources of information more objective at the disposal of the health professionals between their influenced does not seem to be in keeping with quality. For many years physicians have had to cope with the accusation that only 10-20% of the treatments they provide have any scientific foundation. Their interventions, in other words, are seldom "evidence based".[110] Incorporation of evidence based medicine meetings into hospital routine practice has resulted in treatment guidelines being more

closely based on published evidence and improvements to care of patients. Written summaries of the meetings are important to facilitate change.[111]

The small impact that scientific journals seem to have is probably due to the great amount of existent literature that makes it difficult to read all the relevant material. In this sense, surveillance bulletins can constitute an intermediate step between the large amount of scientific literature and the information on surveillance of medicines that the health professionals needs. The best ways of publishing suspected ADR are spontaneous reporting to drug monitoring centres, pharmaceutical companies and publication of case reports in medical journals. Spontaneous reporting is probably the quickest and most effective way of alerting physicians and pharmacists.[112] Despite limitations of the available data, the asymmetry between the information available to the company and the information available to the patients and physicians seems striking. A subjective element is present in the effort to infer whether or not the occurrence of untoward outcomes in users of a particular drug was actually the consequence of the use of that drug, and, under the current system, a pharmaceutical company's appraisal of spontaneous adverse drug reaction may be influenced by economic considerations. Such an appraisal would best be made by an independent group.[12]

In relation to the commercial sources of information, according to some authors, the pharmaceutical industry covers the formative deficit the health systems suffers from, which is larger in less developed countries, where the influence of industry is greater.[113,114]

Publicity of medicines is another important method of communication between pharmaceutical companies and prescribes. Prescription drugs comprise approximately 9% of the total cost of health care in the US.[115] The manner in which physicians obtain information about new and changing pharmaceuticals obviously has the potential to have a profound impact on health care costs, pharmaceuticals companies' profits, and the quality of health care. The industry feels that publicity is a good method to keep physicians up-to-date, which seems to contradict the large amounts of money that laboratories design to promotion. The target of publicity should be to inform according to scientific criteria and that is why, although it can be easily noticed on many occasions, the language and the scientific images used mainly appeal to the physicians' fantasy. In other situations the publicity of medicines comes in the form of reports resembling magazine editorial material, which can induce confusion. Advertisements are a major source of income for medical journal. Most adverts in medical journals are about drugs and medical devices. Articles are mean to inform, instruct, comment and,

possibly entertain, whereas adverts are meant to persuade. A study[116] carried out in US medical journals editors, showed that a large percentage of editors favoured more stringent review of drug advertisements and the reviewers felt that the advertisement would lead to improper prescribing if a physician had no other information about the drug, this publicity has little or no educational value, according to the reviewers that participated in this study. Nevertheless, in a study[117] investigates the influences of pharmaceutical companies' advertising programs on physicians, 67.7% of them thought that information delivered by industry it was not reliable and 62.8% reported that it had no effect on their prescription writing.

Readers should not request claims in journal adverts, with or without credible-appearing references, on face value.[118] In a study performed in Spain[119], the investigators report the extent to which claims made in adverts for anti-hypertensive and lipid-lowering drugs in Spanish medical journals are supported by the citations attached to those claims. The citations were typically from strong studies in prestigious journals, suggesting that advertisers value the best available evidence or want to associate their demands to a respectful source, however; nearly half of the promotional statements were not supported by the associated references.

Numerous studies[36,39,41-48,51,120] have been carried out with purpose of studying health professionals' opinions and attitudes to the spontaneous report of ADR. Post-marketed surveillance is essential to evaluate the safety of medicines and spontaneous reporting by physicians and pharmacists are necessary to detect ADR, especially the rare ones and in the new drugs. The total rate of reporting was substantially smaller than expected based on studies about morbidity incidence and mortality induced by drugs. Even in countries with high report rates, only between 10 and 50%of serious ADR are reported.[121,122]

The reasons for the under-reporting are numerous and complex, physicians and pharmacists failing to report for several reasons, such as compliance, the ambition of collecting and publishing serious cases personally, ignorance of reporting rules, distrust about reporting merely suspicious, indifference about the physician's individual role as a scientific investigator, lack of confidence in the diagnosis of a particular ADR, lack of time, lack of interest, lack of yellow cards.[36-40,48]

Although, existing factors important in the decision to report such as: seriousness and unusual reaction, new product, need to build drug safety profile, the degree of confidence in

ADR diagnosis and awareness of similar reports (some previous publicity to a specific ADR) [21,70,123,124] are important in health professionals' decision of reporting however, in some studies it was observed that physician[125,126] and pharmacists[105] were unaware of the criteria of the National Drug Regulatory Agency indicating the need for additional education and information on this point. It is know that ADR constitute a serious problem in our society and in therapeutics, both as a health care problem and as a problem with high financial costs.[4-6]

2.3.2 Extrinsic condition

According to the mixed theoretical model, the knowledge of surveillance is not expressed directly in report habits, because different extrinsic factors can significantly condition determinism in the *knowledge-attitudes-practices* relationship. In the circumstances under which health professionals develop their activity, they are in interaction with industry, health administration and patients, which will also be important in conditioning their reporting.

Probably, it is not possible to explain the influence of industry on ADR reporting only through the information that it facilitates, therefore it is necessary to incorporate the model of *satisfaction of needs*, which considers a health professional's need to be in harmony with them work environment. In same countries as US and Germany, physicians[68,114] and pharmacists[47] report more often to the pharmaceutical industry than to the National Drug Regulatory Agency. Some authors[113,117,127-129] feel that the pharmaceutical companies take advantage of a physician's position in the health system to create personal links with them, reinforcing the incentives, which can be reflected in the nature of the prescription. Physicians have a major role in the prevention of ADR and should resist marketing pressures to prescribe new and potentially more toxic drugs and preferably to prescribe well-established and safer drugs. The majority of the adverse reports that the FDA receives come from drug manufacturers. Therefore, most of these reports are available to the manufacturer before the authorities. Drug manufacturers have a responsibility to analyse these reports thoughtfully and to act on their conclusions and not just to focus on delivering their reports to the authorities in a timely approach. Despite limitations of available data, the asymmetry between the information available to the company and the information available to patients and physicians seems striking, and under the current system, a pharmaceutical company's appraisal of suspected ADR may be influenced by economic considerations.[12] For example, it is surprising that *terfenadine* was removed from the market, not when the adverse effects were identified, but after the manufacturer had developed a new product to substitute for it.[130] Drug safety will

only improve when it is viewed as a cooperative venture between authorities, industry, and health professionals.

Unlike industry, which traditionally maintains a good relationship with health professionals, the administration is usually seen as the control element, indifferent to the health technicians' daily problems. The polities that integrate health professionals into the system to that they also may feel responsible for its defects and advantages brought about widespread improvements in the relationship between professionals and the administration, thereby resulting in improvements in the health technicians' activity. The administration should strike a balance between the necessary measures of control on the professional and the more important political incentives for the professional. In some studies[131,132] carried out in UK and US about physicians-administrators relationships, were observed that is very important to implement several strategies to improve these relationships, including greater organizational transparency in decision-making, more frequent communication, and more physician involvement in decision making, and in organizational governance. Despite the tensions created by competition and rapid change, transformation from a blaming to a learning environment may be a key strategic advantage in today's health care marketplace. In relation to pharmacists[133-135] studies suggested that expertise in drug use can benefit patients, physicians, and the hospital administrators who are confronted with ever increasing costs. Cost reductions due to the pharmacists' clinical interventions, such as monitoring overuse of drugs, unnecessarily prolonged hospitalization, correction of medication errors, and reassessment of prescriptions. Hospital administrators had a positive perception of the abilities of pharmacy responsible but believed that there is still room for improvement. In a study carried out in China, the knowledge about ADR by hospital administrators was consider as a important factor for the increased of ADR report by health professionals,[125] other study[48] refer a written hospital policy for ADR reporting as an encourage measure to professionals reports, the unavailability of reports cards is refer from health professionals as an deterrents to report, in this issue the policy of hospitals could be very important too.[21] Providing financial incentives for the time spent by a health professional' in filling the yellow card is an often-used approach, and according to Inman[126] this is a potential factor of under-reporting, seen that for example pharmaceutical industry, pays to the physicians for the patient's inclusion in the clinical trials. However, in most of the studies reviewed it does not seem to be a potential cause of under-reporting because pharmacists[46] and physicians[36,41,44,51] believe that they must not to be paid for something they consider a professional obligation, a fee was not con-

sidered to be an incentive to report, but in literature appear two articles that appoint for the stimulation of ADR reporting with financial recompense.[136,137] Fear of legal responsibility[38,138] appears to be an important factor in under-reporting. The physicians responsibility is based on negligence contributes to a patient's damages. It is part of the patient-physician relationship that physicians are allowed to treat their patients with the most appropriate treatment except in case of medicines in the investigation phase that it is necessary the patient authorization previous. In studies[41,51] carried out in Europe it was found that physicians believed it was their duty to report ADR and they did not consider that it increased their professional responsibility. This discrepancy between the studies carried out in US[138,139] and Europe[41,51] may signify a greater concern about potential legal consequences ADR reporting on the part of US physicians. Physicians fail to report ADR for several reasons and neither financial incentives nor compulsory legislation seems to be the solution.

Another important condition of spontaneous reporting of ADR is the interaction with patients. The surveillance system is spontaneous and therefore it is only their professional responsibility that compels physicians to report an adverse experience with a medicine involving their patients.[36,66] In some studies physicians and pharmacists have pointed out that the cause for under-reporting is the confidentiality of the physician[36,41] and pharmacist-patient relationship[48] and the sense of guilt for having prescribed or recommend a treatment that provoked damages to their patient. Pharmacists are excellently placed to provide valuable post-marketing information on drug products owing to the fact that, they are a vital link with the patient before and during a course of drug therapy.[30,46] Pharmacists are the only professionals in contact with herbal[35] and over-the-counter medicines.[32-34] Studies[140-142]about geriatric and asthmatic patients referred the importance of pharmacy practice in these groups of patients because the long-term care, over prescription, drug interactions, ADR reports, and communication with the elderly, the quality of this relationship between patients and pharmacists seems to be important medication management. An study[143] appoint patient as another potential source for case reports of suspected ADR, the reports were less sensitive than physician's report, large scale reporting of events from patients might be valuable for earlier detection of symptomatic reactions to new drugs. Direct patients yielded a significantly higher rate of ADR detection in an ambulatory care stetting than did passive ADR reporting system.

There are other factors that are pointed by health professionals as reporting barriers. The barriers such as lack of availability of report forms and shortage of time were appointed in several studies[38,40,42,43,45] as an important reason for non-reporting. Health professionals referred in bibliography that: (1) reporting of ADR takes too much time; they have insufficient time, give priority to other matters and they lack time to fill out the reporting form; and (2) there are lack of report forms, there are no reporting forms available in workplace.

The results of this bibliographic review indicate that there are several factors that might interfere in the ADR report. Moreover, the combination of *knowledge-attitudes-practices* and the theory of the *satisfaction of needs* seemed very adequate for ADR systematization. To improve the participation of health professionals in surveillance systems through spontaneous reporting it may be necessary to designed combined strategies that modify both intrinsic (knowledge, attitudes) and extrinsic (relationship between health professionals and their patients, the national health system and pharmaceutical companies) factors.

3 HYPOTHESES AND OBJECTIVES

3.1 Hypotheses

1. There are socio-demographic and personal factors related with under-reporting.

2. The knowledge and attitudes of health professionals related to ADR are not adequate.

3. The knowledge and attitudes of health professionals related to ADR influence the under-reporting

4. An educative intervention designed base on knowledge and attitudes marked as inadequate and associated to under-reporting improve the number and quality (relevance) of ADR reporting.

5. Provide a report card during the intervention improves spontaneous reporting of ADR.

3.2 Objectives

3.2.1 General objective

Increase quality (relevance) and quantity of spontaneous ADR reporting by health professionals (physicians and pharmacists).

3.2.2 Specific objectives

1. Identify socio-demographic and personal factors related with under-reporting by health professionals (physicians and pharmacists).

2. Identify the knowledge and attitudes of health professionals (physicians and pharmacists) related to under-reporting of ADR.

3. Analyse if an educative intervention –designed for change knowledge and attitudes related with under-reporting of ADR found in the second specific objective– increases the quantity and quality (relevance) of spontaneous report of ADR by health professionals (physicians and pharmacists).

4. Evaluate the duration of the effect of the educative intervention both in quality (relevance) and quantity by physicians and pharmacists.

5. Evaluate if providing a report card during the intervention increases the probability of spontaneous reporting of ADR.

4 METHODS

To achieve the objectives of this work, two different studies have been carried out. A case-control study to identify the knowledge and attitudes of health professionals (physicians and pharmacists) related to ADR reporting and a cluster-randomized trial study where an intervention have been carried out to change this knowledge and attitudes related to under-reporting to increase ADR reporting.

4.1 Case-control studies

4.1.1 Design

Two case-control studies were performed; one for physicians and other for pharmacist. The cases are subject (physicians or pharmacists) with a determinate characteristic. In this case the characteristic is report at less one time for the Northern Pharmacovigilance Unit on north region of Portugal, since the begin of function the Northern Pharmacovigilance Unit until the date the study begin. The controls are a sample of the non-reporters. The criterion for selection the study population was the presence or absence at least the one report.

4.1.2 Subjects

The target population in this study is composed of physicians (working for the National Health System) and pharmacists (working in community and hospital pharmacies) who work in geographic area corresponding to the Regional Health Administration of the North. The database for physicians was provided by the Regional Health Administration of the North at the beginning of the study (year 2002) and for pharmacists by the National Association of Pharmacies and by the Portuguese Association of Hospital Pharmacists also at the beginning of the study (year 2003).

To ensure reliable results, it is necessary to define a representative sample of the population. In this study, 2 sub-samples (cases-controls) for each study (physicians/pharmacists) were created.

4.1.3 Sample settings

Sample is a set of really studied subjects. The number of subjects necessary for the study is lower than the study population. Therefore this study works with a sample of all the population; in particular two sub-samples were defined.

4.1.3.1 Sub-sample of Cases

The case group is composed by 2 sub-samples: (1) all the physicians registering in Regional Health Administration of the North and (2) all pharmacists that work in community and hospital pharmacies registered in respective associations. In each case they must fulfil the following inclusion criterion: work in geographic area corresponding to the Regional Health Administration of the North in the beginning of the study and report at least one ADR, for Northern Pharmacovigilance Unit between the beginning of this operation and the beginning of the study. The exclusion criterions are: (1) work only in the private hospitals sector (small sector in Portugal) for physicians and pharmacists and (2) work as teachers, administration areas or pharmaceutical and distributors companies for both pharmacists and physicians.

4.1.3.2 Sub-sample of controls

The control group is composed by 2 sub-samples: (1) physicians registered in Regional Health Administration of the North and (2) pharmacists that work in community and hospital pharmacies registered in respective associations. For physicians and pharmacists, the approximate ratio with respect to the cases is 1:8. They must fulfil the following inclusion criterion: work in geographic area corresponding to the Regional Health Administration of the North in the beginning of the study and never reported an ADR for Northern Pharmacovigilance Unit between the beginning of this operation and the beginning of the study. The exclusion criterions are the same used for cases.

4.1.3.3 Determination of sample size

The determination of the size of the samples took into consideration that if a sample were excessively small it would be impossible make reliable extrapolations from the resulting data to the population. Oppositely, if an excessive large sample is used it will be a waste of recourses. In this study, all the cases were included and a proportion of about 8 controls for

each case (in physician's sub-sample this proportion is about 10% and in pharmacists is about 20% of the population in each stratus) were used. Nevertheless, a proportion of 1:4 was considered theoretically more efficient.[144] In this study, we take account that the number of cases is very small and that normally in this type of studies, the number of non answers by control group is higher (about 50%).[36,41,68]

4.1.3.4 Type of sample

The type of sample used was the stratified sample with proportional selection. This method consists firstly in distributing the population in subgroups or stratus, accordingly to one or more characteristics and secondly for creating a random sample independent in each stratus. This sampling method ensures that for each stratus the number of subjects is proportional to the number of the population subjects within that stratus. The sub-sample for the control group was determined by stratification of each health sub-region, proportional to the number of subjects belonging to each sub-region (Table 1).

Table 1. Stratified sample by sub-region of health (physicians)

Sub-region	Nº of physicians	Nº of reporters (cases)	Sample of non reporters (controls)
Porto	5224	67	522
Braga	1338	16	134
Viana do Castelo	538	1	54
Bragança	232	2	23
Vila Real	384	2	38
TOTAL	7716	88	771

For physicians, the method was as follows. For each stratus, a random selection of the sample was realized by attributing a random number between 0 and 1 to each subject in his sub-region. This procedure used the random function of Microsoft Excel for the generation of random numbers. After that, subjects were sorted in an ascendant order of the random numbers. The selected subjects for each sub-sample were the first in the ordered list. The five sub-samples were assembled to constitute a unique database with all sample components, about 770 subjects.

For pharmacists the process is the same used for physicians with the exception that the number of subjects was about 280 (Table 2). In sub-region of Vila Real, we did not have any reporter and consequently it was assumed the existence of one for computational reasons.

Table 2. Stratified sample by sub-region of health (pharmacists)

Sub-region	Nº of pharmacists	Nº of reporters (cases)	Sample of non reporters (controls)
Porto	850	24	192
Braga	264	6	48
Viana do Castelo	98	1	8
Bragança	51	3	24
Vila Real	90	0	8
TOTAL	1353	34	280

4.1.4 Data collection

The two methods for collecting data that could be better adjusted to the study objectives were the postal questionnaire and the personal interview. Nevertheless, considering the population characteristics (higher dispersion) and subjects (licentiate) it was decided that the auto-fulfilling postal questionnaire was the most indicated for the study. The main limitation of the postal questionnaire method is the small index of participation.[144] Therefore, it is very important that materials are carefully elaborated. The materials sent were a letter of introduction, presenting the study, and a questionnaire. In a study with these characteristics the questionnaire is very important. In fact the questionnaire is the measure instrument and also the element of motivation or dissuasion of the subject participation in the study. The questionnaire was building with the intention to be comprehensible, succinct and attractive. The objective was to produce in subjects a favourable attitude to fulfil the questionnaire.

4.1.5 Questionnaire elaboration

The questionnaire was built based in an intensely bibliographic review. The questions were elaborated accordingly to previous studies,[36,38,39,43-45] the main reference being a study performed in Spain.[41] The questions were based in the "seven deadly sins" of Inman[37] and the scale used for measuring the answers is that reported in Spanish study.[41]

The questionnaire contains 25 variables in two pages (one sheet). The brevity of the questionnaire was felt to be of great importance, since according to some authors[145-149] this feature is essential for motivating answers. In the upper part of the page, the logotype of the responsible institutions (Northern Pharmacovigilance Unit and INFARMED) for the study was placed.[145]

The questionnaire was divided into 4 parts (Appendix B). The first part, include the fulfilling instructions, with intention to facilitate a fast lecture and comprehension of the fill of questions. Accordingly with the instructions, the 15 questions of the second part was the questions about knowledge and attitudes related with ADR reporting by health professionals and were measure using a visual analogical scale, horizontal continuous of 8 cm and not numerate. The answer is marketed in a segment, with left and right extremes representing, respectively, *total disagreement* and *total agreement* with the question. The subject must do a cross in the area of the segment that represent its opinion, as much to the right all that his agreement with the question and as much to the left all that his disagreement with the question. An equal scale drawn in a transparency and divided into 20 parts is placed over the questionnaire to make the reading of the answers easier. The visual analogical scale was divided into 20 parts, from 0 to 20, to transform it in numerical values. The value 0 means *total disagreement* and 20 means *total agreement*. For statistically analysis, this scale was later transformed in a 0 to 10 scale, with 0.5 precision.[150]

This type of shape had as objectives: easy fulfillment and reduction of the necessary time to do it and realize a statistic measurement consider the variable as quantitative. In the third part of the questionnaire 3 questions about the spontaneous report system of ADR and availability of cards are made. For this answers verification windows were used. The last part of the questionnaire included affiliation questions (age, gender), education data (specialty and type of activity) and questions about the environment where the health professional works (number of patients, level of prescription, and level of drugs dispensation).

4.1.5.1 Validity

In this study the validity consensus was evaluated, that consists in the evaluation of one characteristic by several experts. The questionnaire was submitted to the experts of the National Pharmacovigilance Department of National Institute of Pharmacy and Medicine, Northern Pharmacovigilance Unit, National Association of Pharmacies, (Pharmacoepidemiology studies centre), Pharmacology Department of the Pharmacy Faculty of the University of Coimbra, Porto and Institute Superior of Health Sciences North (Appendix C).

4.1.6 Material

The motivator material was composed by the letter of introduction and the envelopes. Additionally, the questionnaire was re-sent 4 times.

4.1.6.1 Letter of introduction

Letter of introduction is the first contact between the subjects and the study it gives the introduction and motivation to participate. Consequently, reference to the responsible institutions for the study was clearly stated because according with some authors[145] this could increase the answer ratio. The letter was signed by the responsible for the study, and wording was done with objective to be personal and convincing[151]. The four letters sent during the study were always different. Each letter had more acute contents trying to motivate the subjects about the importance of answering the questionnaire (Appendix D). Each letter is personalized to the subject in terms of gender. The letters of physicians and pharmacists, had the same contents, but additionally, some differences related with some professional differences.

The questionnaire and letter of introduction were evaluated in terms of linguistic content by Communication Department of University of Aveiro and in terms of interpretation by Psychology Clinic Department of Institute Superior of Health Sciences North. After this evaluation, small linguistic adjustments were done in the questionnaire and in the letter.

4.1.6.2 Envelopes

To avoid a possible confusion with the postal publicity, the envelope sent bears the institution logotype. With the intention of facilitate the devolution of complete questionnaire inside of the sent envelope was a pre-paid envelope with the address filled and the questionnaires were duly folds.

4.1.7 Pilot test

The questionnaire is an instrument that used the language as a strong support, but there is no guarantee that the language of the investigator and the subjects are in agreement[145]. Because of that, it was considered important to submit the letter of introduction and the questionnaire to a sample where the subjects belong to the Regional Health Administration of the Centre, before the data collect. With this data it was possible to have a notion of the aptness

of the collection method. The questionnaire was tested relating to its reproducibility in a sample of 30 physicians; ten general practitioners (Health Centre of Aveiro) and twenty hospital physicians (Aveiro hospital), from which ten surgeons and ten general medicine specialists and twenty pharmacists; fifteen communitarian pharmacies (Aveiro region) and five hospital pharmacists (Aveiro hospital). The letter of introduction was built with the same format as the letter used in the study, with the difference that refers the pilot test as a necessity to validate the questionnaire, and ask the subjects for their comments and difficulties in the completion of the questionnaire.

The same questionnaire was mailed twice for the same sample, during the pilot test, with an intervening period of four weeks. The first mailing was at the beginning of May in 2002 and the second in June. The questionnaire fulfil did not have any difficulty comments in respect to the use of visual analogical scale, for the 15 questions. Nevertheless, some subjects (hospitals pharmacists) reported some difficulties in completing the questionnaires (in particular the question relating to the dispensing of drugs).

At the end of the study, a letter of thanks was sent to the health centre, to each hospital service director and to the community pharmacists.

4.1.8 Questionnaire sent

After the pilot test, the questionnaire underwent some minor changes and was sent to the cases and controls subjects. Exactly the same material was sent (questionnaire, letter and envelopes) to the case and to the controls. The questionnaire was re-sent to those that had not answered the previous questionnaires a maximum of 4 times. The mailings were carried out between December 2002 and June 2003 (physician sub-samples) and between June 2003 and December 2003 (pharmacist sub-sample) for a period of six months with an interval of 8 weeks. In review literature, the time period between each mailing varies between 2 to 8 weeks.[41-43]

4.1.9 Statistical Analysis

4.1.9.1 Pilot test

The questionnaire's reproducibility was evaluated in the test pilot using the intraclass correlation coefficient, based on the results obtained for the first and second answers, for each physician and pharmacist.

The statistical analysis was carried out using a logistic regression that allows the representation of a dichotomy dependent variable as a function of several other variables, either qualitative or quantitative. A transformation of the dependent variable must be made in order to make the relation linear and the techniques of classical regression can be used. In logistic regression analysis the technique for calculation of the regression coefficients uses an iterative procedure using the maximum likelihood of the coefficients and their standard deviations. This minimizes the weighted sum of squares of the deviations.

The advantage of logistic regression is that, although the coefficients and their standard deviations obtained directly from the calculations are difficult to interpret epidemiologically, with a simple transformation is possible to transform them in *odds ratios* (OR) and the values of the standard deviations of these in confidence intervals (CI) of OR.

When logistic regression is applied to case-control studies, as is the case of this study, the dependent variable will be the case (report) or the control (non-report) and the calculated OR are a good estimation of prevalence ratio, since the prevalence of report in the population is rather low. When using this technique the following points must be taken into consideration: a) the dependent variable is dichotomy, being the reference category the value zero (in this case non-report = 0 and report = 1); b) all the possible control and exposition variables must be initially incorporated in the model so that can be later removed those that do not cause a confusion effect or a changing of the effect and that, from a theoretical perspective, lack importance; c) when an independent variable is dichotomy (for instance gender) the reference category should have the lower value (male = 1; female = 2); d) if an independent variable has more than 2 categories (for example, speciality: K = 4 categories), it shouldn't be used as a single variable since in this way a linear relation is assumed for the variable, and in reality, the codes used for each category are arbitrary; therefore the variable must be transformed, using a category as reference and creating new variables (K-1 dummy variables) relating each value of the variable with the reference value; e) when an independent variable is continuous (for example age) it should be categorised, at once is include as continue in the model and guess again an effect of linearity over the dependent variable.

In the present study three categories were created for each continuous variable. The categories were created using the percentiles 33 and 66 for all the subjects. This new variable is created using the dummy variable generation process.

Logistic regression analysis was used to model the associations between independent variables and the outcome of having reported an ADR. Two sets of statistical models were created: (i) in the first, we evaluated all the personal and professional variables using crude and adjusted analyses; (ii) in the second, we evaluated the influence of attitudes related to ADR reporting, such as those quantified in the questionnaire, adjusting for personal and professional variables that proved significant in the first model. Results were expressed as OR with their 95% CI, which indicated the increase/decrease in the probability of being a responder for an increase of one unit on the continuous visual analogy scale (score range 0=total disagreement to 10=total agreement). To take into account the independent variable's distribution among the study subjects, we calculated the interquartile OR (IqOR), which is based on an incremental exposure corresponding to the interquartile range of these attitude measures. Since most OR assume values lower than unity, we calculated the inverse of the IqOR (1/IqOR), which can be interpreted as the increase in the probability of being a responder when exposure decreases from the 75th to the 25th percentile of the distribution.

4.2 Cluster randomized trial

4.2.1 Design

A controlled randomized trial was carried out in two groups: intervention and control group, in Regional Health Administration of the North. To eliminate the cross-contamination between groups and units, spatial-clusters have been created. All the physicians and pharmacists that work in hospitals, health centres and community pharmacies of the selected geographic area make each spatial-cluster. The clusters are formed with minimum size to minimize the contamination between communitarian pharmacies, primary care and hospitals. Thus, each spatial-cluster was formed by one reference hospital together with health centre and communitarian pharmacies and other eventual hospitals of its influence zone. The 15 geographical zones were created based on reference central and district hospitals (for small hospitals located in the same area).

4.2.2 Subjects

The population object of the study is composed by all physicians (that work for National Health System) and all pharmacists (that work in community and hospital pharmacies) who

work in geographic area corresponding to the Regional Health Administration of the North; the database was provided by Regional Health Administration of the North for the physicians and by National Association of Pharmacies and Portuguese Association of Hospital Pharmacists for pharmacists.

The exclusion criterions for pharmacists and physicians are: (1) work only in the private hospitals sector (small sector in Portugal) and (2) work as teachers, administration areas or pharmaceutical and distributor's companies (3) work in Northern Pharmacovigilance Unit and (4) work directly with Northern Pharmacovigilance Unit protocols for ARD reporting. The pharmacists and physicians who work in specific hospitals or services are too excluded because it is not possible to limit them to a specific area, such as specific hospitals, histocompatibility and genetic centres. Were exclude too the physicians who work in centres of toxicodependence.

4.2.3 Randomization

Most cluster-randomized trials allocate approximate equal numbers of clusters to experimental and control groups. This is the most efficient randomization ratio, but this may not be the most economically. When the intervention under evaluation have an important cost difference respect a control group, may be more economically efficient to randomize fewer clusters to the intervention group than the control group.[152] Therefore, the 15 spatial clusters were distributed using an unequal randomization.[153,154] Four spatial clusters to the intervention group and 11 to the control group, approximately 1:4 for intervention:control group. The randomization distribution was performed with computer-generated procedure and was made assigning a random number to each cluster and choosing the 4 clusters with higher number for the intervention group and the other 11 were left to the control group.

4.2.3.1 Intervention group

The 4 randomly select clusters make the intervention group. All the physicians that work in hospitals and health centres and all the pharmacists that work in community pharmacies and hospitals of the same area of the selected geographic area at the beginning of the study (year 2004) are included in the cluster.

4.2.3.2 Control group

The control group is made up of the other 11 clusters. The conditions for physicians and pharmacist are the same that were used for intervention groups.

4.2.3.3 Sampling criteria

The sampling process was carried out as follows: the geographical area, corresponding to Regional Health Administration of the North, was divided in 15 zones relatively similar; each zone has one or more hospital, health centre and communitarian pharmacies of the influence area of the hospital/s.

The educational intervention was carried out in every hospitals, health centres and community pharmacies belonging to the geographical area of intervention.

Table 3. Distribution of physicians in each 15 zone, in relation to study group (control or intervention), per each sub region. Number of hospitals/health centers (nº of physicians in each one).

TYPE	SUB-REGION	ZONE	PHYSICIANS		
			Hospitals	Health Centre	Specific Hospitals
Intervention	Porto	2	1(741)	6(138)	5 (432)
	Bragança	12	1 + 1[a] (61)	7(62)	
		13	1(54)	5(54)	
	Vila Real	14	1 + 1[b] (173)	11 (105)	
Control	Porto	1	1 (964)	3 (114)	
		3	1 + 1[b] (455)	6(164)	
		4	1 (235)	8 (178)	
		5	1 (382)	8 (173)	
		6	1+1[b] +1[a] +1[a] (187)	10 (246)	
		7	1 (77)	3(74)	
	Braga	8	1 + 1[a] (263))	9 (121)	
		9	1 (106))	2 (107)	
		10	1 + 1[a] (390)	8 (248)	
	Viana do Castelo	11	1[b] (238)	13 (219)	
	Vila Real	15	1 (67)	5(55)	

[a] Small hospital that was grouped to the reference hospital or several small hospitals in same geographical area; [b] Hospital centre constituted by 2 hospitals.

From the existent 25 hospitals, 5 are specific hospital (ex: cancer, maternity, etc.) and were excluded from the study because treatment very specific pathologies of all north region and could be a mistake factor, possible cross-contamination between the clusters.

Remaining 20 hospitals, 5 of them are very close or very small and because this were included in the same zone.

The health centres were grouped by the influence areas of hospitals, accordingly to information provided by Regional Health Administration of the North. Community pharmacies were grouped based on information provided by National Association of Pharmacies. Table 3 and Table 4 present for each of the 15 zones the number of hospitals, health centres and community pharmacies as well as the number of physicians and pharmacists (between brackets). Figure 3 shows a map of Portugal, with five sub-regions of Regional Health Administration of the North and the geographical representation of 15 zones used in the study.

Table 4. Distribution of pharmacists in each 15 zone, in relation to study group (control or intervention), per each sub region. Number of hospitals/communitarian pharmacies (nº of pharmacists in each one).

TYPE	SUB-REGION	ZONE	PHARMACISTS		
			Hospitals	Communitarian pharmacies	Specific Hospitals
Intervention	Porto	2	1(16)	79 (195)	5 (16)
	Bragança	12	1 + 1[a] (2)	20 (28)	
		13	1(3)	19 (33)	
	Vila Real	14	1 + 1[b] (4)	42 (61)	
Control	Porto	1	1 (22)	46 (91)	
		3	1 + 1[b] (5)	58 (120)	
		4	1 (6)	57 (90)	
		5	1 (6)	56 (122)	
		6	1+1[b] +1[a] +1[a] (6)	37 (75) + 23 (41) + 32 (56)	
		7	1 (4)	27 (36)	
	Braga	8	1 + 1[a] (6)	37 (63) +28 (30)	
		9	1 (3)	27 (45)	
		10	1 + 1[a] (5)	61 (87) + 27 (40)	
	Viana do Castelo	11	1[b] (9)	62 (91)	
	Vila Real	15	1 (3)	23 (29)	

[a] Small hospital that was grouped to the reference hospital or several small hospitals in same geographical area; [b] Hospital centre constituted by 2 hospitals.

4.2.3.4 Type of sample

There are a number of quantitative designs that could be used to evaluate quality improvement interventions: (1) randomised designs, like individual patients randomised controlled trials and cluster randomised trials; (2) non-randomised designs, like uncontrolled before

and after studies, controlled before and after studies and time series designs.[155] Cluster randomised trials are becoming increasingly important in health technology assessment.

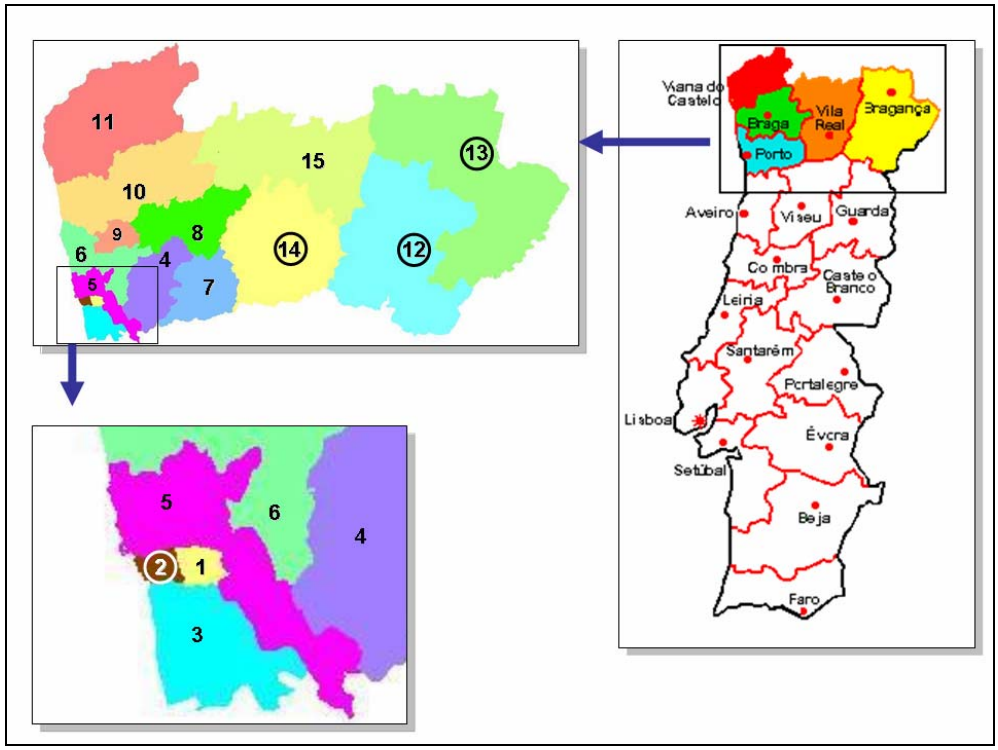

Figure 3. Portugal map and 5 sub-regions of Regional Health Administration of the North. Region numbers circled are those where the intervention has been carried out.

Cluster randomised trials designs are used not only to evaluate group interventions but also individual interventions where group level effects are relevant. In cluster randomised trials clusters of people, or intact social units, rather than individuals are randomised to intervention and control groups and outcomes are measured on individuals within those clusters. Cluster randomised trials are also known as group randomised trials or community randomised trials.

There are several reasons to consider cluster randomisation: one of them is avoid the possibility of cross-contamination between intervention and control groups. When designing the educative intervention, the intervention group was randomly selected. In the selection of

geographical areas, the cross-contamination has been considered. Cross-contamination can occur when health professionals, physicians, pharmacists or others, work nearby, thus transferring between them the information received during interventions. This situation can be minimised when clusters are used (for example, health centre/hospital/pharmacy at the same geographical area).[103]

The physicians and pharmacists that belong to spatial-clusters of group control did not receive the intervention but as the intervention group arriving the information usual give by Northern Pharmacovigilance Unit and National Institute of Pharmacy and Medicine.

From September 2004 and March 2005, Northern Pharmacovigilance Unit give post-graduate education only for physicians who work in health centres belong to group control for sub region of Braga and Viana do Castelo (in a total of 18 health centres). For pharmacists this situation is different and Northern Pharmacovigilance Unit in collaboration with National Association of Pharmacies and other institutions, give education in the five sub regions, between March 2004 and March 2005, for pharmacists who belong to group control or intervention. It is necessary to say that the Northern Pharmacovigilance Unit has an annual compromise of education with Health Authorities.

4.2.4 Data collection

The purpose of this study is the comparison of reports arrived at the Northern Pharmacovigilance Unit before, during and after the educational intervention. The studied period ranges from January of 2003 to June 2005. Additionally, the following parameters have also been studied: (1) severity; (2) causality; (3) type (expected/unexpected); and (4) date of Marketing Authorisation Holder (new medicines).

4.2.5 Educative intervention

Factors that affect effectiveness of an educative intervention are rather complex. Among these the design and the production need special attention and are detailed next.

4.2.5.1 Design of intervention

The type of intervention used, results from the combination of an active intervention (group sessions) with a passive intervention (distribution of press material). The passive interven-

tion acts as a support for the active intervention. This strategy is referenced in several studies.[93,97,101] Another study[103] indicated that personalisation of these sessions, as is commonly used by the pharmaceutical industry is more effective, however, this is rather costly. Accordingly to some authors[94,97] the intervention projects seem to have a positive impact on reporting, but should be carried out continuously.

4.2.5.2 Elaboration of educative intervention

The educative intervention was elaborated taking into account the knowledge and attitudes of the health professionals that lead to the under-reporting, as detected in the case-control study. Technical-scientific material was prepared (presentation in PowerPoint) with the object of helping the health professionals to reduce the under-reporting and if possible to create a "culture of reporting".

The educative intervention had as its main didactic material a presentation in PowerPoint, which is included in Appendix E. A sample slide from this presentation can be seen in Figure 4. The presentation was created taking into consideration some presuppositions such as being of short duration and objective.

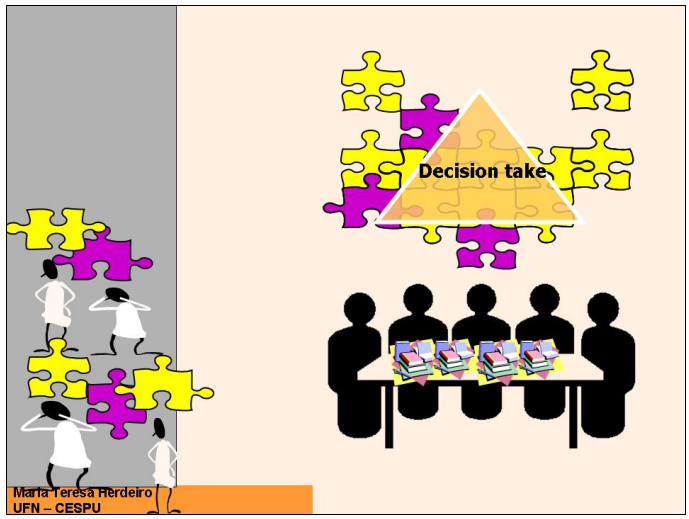

Figure 4. Sample slide from presentation.

At the beginning the presentation contains the pharmacovigilance and ADR definition (2 slides), followed by a presentation of some international studies on the effect of ADR, in

studies of mortality and morbidity, hospital admissions and costs for the health systems. One slide is dedicated to each of these subjects (4 slides). Next, the methods used in pharmacovigilance and the spontaneous reporting of ADR (and in particular of under–reporting) are presented (3 slides).

Eighteen slides were created, animated with some pictures that represent the respective medical and pharmaceutical health professionals, talking amongst themselves about the possible factors effecting under-reporting. The factors that appear in the presentation are those found in the case-control study as being the causes of under-reporting: (1) "belief that really serious adverse drug reactions is well documented by the time a drug is marketed", for this possible factor several slides had been created, explaining the limitations of the clinical tests, giving examples descriptions of low incidence of ADR in the literature and well-known by the professionals (these slides also described the types of ADR); (2) "belief that it is nearly impossible to determine whether a drug is responsible for a particular adverse reaction" and (3) “belief that I would only report an adverse drug reaction if I was sure that it was related to the use of a particular drug” several slides were created in order to make it clear that suspicions of ADR must be reported, even if it is not absolute certain and that there exists a commission of experts that evaluates all the reports; (4) "belief that the one case an individual physician might see, could not contribute you medical knowledge”, was given much importance to this factor of possible under-reporting, several slides had been elaborated to become evident that the participation of each one of us is essential for the system, and the system depend from our individual participation and finally (5) “belief that it is only necessary report serious or unexpected ADR”, about of this possible factor of under-reporting, it has been passed the message that is important to report all the serious ADR wherever they are expected (described in the summary of product characteristics) or unexpected (not described in the summary of products characteristics), all the unexpected ADR; additionally, special care should be taken to new drugs in market (that are in the market for less than five years) and to all the ADR that although described in the summary of products characteristics, are considered as being rare.

After talking on the "seven deadly sins" from Inman, one slide is presented that shows that is with the participation of all by sending of the respective report forms that is possible to the Health Authorities to evaluate each one of the report and to make decisions (this image meets in the pamphlet to give of some form continuity to the presentation). Slides also de-

scribed the process of evaluation of ADR and the process of decision making, because it was observed in the case-control study that is important for professionals to know how the system works, what it is made with the information that they send to the system (they do not know the information reported in the report card is used). Finally the question of how much time is need to fill the report card is also focused (and an example of filling the form is carried out in real time, with a clock counting the time) because they gave very importance to the question "do not have time to complete the report card". The minimum parameters needed to fill the form is also presented (this information is also included in pamphlets).

In the end of the presentation all the possible ways to contact the Northern Pharmacovigilance Unit are presented (this information is also included in all the other supplied material in this intervention).

The contents of the slides were evaluated in terms of linguistic content by the Department of Communication and Art of the University of Aveiro and in terms of technical-scientific content by the Northern Pharmacovigilance Unit.

The period of intervention elapsed between March and July of 2004. In the sub-regions of Bragança and Vila Real, the educative intervention became fulfilled during the months of March and April and in the sub-region the Porto between May (communitarian pharmacies) and July (health centres and hospitals). None of the 4 zones enclosed for the sub-regions of Viana do Castelo (1 zone) and Braga (3 zones) had been selected. In the sub-region of Bragança the intervention was carried through in the 3 hospitals, 12 health centres and 39 pharmacies. In the sub-region of Vila Real the intervention was carried through in the Hospital Centre of Vila Real/Peso da Régua (Hospital D. Luíz I – Peso da Régua, Hospital of S. Pedro – Vila Real), in 11 health centres and in 42 communitarian pharmacies; finally, in the sub-region of the Porto, the intervention occurred in one of the Central Hospitals, Hospital Geral de Santo António, SA; in the 6 health centres, considered of reference and the intervention still enclosed 79 pharmacies.

The used didactic material was the same for all the sessions. The speaker of the interventions was always the same in order to prevent errors of methodology and evaluation of each intervention. Intervention took 1 hour, 30 minutes for the presentation and other 30 minutes for conversation with participants about these issues. The groups were formed with 10 to 20 physicians depend the size of service and with 1 to 5 pharmacists, normally.

4.2.6 Material

The material for this study is constituted by: (1) letters, (1.a) letter of introduction of the educative intervention and (1.b) letter of confirmation of the day, hour and place of the same one; (2) the purple form or the yellow form; (3) pamphlets on the fulfilling of the report form; (4) a folder with article copies published in international journals, on the subjects that appear in the intervention; (5) participation certificate.

In the beginning of the study a letter of introduction was sent to all the selected institutions (hospitals, health centres and pharmacies); the content of the letter consists on the objectives of the study, its purpose and importance and the marking of a meeting to appointments the date for the intervention (Appendix F). Additionally, a letter to the Regional Health Administration of the North (Appendix G) was sent to give knowledge of begin of the study, and of the educative interventions that will be made in the institutions of health of the area of this administration.

After scheduling each one of the interventions, a letter was always sent (for fax or post office) 2 or 3 days before the intervention re-confirming the date and hour of the intervention and requesting, when necessary, the listing of the subjects to be present (Appendix H).

The report forms had been provided by the Northern Pharmacovigilance Unit and delivered to the participants in each intervention (yellow form to the physicians and purple form to the pharmacists). The report forms had not been distributed to five heath centres, three hospital services, one pharmacy hospital service and ten communitarian pharmacies (approximately 10% of intervention group). The report form was not distributed to any pharmacist or physician that was not present into the intervention.

The pamphlets consisted of a leaflet with the same exterior dimensions of the report form and of the same colour (yellow for physicians and purple for pharmacists) had been distributed by all subjects participating in the intervention. The pamphlet was elaborated to constitute a remainder of the presentation, containing its main messages, as well as the key image of the presentation. All the available contacts of the Northern Pharmacovigilance Unit are also in the leaflet. The pamphlet was evaluated in terms of linguistic content by the Department of Communication and Art of the University of Aveiro and in terms of technical-scientific content by the Northern Pharmacovigilance Unit. The design of pamphlets was elaborated by a graphical designer and can be found in the Appendix (Appendix I).

The didactic material that was delivered consisted of articles published in international journals. The copies of articles delivered corresponded to articles shown during the presentation and that had been considered important to base the related data on the importance of the ADR in mortality terms,[1,156,157] morbidity,[2,3] hospital admissions[59,158] and costs.[4,,60] These articles had been delivered to the directors of the health centres, hospital services and communitarian pharmacy technical directors in a folder of the Northern Pharmacovigilance Unit (this folder contains all the contacts of the Northern Pharmacovigilance Unit). Since it is considered important the role of the pharmacists in herbal[35] and of over-the-counter medicines[32,33,34], copies of articles on each one of these subjects had also been delivered.

The certificates of participation (Appendix J) contained the same layout of the presentation and had been printed in colour paper of high quality. In the end of each session, the certificates had been distributed individually to each participant, as a way to control the presences of the subjects without questions.

4.2.7 Statistical analysis

Separately statistic analyses were performed for physicians and pharmacists. All statistical analysis was carried out by intention to treat[159] and for this reason the subjects who, although assigned to an intervention group, were not subjected to intervention were also included in the analysis as belong to intervention group. Inclusion of all randomized subjects in statistical analysis avoided any bias incurred by non-assistance (equivalent to non-compliance) of physician to the intervention.

Generalized Linear Mixed Models (GLMM) using Penalized Quasi-Likelihood were applied to statistical analysis.[160,161] This statistical method allows longitudinal data analysis (repeat and multiples observations over the time on each of many individuals) adjusted by baseline values of the depending variable. This adjustment is very important when the study groups can become unbalanced due to a low number of random assignment units (as is the case in our study, with only 15 clusters). Moreover, these models offer additional advantages: first, they allow for the control of cluster effects derived from random assigning by subject groups rather than by individual subjects; and second, they allow for the introduction of random terms to control heterogeneity among subjects.

For producing models, we took the number of reports from each month as a dependent variable (that is a count variable, and for this we use a Poisson-GLMM), the independent term as

a random effect (to control initial heterogeneity among subjects), and the random distribution spatial cluster as cluster effect. The models were adjusted according to personal and socio-demographic variables (age, gender, specialty and primary/hospital) for avoid the possible not equally distribution after randomization. Since that Poisson assumption (mean and variance of the dependent variable are equal) was not found in our data, models were adjusted using the over-dispersion parameter.

In order to measure the intervention effect, an indicator dichotomous variable was created. This variable -called *period*- takes value 0 for baseline period and value 1 for months between the start of the intervention to the end of the follow-up. The intervention effect was evaluated through the interaction between the variable *group* (1 for intervention group and 0 for control group) and *period* variable. This interaction, allows quantification of the possible contamination of the control group by the intervention (measure in the interaction through variable *period*) and the baseline differences between studied groups (through variable *group*)

For the effect of analysis duration, another variable was built with 5 categories (value 0 for baseline period, 1 for the first 4 months after intervention and 2, 3 and 4 for subsequent periods of 4 months). The intervention effect in each 4 months period was evaluated through the interaction between this indicator variable and the variable group.

All the analyses were carried out using the S-Plus software. Results were expressed in relative rate (RR) with their respective 95% CI that indicate the number of times that the reporting probability increases.

5 RESULTS

5.1 Case-control studies

In the pilot test, all the physicians and pharmacists fill the questionnaire, in the 1st and in the 2nd sent. The pilot test was design to investigate possible difficulties in the filling of the questionnaire by health professionals and to test the reproducibility of the questionnaire between two consecutive sends in the same sample. The pilot tests had the following results in physicians, the correlation coefficients yielded by assessment of the questionnaire's reproducibility exceeded 0.75 for all fifteen attitudes and opinions, save the attitudes, "It is only necessary to report serious or unexpected ADR" and "When I read medical literature I am interested in articles about adverse drug reactions", in which the coefficients were 0.65 and 0.70, respectively ($p<0.005$). For pharmacists, the pilot tests had the following results; correlation coefficients yielded by assessment of the questionnaire's reproducibility exceeded 0.75 for all fifteen attitudes and opinions, except for the attitudes, "I should be financially reimbursed for providing the ADR service" and "I do not have time to think about the involvement of the drug or others causes in ADR", in which the coefficients were 0.71 and 0.74 respectively ($p<0.005$).

After pilot test, postal questionnaire was sent to all the health professionals participating in the study. Due to the low participation level found in similar studies[36, 68] where the answer level varies from 30 to 38%, a series of consecutive sends was decided. On the other side, from a total of 859 questionnaires mailed for physicians, 110 were returned by the postal service due to error in the postal addresses (100 from controls and 10 from cases), and 18 from controls were excluded because the physicians concerned were engaged in specializations such as anatomy pathology, in which they neither prescribed nor administered drugs. A total of 397 questionnaires were completed by 731 eligible practitioners (54.3 %), 66 by cases (84.6 %) and 331 by controls (50.7 %). From the 331 questionnaires received by the control group, 127 (38.4%) were received during the 1st sent, 80 (24.2%) and 63 (19%) respectively after the 2nd and 3rd sent and, finally, 61 (18.4%) in the last re-sent. In the case group, during the 1st sent 33 (50.0%) questionnaires were received, in 2nd, 3rd and 4th re-sent the received questionnaires were 16 (24.2%), 10 (15.2%) e 7 (10.6%) as can be seen in Table 5.

Table 5. Distribution of physicians questionnaire sent and arrival

	SENT	RECEIVED BY SENT				TOTAL RECEIVED	*RETURNED	**NON PROCESSED
		1º	2º	3º	4º			
Non-Reporters	771	127	80	63	61	331	100	18
Reporters	88	33	16	10	7	66	10	0
Total	859	160	96	73	68	397	110	18

*return by post, **specialities of anatomy and pathology

In the next graph (Figure 5), the cumulative percentage of received questionnaires in each send is shown.

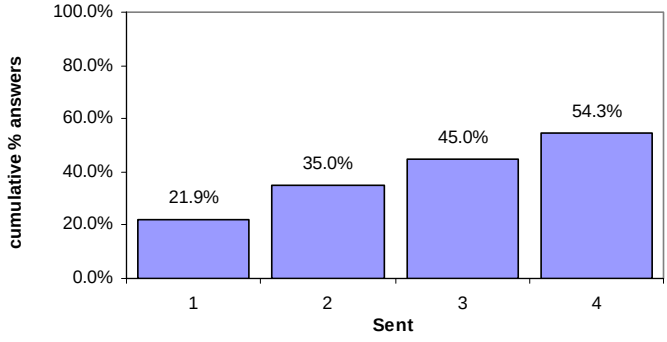

Figure 5. Level of accumulated answers for the total population of physicians.

In Figure 6, the answer level is presented for cases and controls separately. The differences between the two groups are clear: in the first sent 42.3% of cases answered to the questionnaire while in the control group only 20% answer it. This tendency is observed during all the re-sends being in the final of 4th re-sent of 85% for cases and 50% for controls.

Of a total of 314 questionnaires mailed for pharmacists, 19 (16 from controls and 3 from case) were returned by the postal service. In all, 256 questionnaires were returned by 295 eligible pharmacists (86.8%); of these, 31 were returned by cases (100%) and 225 by controls (85.2%). From the 225 questionnaires filled by the control group, 90 (40%) were filled after 1st sent, 65 (28.9%) after 2nd sent, 42 (18.7%) after 3rd sent and, finally, 28 (12.4%) after 4th sent. For cases, the answers to questionnaires were 14 (45.2%) for 1st sent, and 9 (29%), 6 (19.3%) and 2 (6.5%) respectively for 2nd, 3rd and 4th sends (Table 6).

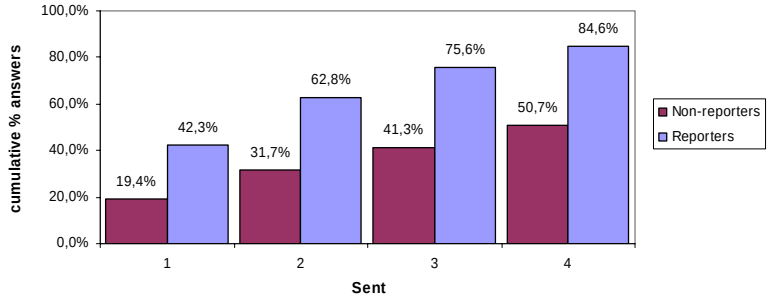

Figure 6. Level of answers of accumulated for reporters and non-reporters.

Table 6. Distribution of pharmacists questionnaire sent and arrival

	SENT	RECEIVED BY SENT				TOTAL RECEIVED	*RETURNED
		1º	2º	3º	4º		
Non-Reporters	280	90	65	42	28	225	16
Reporters	34	14	9	6	2	31	3
Total	314	104	74	48	30	256	19

*return by post

In the graph of Figure 7, the cumulative percentage of received questionnaires in each send is shown. A tendency for the decreasing of the number of answers is clearly observed for each re-sent as was observed for physicians.

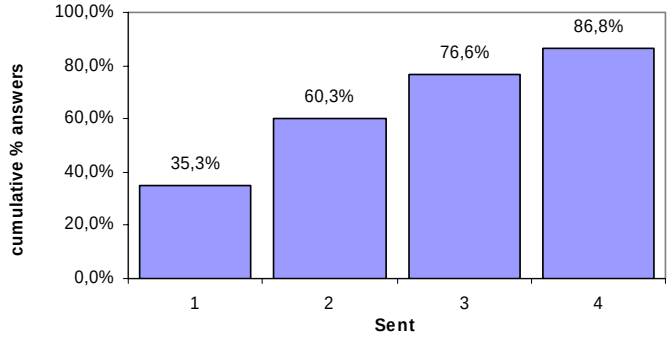

Figure 7. Level of accumulated answers for the total population of pharmacists.

In Figure 8, the answer level is presented for cases and controls separately. There are differences between the two groups although not so evident as for physicians; in the first sent 45% of cases answer to the questionnaire while in the control group only 34.1% answer it. This

tendency is observed during all the re-sends being in the final of 4th re-sent of 100% for cases and 85% for controls.

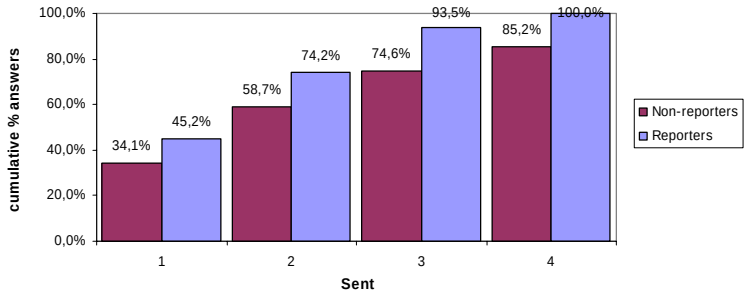

Figure 8. Level of answers of accumulated for reporters and non-reporters.

5.1.1 Description of the study sample

Age and gender (physician sample)

As can be observed in Figure 9, the population object of study distributes in a different form in relation to the gender and to the age. The average of the age between the men is of 46.0 (median 47) while in the women it is of 41.5 (median 41). There are also a bigger number of men 52% compared to women 48%. Additionally, there is a bigger predominance of citizens of medium age, for the men between the 45 and 54 years and for the women between the 35 and 44 years.

Comparing the resultant graphs of the stratification as a function of reporters' character (Figure 10) it can be observed that in the group of reporters the percentage of women is larger for cases than for controls (61% against 46%). It is verified that the reporters are distributed mainly in the segment between 45 and 54 years. The distribution of the reporters in terms of ages is similar to the one of the sample of the population.

Age and gender (pharmacist sample)

As can be observed in Figure 11, of the subjects that had answered to the questionnaire, the number of women, 199, are much more than men, 52. The average of the age between men 39.3 (median 37.3) and women is 37.0 (median 33.0). A clear predominance of subjects of young age exists, between 25 and 34 years for both men and women.

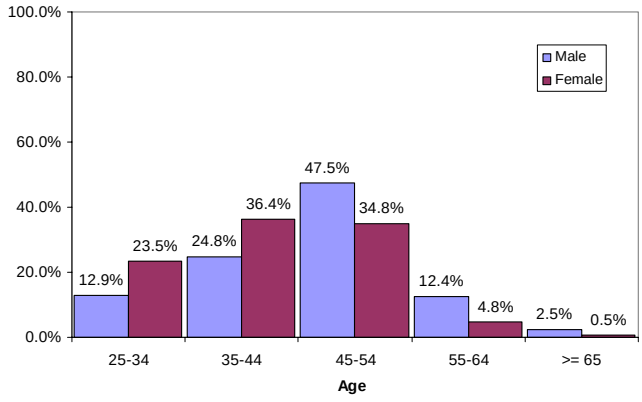

Figure 9. Distribution of the physicians in function of gender and age.

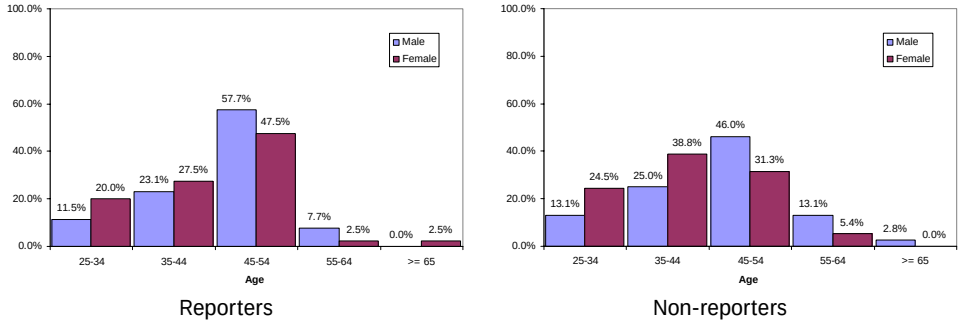

Figure 10. Distribution of the subjects in function of age and gender, divided in repot and non reporter.

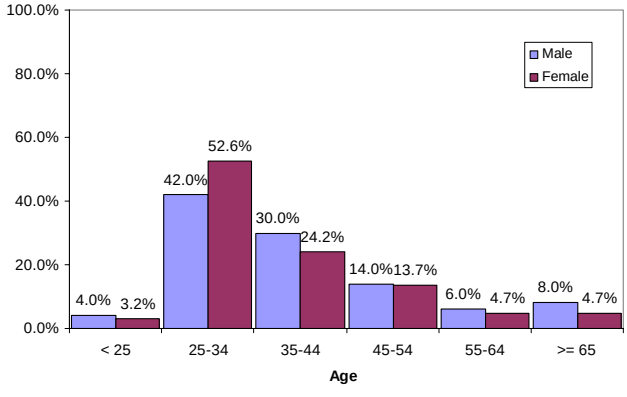

Figure 11. Distribution of the pharmacists in function of gender and age.

Comparing the graphs of Figure 12 resulting from stratification in function of character reporter we verify that in the group of reporters the percentage of men is lower than in the group of non-reporters (10% against 22%). It is verified that the reporters were distributed in bigger number in the segment of ages between 25 and 34 years. The distribution of the reporters and non-reporters in terms of ages is similar to the sample of the population studied.

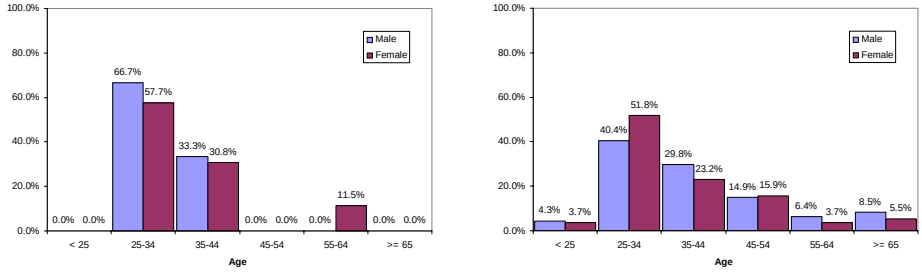

Figure 12. Distribution of the subjects in function of age and gender, divided in report and non reporter.

Number of patients seen per day

The average number of patients who had been received by the subject object of this study was of 16.4 per day (Figure 13). Dividing the population study in reporters (cases) and non-reporters (controls), we verify that the reporters had received in average 16.5 patients per day, while the non-reporters had taken care of in average 15.8 patients.

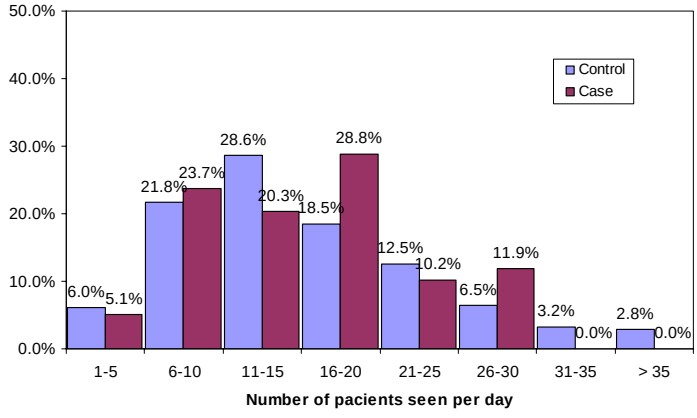

Figure 13. Number of patients seen per day

Number of prescriptions written per day

Globally an average of 22.4 prescriptions per day could be observed (Figure 14). Reporters exhibit an average of 25.0 prescriptions per day, while non-reporters realize an average of 21.9 prescriptions per day. In the reporters group there is a large percentage of general practitioners, which means that these physicians made more prescriptions. The type of clinical speciality is not uniformly distributed between the group of reporters and non-reporters.

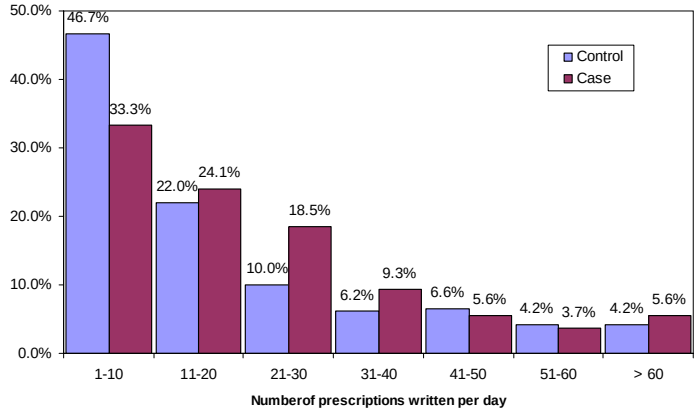

Figure 14. Number of prescriptions written per day

Physician speciality

The questionnaire asked for physician's specialty through an open question. The answers had been grouped in 4 sub-groups: general medicine (where it was included the public health and labour medicine), the medical specialties, the medical-surgical and surgical specialities and finally others where specialties such as pathological anatomy and clinical pathology. In Figure 15 it can be observed that in the group of non-reporters more than half (52.2%), exerts its functions in medicine specialist, while in the group of reporters these are only 45.5% of those that had answered. It is verified that in the group of non-reporters only 21.4% belongs to the general medicine specialty while in the reporters group half of the subjects that had answered belongs to this specialty.

In the group of non-reporters it is observed that the percentage of pertaining subjects to the specialties, grouped in surgery and medical-surgery, is very bigger (24.8%) than in the group

of reporters that it is only of 3%. It is still interesting to observe that the percentage of subjects with other specialties is the same in the two groups.

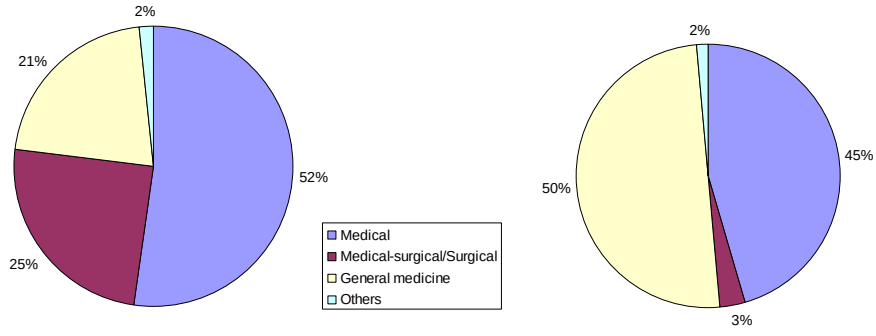

Figure 15. Type of speciality for non-reporters (left) and for reporters (right).

Questions about specialization were not collocated in pharmacist's questionnaire, because communitarian pharmacists did not have this type of education, in Portugal, at the moment.

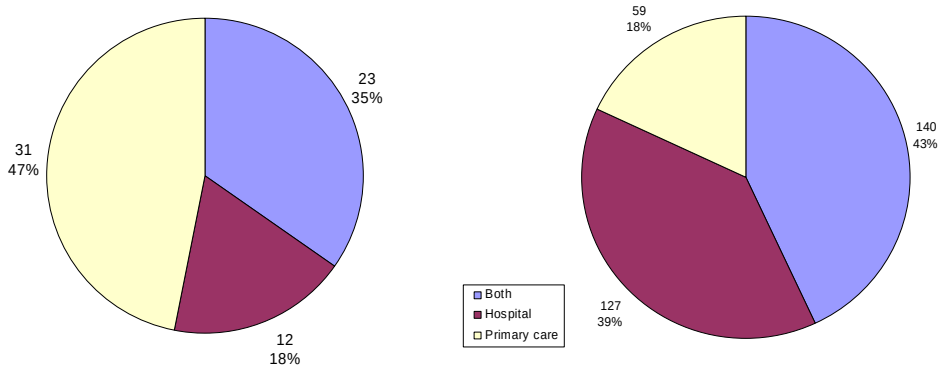

Figure 16. Work place for reporter physician (left) and for non-reporters' physician (right).

Work place

Questions about the place where physicians exert its professional activity were carried out to both physicians (hospital, primary care or both) and pharmacists (hospital, communitarian pharmacy or both). In relation to the physicians, the results can be seen in Figure 16 respectively to the group of reporters and non-reporters that had answered to this question. In the group of reporters we observe that 47% (31 subjects), exclusively exert its activity in primary

care and only 18% (12 citizens) in hospitals, while in the group of non reporters only 18% work in primary care and 39% (127 subjects) worked in hospital.

The percentage of subjects that work in both places, hospital and primary care, is superior in the group of non-reporters (43%) than in the group of reporters that it is 35%.

In relation to the group of the pharmacists, all the subject of the sample answered to this question. In the following figure (Figure 17), it can be observed that in the group of reporters 30% (9 pharmacists) work in hospitals, while in the group of non-reporters only 4% work in hospitals. It is interesting to note there isn't any subject that works in both the places.

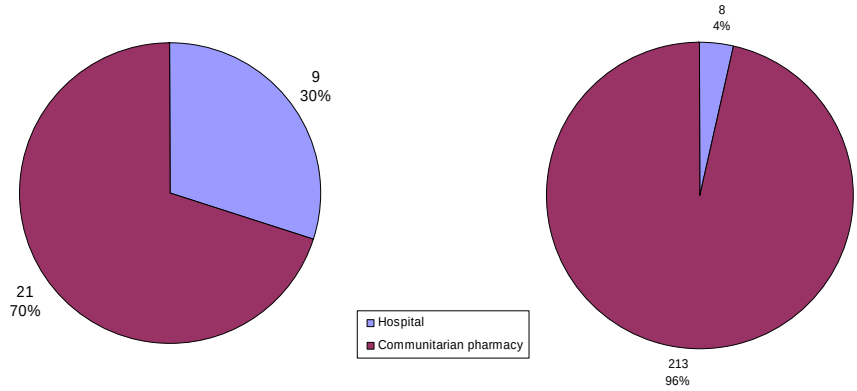

Figure 17. Work place for reporting pharmacists (left) and for non-reporting pharmacists (right).

5.1.2 Personal and professional characteristics associated with ADR report

Once individually analyzed the professional and demographic characteristics of the participant subjects in the study, a logistic regression was carried out to identify those ones that are associated with a greater or minor reporter character, eliminating the influence of the other variables.

Table 7 and Table 9 show the OR and the CI of all the professional and demographic characteristics that have been enclosed in the study. These calculations were carried out using a logistic regression multivariate model, including for the sample of physicians the following variables: age, gender, type of medical specialisation, number of patients seen/day, number

of prescriptions written/day, workplace (hospital, primary care, both) and for the sample of pharmacists the following variables: age, gender, job function, workplace (hospital, community pharmacy). Each value of the OR is compared with the category of reference (OR=1.00).

In this way, an OR small than unity indicate a smaller trend to report. On the contrary, an OR high than unity indicate a higher trend to report. These conclusions can be extrapolated to the original population, with 95% confidence, presupposing that the 95% CI of the OR does not include the unity.

Table 7 shows the personal and professional characteristics of responding practitioners for cases as well as controls. Although the probability of reporting any ADR was higher for females than for males [OR=1.86 (95% CI: 1.06-3.11], this was no longer significant after adjustment for the remaining variables.

Table 7. Personal and professional physicians characteristics associated with ADR spontaneous report

	Ever reported an ADR (n)*		Crude analysis		Adjusted analysis**		
	Yes	No	OR	95% CI	OR	95% CI	*P value*
GENDER							
Male	26	176	1.00	-------	1.00	-------	
Female	40	150	1.86	1.06-3.11	1.23	0.61-2.48	0.565
AGE							
<40	21	116	1.00	-------	1.00	-------	
40-48	28	112	1.38	0.74-2.57	0.81	0.35-1.86	0.619
>48	17	94	1.00	0.50-2.00	0.67	0.27-1.67	0.393
TYPE OF MEDICAL SPECIALIZATION							
Medical	30	167	1.00	-------	1.00	-------	
Medical-Surgical/surgical	2	80	0.14	0.03-0.60	0.10	0.02-0.46	0.003
General Medicine	33	69	2.68	1.52-4.78	1.05	0.30-3.69	0.942
Other	1	5	1.12	0.13-9.93	7.20	0.35-148.73	0.201
NUMBER OF PATIENTS SEEN/DAY							
<12	20	101	1.00	-------	1.00	-------	
12-18	20	64	1.50	0.76-2.99	1.82	0.73-4.55	0.197
>18	17	83	1.04	0.52-2.09	0.64	0.23-1.79	0.391
NUMBER OF PRESCRIPTIONS WRITTEN/DAY							
<10	18	120	1.00	-------	1.00	-------	
10-23	13	57	1.52	0.70-3.32	0.79	0.32-1.95	0.613
>23	23	81	1.89	0.96-3.73	0.68	0.24-1.90	0.465
WORKPLACE							
Hospital	12	127	1.00	-------	1.00	-------	
Primary care	31	59	5,56	2.67-11.59	7.74	1.85-32.30	0.005
Both	23	139	1.74	0.83-3.64	2.71	0.97-7.55	0.057

*Continuous variables categorized in tertiles for all participants.

**Adjusted for the effects of the other variables included in the table.

95% CI = 95% Confidential interval; OR = Odds ratio.

Age failed to evince any influence on ADR reporting. In terms of specializations, while the crude analysis showed general medicine practitioners as being two and a half times more likely to report ADR than other specialists [OR=2.68 (95% CI: 1.52-4.78)], this relationship nevertheless disappeared in the adjusted analysis. Surgical specialists registered the lowest probability of reporting in both the crude [OR=0.14 (95% CI: 0.03-0.60)] and adjusted analyses [OR=0.10 (95% CI: 0.02-0.46)]. Physicians' workplace appeared to exert an influence on reporting probability. Practitioners who worked in primary care were over seven times more likely to report [OR=7.74 (95% CI: 1.85-32.30)] than those who worked exclusively in hospitals.

Table 8. Personal and professional physicians (responders and non responders) characteristics associated with ADR spontaneous report

	Adjusted analysis**		
	OR	**95% CI**	***P value***
GENDER			
Male	1.0	---------	
Female	1.7	0.99-2.86	0.06
AGE			
<40	1.0	---------	
40-48	1.0	0.52-1.83	0.93
>48	0.8	0.40-1.62	0.55
TYPE OF MEDICAL SPECIALIZATION			
Medical	1.0	---------	
Medical-Surgical/surgical	0.1	0.03-0.49	0.004
General Medicine	0.6	0.21-1.64	0.315
Other	0.4	0.05-3.43	0.430
WORKPLACE			
Hospital	1.0	--------	
Primary care	4.0	1.28-12.20	0.02
Both	3.6	1.75-7.50	0.00

*Continuous variables categorized in tertiles for all participants.
**Adjusted for the effects of the other variables included in the table.
95% CI = 95% Confidential interval; OR = Odds ratio.

Since our results might have been affected by the professional and personnel characteristics of non-responders (answer level was about 50%), data were collected on aspects such as age, gender, specialty and workplace for non-responders and a new logistic regression model for both responders and non-responders constructed. The results (Table 8) of this model are in line with the results in Table 7, and indicate that, whereas age and gender are not related to notification, specialty and workplace do indeed influence reporting.

Table 9 sets out responding pharmacists' personal and professional characteristics for both cases and controls. Also shown in Table 9 the influence exerted by personal and professional's characteristics on reporting. As can be seen, after adjusting for the remaining inde-

pendent variables only workplace was associated with reporting, with hospital pharmacists being 20 times more likely to report than community pharmacists [1/OR=1/0.05=20, p=0.001]. The variables of gender, age and job function failed to display any influence on ADR reporting.

Table 9. Personal and professional pharmacists characteristics associated with ADR spontaneous report

	Ever reported an ADR (n)*		Crude analysis		Adjusted analysis**		
	Yes	No	OR	95% CI	OR	95% CI	*P value*
GENDER							
Male	3	49	1.00	-----	1.00	----	
Female	27	172	2.56	0.75-8.80	2.08	0.57-7.58	0.271
AGE							
<29	7	63	1.00	-----	1.00	-----	0.982
29-39	18	83	1.95	0.77-4,96	1.39	0.49-3.89	0.537
>39	4	73	0.49	0.14-1.76	0.36	0.09-1.50	0.163
JOB FUNCTION							
Registered pharmacist	10	98	1.00	-----	1.00	-----	
Assistant pharmacist	9	80	1.10	0.43-2.84	0.81	0.28-2.28	0.685
Other	11	43	2.51	0.99-6.34	0.39	0.07-2.11	0.275
WORKPLACE							
Hospital	8	9	1.00	-----	1.00	-----	
Community pharmacy	21	213	0.09	0.03-0.25	0.05	0.01-0.30	0.001

*Continuous variables categorized in tertiles for all participants.
**Adjusted for the effects of the other variables included in the table.
95% CI = 95% Confidential interval; OR = Odds ratio.

5.1.3 Knowledge and attitudes associated with physician ADR spontaneous report

Spontaneous ADR reporting attitudes and opinions, and their influence on reporting are shown in Figure 18 and Figure 19, for each one of the 15 questions of the physician's questionnaire. The attitudes in respect of which physicians' recorded highest agreement were the following: "I would only report an adverse drug reaction if I were sure that it was related to the use of a particular drug", (median 9.0) and "I have a professional obligation to report ADR" (median 10). The attitudes in respect of which physicians showed the least agreement were as follows: "I should be financially reimbursed for providing the ADR service" (median 0.5), "Reporting ADR puts my career at risk" (median 1.0), "It is only necessary to report serious and unexpected ADR" (median 2.0) and "I do not have time to think about the involvement of the drug or other causes in ADR" (median 2.5). Some of the practitioners' atti-

tudes displayed certain discrepancies, with some physicians being in total agreement and others in total disagreement, e.g., "Really serious adverse drug reactions are well documented by the time a drug is marketed", "The one case an individual physician might see cannot contribute to medical knowledge", and "I do not have time to think about the involvement of the drug or the other causes in ADR".

The following attitudes and opinions registered a statistically significant inverse relationship with reporting probability (see Table 10), inasmuch as a lower degree of *complacency* (the belief that really serious adverse drug reactions are well documented by the time a drug is marketed), *insecurity* (the belief that it is nearly impossible to determine whether a drug is responsible for a particular adverse reaction), *diffidence* (the belief that one would only report an adverse drug reaction if one were sure that it was related to the use of a particular drug), *indifference* (the belief that the one case an individual physician might see, could not contribute to medical knowledge) and *ignorance* (the belief that it is only necessary to report serious or unexpected ADR) were all associated with a higher probability of reporting. Hence, a one-unit decrease on the visual analogy scale (score range 0=total disagreement to 10=total agreement) increased the probability of reporting by 12% in the case of complacency and ignorance (1/OR=1/0.89=1.12), rising to 20% in the case of insecurity (1/0.83=1.20), diffidence (1/0.84=1.19) and indifference (1/0.84=1.19).

The OR for a change in exposure corresponding to the interquartile range of these measures (see Table 10), indicates that a change from the 75th to the 25th percentile in assessments of the following attitudes or opinions would lead to reporting probability rising by 87% for complacency, 109% for insecurity, 143% for diffidence, 220% for indifference, and 71% for ignorance.

Other attitudes and opinions that showed an association with under-reporting were linked to: (1) lack of time, e.g., "I do not have time to complete the yellow card", and "they do not have time to think about the involvement of the drug or other causes in ADR"; and (2) method of reporting, e.g., "would be more likely to report ADR if there were an easier method" and "they do not know how the information reported in the yellow card is used". Similarly, the variable "When I read medical literature, I am interested in articles about adverse drug reactions" also appeared to be associated with probability of reporting [OR=1.13 (95% CI: 1.00-1.27)].

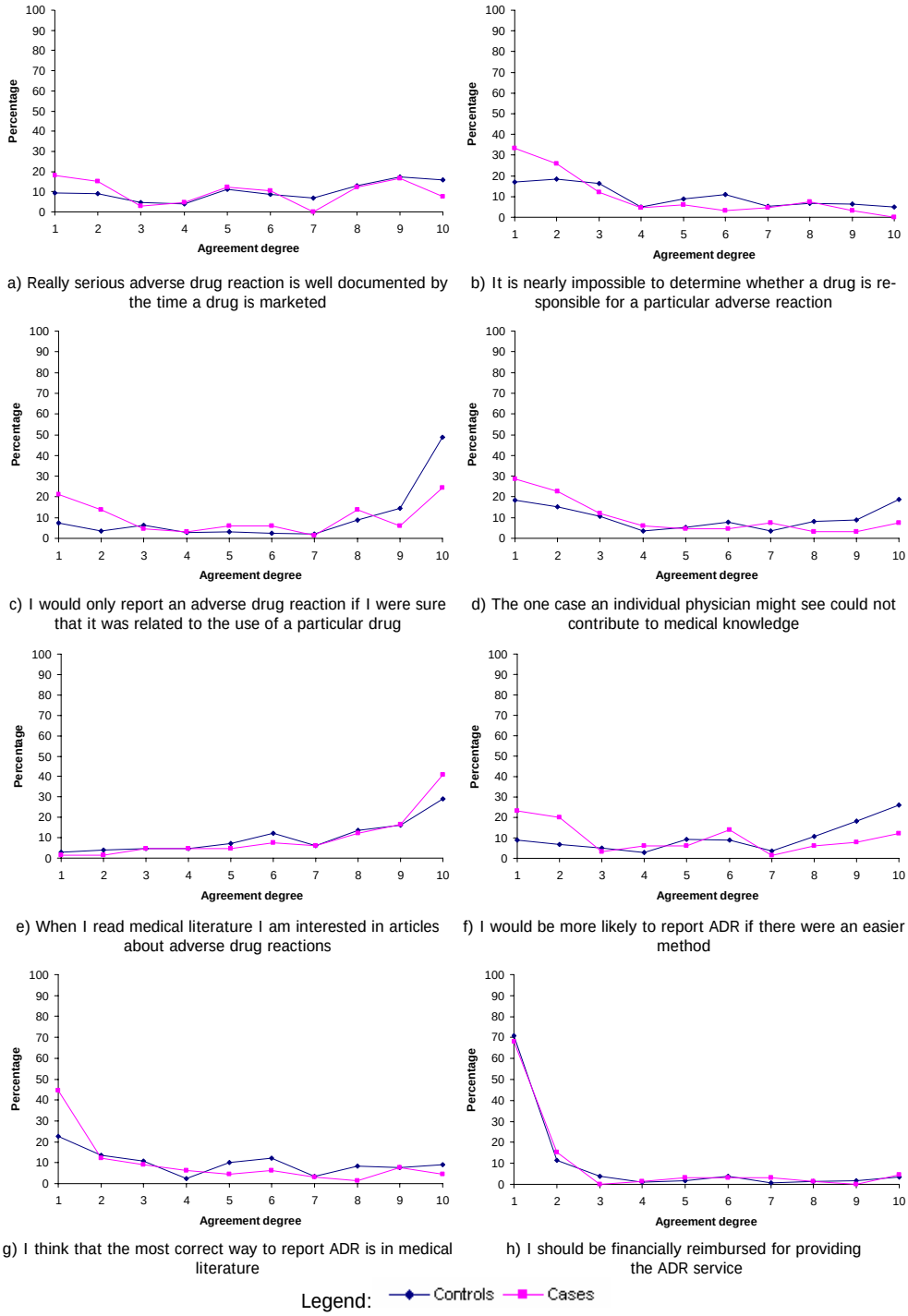

Figure 18. Statements of the physician's questionnaire and their influence on reporting ADR.

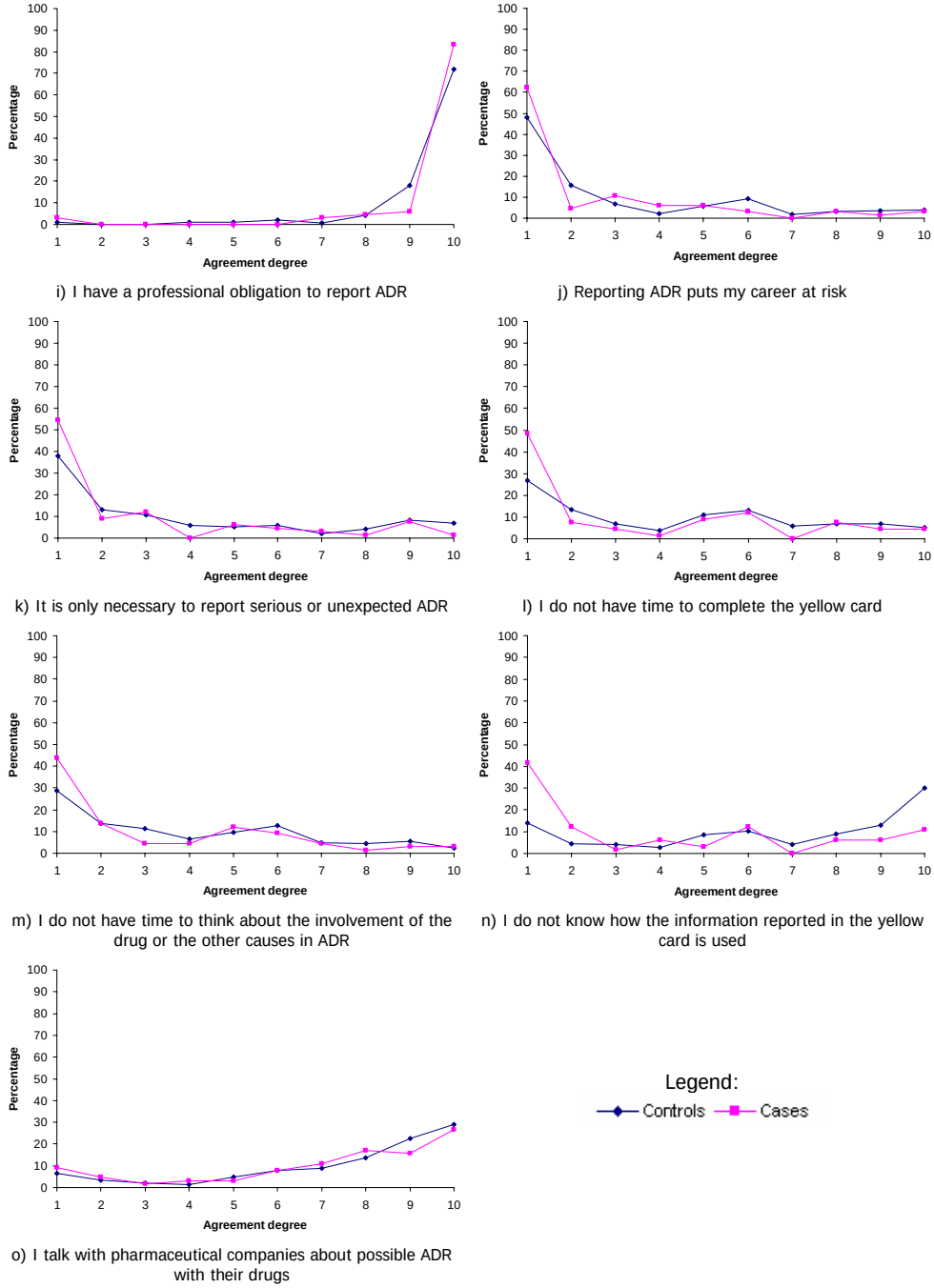

Figure 19. Statements of the physician's questionnaire and their influence on reporting ADR.

Table 10. Influence of several physicians attitudes and opinions (1) on spontaneous adverse drug reaction (ADR) reporting.

ATTITUDE OR OPINION (1)	Percentile			Adjusted analysis (2)				
				OR (3)		1/IqOR (4)		
	25	50	75	OR	95% CI	1/IqOR	95% CI	*P*
Really serious adverse drug reaction is well documented by the time a drug is marketed	3.0	6.5	8.5	0.89	0.81-0.98	1.87	1.13-3.10	0.015
It is nearly impossible to determine whether a drug is responsible for a particular adverse reaction	1.5	3.0	5.5	0.83	0.74-0.94	2.09	1.27-3.41	0.004
I would only report an adverse drug reaction if I were sure that it was related to the use of a particular drug	5.0	9.0	10.0	0.84	0.77-0.91	2.43	1.63-3.65	<0.001
The one case an individual physician might see could not contribute to medical knowledge	1.5	4.0	8.0	0.84	0.76-0.92	3.20	1.73-5.85	<0.001
When I read medical literature I am interested in articles about adverse drug reactions	5.5	8.0	9.5	1.13	1.00-1.27	0.61	0.38-0.99	0.046
I would be more likely to report ADR if there were an easier method	3.5	7.5	9.0	0.80	0.73-0.87	3.46	2.10-5.69	<0.001
I think that the most correct way to report ADR is in medical literature	1.0	3.0	7.0	0.89	0.81-0.99	1.96	1.06-3.62	0.031
I should be financially reimbursed for providing the ADR service	0.5	0.5	1.5	0.99	0.88-1.12	1.01	0.89-1.13	0.937
I have a professional obligation to report ADR	9.0	10.0	10.0	1.04	0.83-1.29	0.97	0.78-1.20	0.751
Reporting ADR puts my career at risk	0.5	1.0	4.5	0.91	0.81-1.02	1.44	0.91-2.28	0.120
It is only necessary to report serious or unexpected ADR	0.5	2.0	5.5	0.90	0.81-0.99	1.71	1.02-2.89	0.044
I do not have time to complete the yellow card	1.0	3.5	6.0	0.88	0.80-0.97	1.91	1.17-3.09	0.010
I do not have time to think about the involvement of the drug or the other causes in ADR	1.0	2.5	5.5	0.87	0.77-0.97	1.90	1.14-3.19	0.014
I do not know how the information reported in the yellow card is used	2.5	6.5	9.5	0.81	0.74-0.88	4.49	2.43-8.23	<0.001
I talk with pharmaceutical companies about possible ADR with their drugs	6.0	8.5	9.5	0.94	0.85-1.04	1.26	0.89-1.80	0.196

(1) Measured using a continuous, horizontal visual analog scale. Recorded answers were read in a range from o (total disagreement) to 10 (total agreement), with a precision of 0.5.
(2) OR adjusted for specialization and workplace.
(3) OR indicates the increase/decrease in the probability of being a responder for every one-unit rise in the value of the visual analog scale (score range 0-10)
(4) The 1/IqOR based on a change corresponding to the interquartile range of attitude or opinion measures.

5.1.4 Knowledge and attitudes associated with pharmacists ADR spontaneous report

Spontaneous ADR reporting attitudes and opinions, and their influence on reporting are shown in Figure 20 and Figure 21 for each one of the 15 questions of the pharmacist's questionnaire. In general, pharmacists tended to agree with attitudes, such as "I would only report an adverse drug reaction if I were sure that it was related to the use of a particular drug" (median 8.5), and "I have a professional obligation to report ADR" (median 10), and disagree with others, such as "I do not have time to complete the report card" (median 1.5), "Reporting ADR puts my career at risk" (median 1.5), and "I should be financially reimbursed for providing the ADR service" (median 0.5). In the case of other attitudes, however,

wide discrepancies were in evidence, e.g., "Really serious adverse drug reaction is well documented by the time a drug is marketed" (interquartile range, 55% of the visual analogical scale), and "The one case an individual pharmacist might see cannot contribute to pharmaceutical knowledge" (interquartile range, 90% of the visual analogical scale).

Table 11 shows the degree of agreement between the study subjects and each of the attitudes studied (in terms of percentiles) and the related influence on reporting (in terms of the OR and IqOR) and also shown the relationship between attitudes and opinions statistically associated with a lower likelihood of reporting ADR. A one-unit decrease on the visual analogical scale (score range 0=total disagreement to 10=total agreement) increased the probability of reporting by: 19% (1/OR=1/0.84=1.19, p=0.01) in the case of 1-*complacency,* "Really serious adverse drug reaction is well documented by the time a drug is marketed"; 20% (1/OR=1.20, p=0.01) in the case of 2-*ignorance*, "It is only necessary to report serious and not expected ADR"; and 37% (1/OR=1.37, p<0.01) in the case of 3-*diffidence*, "I would only report an adverse drug reaction if I were sure that it was related to the use of a particular drug". The OR for a change in exposure corresponding to the interquartile range of these measures, indicates that a change from the 75th to the 25th percentile in assessments of the following attitudes or opinions would lead to reporting probability rising by 223% for *complacency*, 316% for *ignorance*, and 240% for *diffidence* (see Table 11).

Other attitudes and opinions that showed an association with under-reporting were linked to: (1) lack of time, e.g. "I do not have time to think about the involvement of the drug or other causes in ADR" (p=0.020); and (2) method of reporting, e.g., "I would be more likely to report ADR if there were an easier method" (p=0.024).

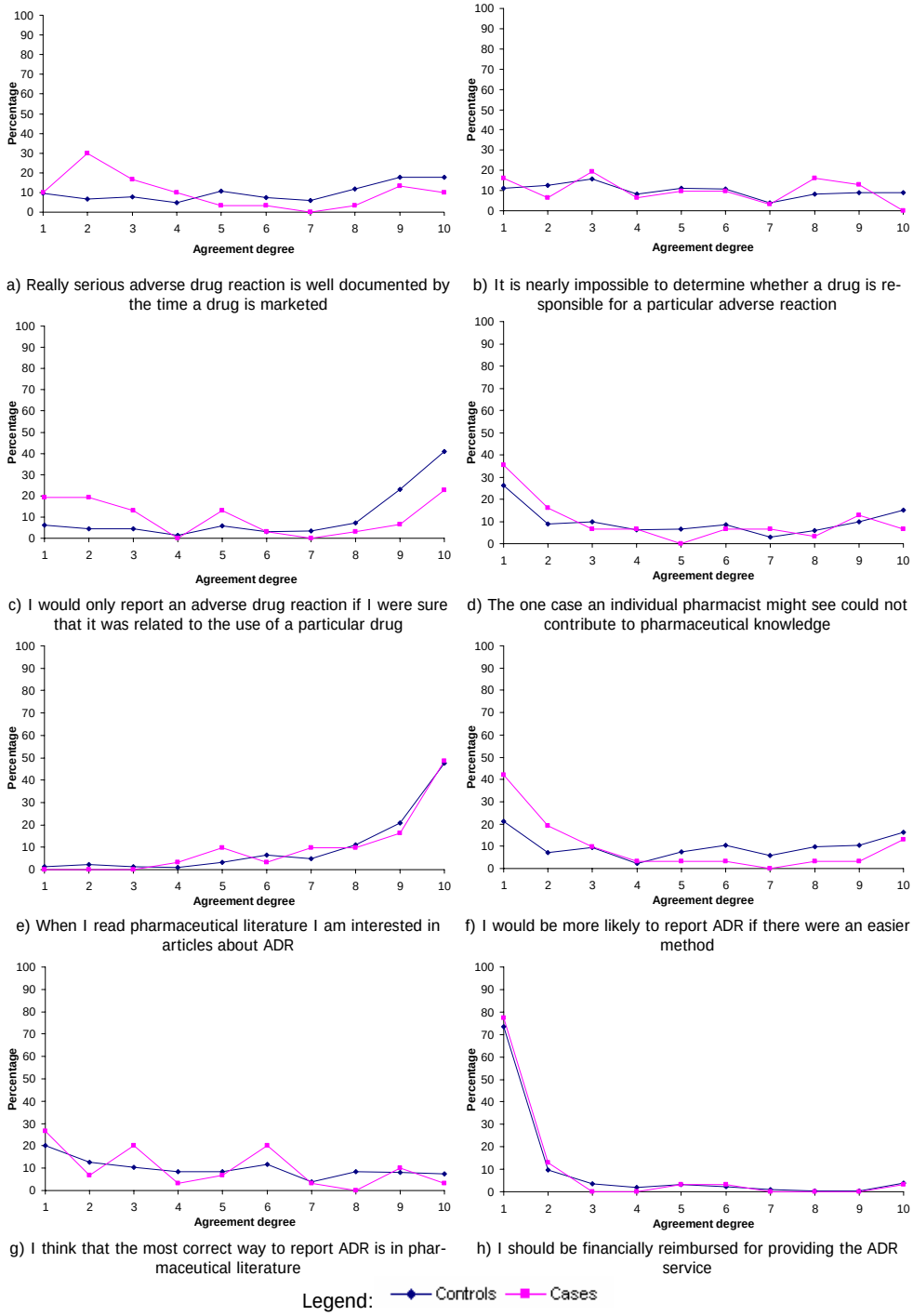

Figure 20. Statements of the pharmacist's questionnaire and their influence on reporting ADR.

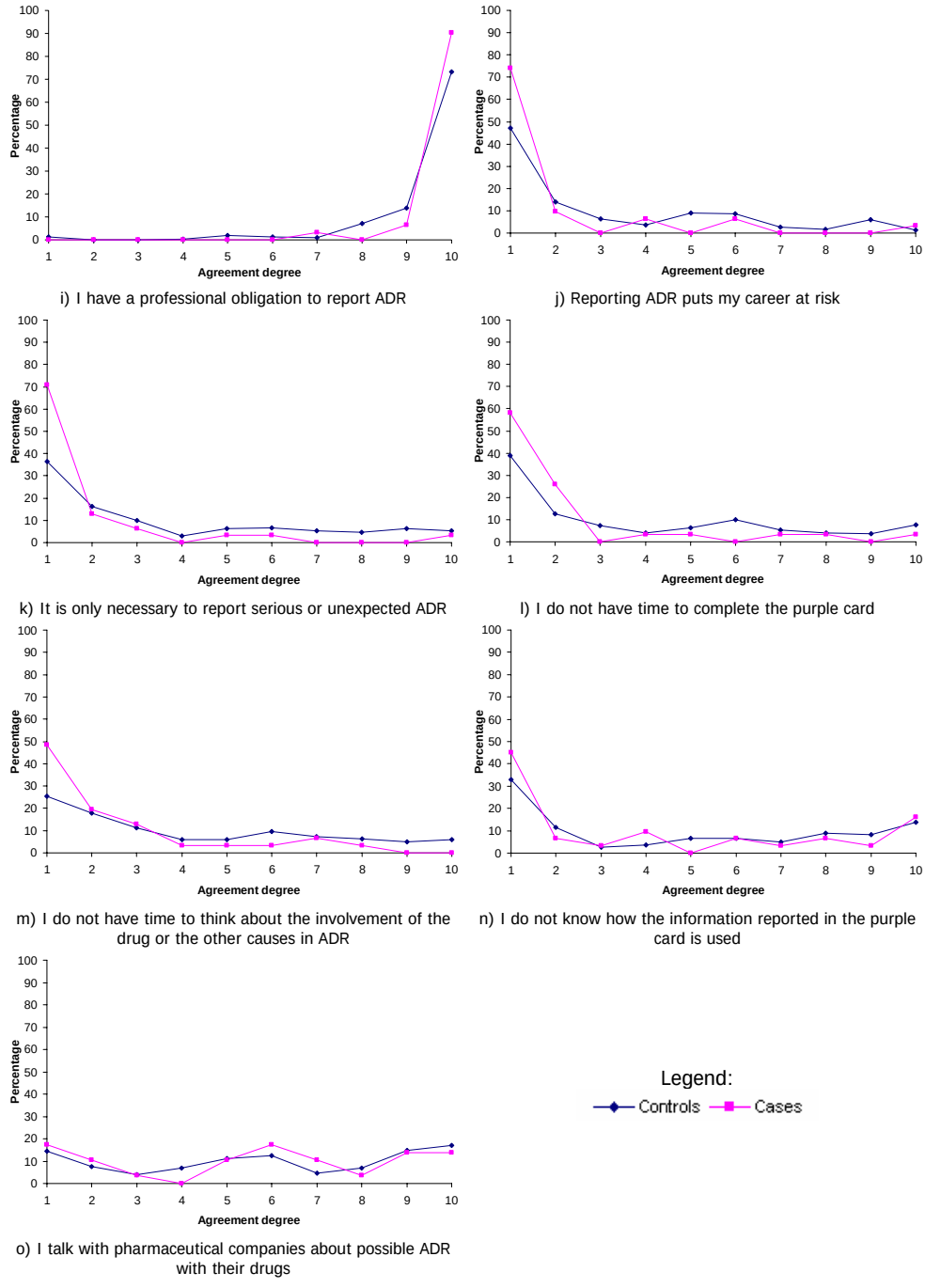

Figure 21. Statements of the pharmacist's questionnaire and their influence on reporting ADR.

Table 11. Influence of several pharmacists attitudes and opinions [(1)] on spontaneous adverse drug reaction (ADR) reporting.

ATTITUDE OR OPINION	PERCENTILE			OR	1/IQOR	P
	25	50	75	(95% CI)	(95%CI)	
Really serious adverse drug reaction is well documented by the time a drug is marketed	3.0	6.0	8.5	0.84 (0.73-0.96)	3.23 (1.51- 6.95)	0.011
It is nearly impossible to determine if a drug is responsible for a particular adverse reaction	2.5	4.5	7.5	0.98 (0.85-1.13)	1.20 (0.59- 2.45)	0.814
I would only report an adverse drug reaction if I were sure that it was related to the use of a particular drug	5.0	8.5	10.0	0.83 (0.74-0.93)	3.40 (1.89- 6.08)	0.002
The one case an individual pharmacist might see cannot contribute to pharmaceutical knowledge	1.0	4.0	8.0	0.93 (0.82-1.06)	1.74 (0.74- 4.08)	0.264
When I read pharmaceutical literature I am interested in articles about adverse drug reactions	7.5	9.0	10.0	0.97 (0.79-1.17)	1.14 (0.72- 1.78)	0.724
I would be more likely to report ADR if there were an easier method	1.5	5.0	8.0	0.86 (0.75-0.98)	4.20 (1.68- 10.45)	0.024
I think that the most correct way to report ADR is in pharmaceutical literature	1.5	4.0	6.5	0.99 (0.86-1.15)	1.58 (0.77- 3.25)	0.896
I should be financially reimbursed for providing the ADR service	0.5	0.5	1.5	1.01 (0.83-1.22)	1.02 (0.85- 1.24)	0.898
I have a professional obligation to report ADR	9.0	10.0	10.0	1.45 (0.81-2.61)	0.66 (0.37- 1.18)	0.217
Reporting ADR puts my career at risk	0.5	1.5	5.0	0.85 (0.69-1.04)	2.23 (0.90- 5.49)	0.110
It is only necessary to report serious or unexpected ADR	0.5	2.0	5.5	0.73 (0.58-0.93)	4.16 (1.44- 12.04)	0.010
I do not have time to complete the purple card	0.5	1.5	5.5	0.86 (0.72-1.01)	2.43 (1.05- 5.66)	0.072
I do not have time to think about the involvement of the drug or other causes in ADR	1.0	2.5	6.0	0.81 (0.68-0.97)	2.71 (1.13- 6.49)	0.020
I do not know how the information reported in the purple card is used	1.0	3.5	8.0	1.00 (0.89-1.12)	1.62 (0.71- 3.72)	0.998
I talk to pharmaceutical companies about possible ADR with their drugs	3.0	5.5	8.5	0.96 (0.84-1.09)	0.92 (0.45- 1.87)	0.492

[*]Measured using a continuous, horizontal visual analogy scale. Recorded answers were read in a range from 0 (total disagreement) to 10 (total agreement), with a precision of 0.5.

5.2 Cluster Randomized Trial

In this study, data was acquired through the cluster-randomized trial. An educative intervention was designed and performed in 4 clusters of the intervention group, with the following results.

For physicians we had a total of 6950 physicians of the initial database, (Figure 22) and according with the exclusion criteria previously defined, 40 were excluded because they work in the administrative or analytic (histocompatibility and genetic centres) areas, 24 because they work in toxic-dependency centres, 2 because they are members of Northern Pharmacovigilance Unit and finally 1 that made a specific protocol (immunoallergology service from a central hospital) with the Northern Pharmacovigilance Unit.

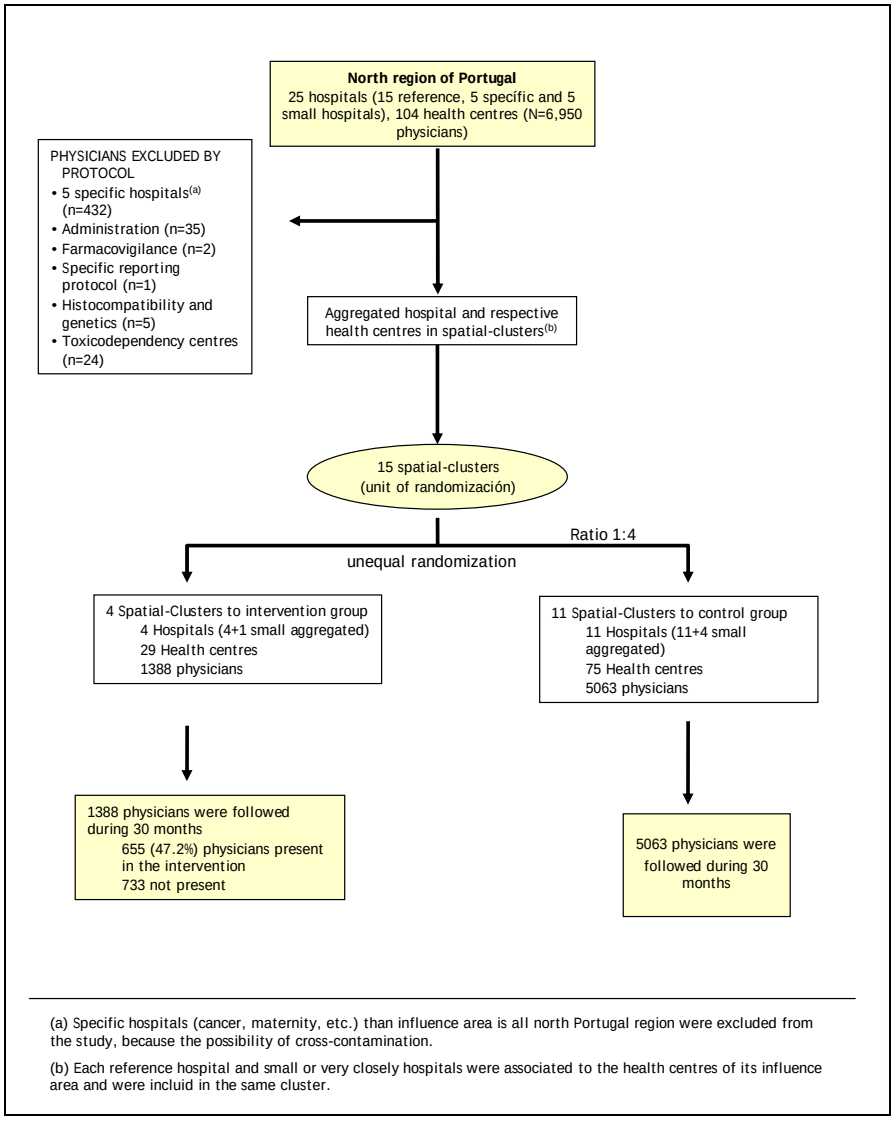

Figure 22. Flow-chart of the study design for physician

Additionally, the 432 physicians working in specific hospitals were also excluded. Finally, 6451 physicians were included, from which 1388 belong to the intervention group and 5063 to the control group. The reporting card was not given to 184 physicians (13.3 %) of the intervention group. The number of physicians belonging to the intervention group that effectively had participated was 655 (47.2%). The median of the following period was 13 months for the pos-intervention period. The design of the study could be observed in the flow-chart (Figure 22).

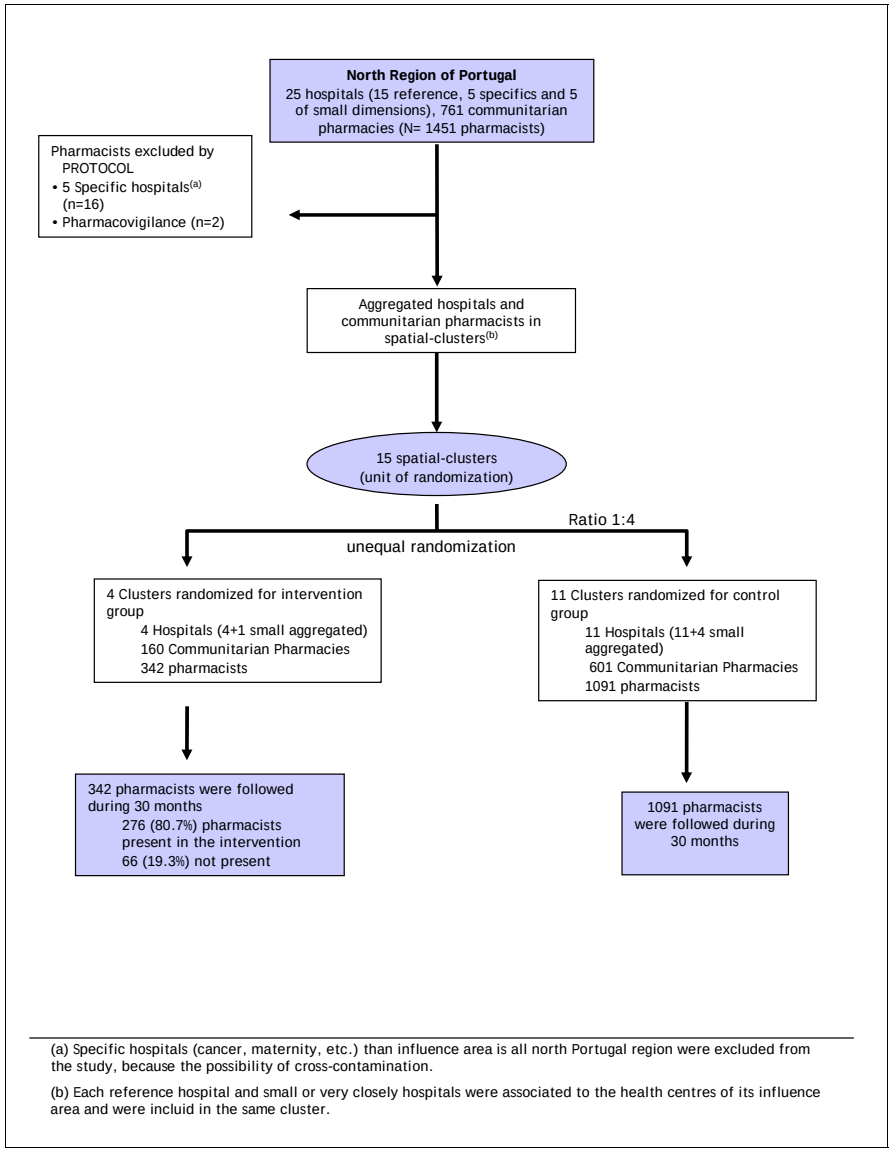

Figure 23. Flow-chart of the study design for pharmacists.

The design of the study for pharmacists could be observed in the Figure 23.

For pharmacists and accordingly with the database we have a total of 1451, that were excluded 2 because they are members of Northern Pharmacovigilance Unit. Additionally, the 16 pharmacists working in specific hospitals were also excluded. Finally, 1433 pharmacist were included, from which 342 belong to the intervention group and 1091 to the control

group. The reporting card was not given to 46 pharmacist of the intervention group. The median of the following period was 13 months for the pos-intervention period. The number of pharmacists belonging to the intervention group that effectively had participated was 276 (80.7%).

5.2.1 Personal and professional baseline characteristics of the study sample

Next tables (Table 12 and Table 13) presented baseline personal and professional characteristics of intervention and control groups, for physicians and pharmacists.

In Table 12, for physicians it was observed that distribution by gender and age are similar, although slightly less general medicine specialists exist in the intervention group clusters, (a possible explication for this fact is that in Portugal the physicians who working in urgency service in hospitals appears in database as general medicine, in spite of had other specialities).

Table 12. Personal and professional physicians characteristics in each study group*

	Intervention group (n=1388)	**Control group (n=5063)**
GENDER		
Male	681 (49.1)	2432 (48.0)
Female	707 (50.9)	2631 (52.0)
AGE		
Average (SD)	43.5 (9.2)	45.1 (8.8)
Median (percentile 25, 75)	43 (34, 50)	46 (38, 51)
SPECIALITY		
General medicine	427 (31.7)	1902 (38.3)
Medical	542 (40.2)	1839 (37.0)
Medical-surgical	195 (14.5)	646 (13.0)
Surgical	115 (8.5)	163 (3.3)
Others	69 (5.1)	136 (2.1)
Not appear	40 (2.9)	96 (1.9)
WORKPLACE		
Primary Care	358 (25.8)	1701 (33.6)
Hospital	1030 (74.2)	3362 (66.4)

* Values are expressed as number (percentage) unless otherwise indicated. SD = Standard deviation.

Table 13 presents baseline characteristics of intervention and control groups for pharmacists. It was observed that distribution by gender, age and workplace are similar, in both groups.

Table 13. Personal and professional pharmacists characteristics in each study group*

	Intervention group (n=342)	Control group (n=1091)
GENDER		
Male	70 (20.5)	221 (20.3)
Female	272 (79.5)	870 (79.7)
AGE		
Average (SD)	38.2 (11.7)	37.5 (11.3)
Median (percentile 25, 75)	35 (30, 43)	34 (29, 42.8)
WORKPLACE		
Pharmacy	315 (92.1)	1013 (92.9)
Hospital	27 (7.9)	78 (7.1)

*Values are expressed as number (percentage) unless otherwise indicated. SD = Standard deviation.

5.2.2 Reporting rate of ADR

In the next tables (see Table 14 and Table 15) the baseline reporting values were compared (the baseline year is 2003), for physicians and pharmacists. The physicians of the intervention group had an average of global reporting and ADR with inferior definitive or probable causality and serious ADR than the control group, whereas they have similar values in new drugs (Table 14).

Table 14. Reporting rate of ADR per 1000 physicians-month. Description by characteristics of ADR, and by period.

Reporting	Group	Period					
		Basal	Post-intervention				
			Overall period	4-month period			
				1º	2º	3º	4º
Totals	Intervention with RF	0.36 (7)	7.71 (130)	17.2 (83)	3.53 (17)	4.76 (23)	2.91 (7)
	Intervention without RF	2.26 (7)	12.8 (31)	16.3 (12)	13.6 (10)	5.4 (4)	24.0 (5)
	Intervention Pooled	0.63 (14)	8.35 (161)	17.1 (95)	4.86 (27)	4.86 (27)	4.61 (12)
	Control	0.94 (79)	1.21 (82)	1.09 (22)	1.09 (22)	1.43 (29)	1.26 (9)
Serious	Intervention	0.36 (8)	2.91 (56)	5.40 (30)	0.90 (5)	3.06 (17)	1.54 (4)
	Control	0.50 (42)	0.66 (45)	0.69 (14)	0.64 (13)	0.64 (13)	0.70 (5)
Unexpected	Intervention	0.13 (3)	2.33 (45)	4.32 (24)	1.08 (6)	1.62 (9)	2.30 (6)
	Control	0.29 (24)	0.15 (10)	0 (0)	0.25 (5)	0.20 (4)	0.14 (1)
High causality	Intervention	0.45 (10)	6.12 (118)	12.24 (68)	3.42 (19)	3.96 (22)	3.46 (9)
	Control	0.63 (54)	1.00 (68)	0.99 (20)	0.79 (16)	1.23 (25)	0.98 (7)
New drugs	Intervention	0.31 (7)	3.94 (76)	7.56 (42)	2.34 (13)	2.33 (13)	3.07 (8)
	Control	0.32 (27)	0.47 (32)	0.49 (10)	0.44 (9)	0.49 (10)	0.42 (3)

RF: Report Form. In the fourth 4-months period the following of all the subjects was not complete.

The pharmacists (see Table 15), of the intervention group had an average of ADR with slightly inferior definitive or probable causality and serious ADR than the control group, whereas have slightly superior values in global reporting and unexpected drugs. All of these possible differences in baselines values between groups do not bias the results, because the Poisson-GLMM adjusts for those baseline differences.

Table 15. Reporting rate of ADR per 1000 pharmacists-month. Description by characteristics of ADR, and by period.

Reporting	Group	Period					
		Basal	Post-intervention				
			Overall period	4-month period			
				1°	2°	3°	4°
Totals	Intervention with RF	2.90 (13)	29.77 (132)	52.36 (62)	29.56 (35)	22.73 (27)	9.39 (8)
	Intervention without RF	1.36 (1)	9.35 (6)	16.3 (3)	5.43 (1)	5.43 (1)	11.11 (1)
	Intervention Pooled	2.69 (14)	27.19 (138)	47.5 (65)	26.3 (36)	20.41 (28)	9.55 (9)
	Control	2.43 (44)	3.97 (58)	2.06 (9)	4.81 (21)	5.50 (24)	2.59 (4)
Serious	Intervention	0.96 (5)	13.00 (66)	16.81 (23)	16.81 (23)	8.75 (12)	8.49 (8)
	Control	1.27 (23)	1.64 (24)	0.46 (2)	2.29 (10)	2.76 (12)	0 (0)
Unexpected	Intervention	0.96 (5)	7.09 (36)	13.16 (18)	7.31 (10)	1.83 (8)	0 (0)
	Control	0.77 (14)	1.30 (19)	0.92 (4)	1.60 (7)	4.37 (6)	2.12 (2)
High causality	Intervention	0.96 (5)	16.15 (82)	25.58 (35)	14.62 (20)	14.58 (20)	7.42 (7)
	Control	1.16 (21)	2.12 (31)	1.15 (5)	1.37 (6)	3.90 (17)	1.94 (3)
New drugs	Intervention	1.15 (6)	11.30 (57)	17.54 (24)	12.43 (17)	7.31 (10)	6.37 (6)
	Control	1.44 (26)	1.50 (22)	0.92 (4)	1.60 (7)	2.06 (9)	1.29 (2)

RF: Report Form. In the fourth 4-months period the following of all the subjects was not complete.

The next 2 figures (Figure 24 and Figure 25) show the monthly evolution of the number of reports by 1000 physician-month and by 1000 pharmacist-month in the intervention group and in control group. In Figure 24, it possible see that from the beginning of the intervention, in first 4 months the spontaneous report increase more than 20-fold (RR=23.3; $p<0.001$, see Table 16) and after decrease, but maintain about 5-fold higher than control group, in the second, third and fourth 4-months period, RR for second, third and fourth 4-months period is between 4.7 and 6.6-fold higher and statistically significance to the control group for second, third and fourth 4-months period (see Table 16, model 2). In Figure 25, it possible see that from the beginning of the intervention, in first 4 months the spontaneous report increase more than 20 times (RR=20.2; $p<0.0001$, Table 17) and after decrease, but maintain about 3.0-fold higher than control group, in the second and third 4-months period, RR for second, third 4-months-period is between 3.0 and 4.8-fold higher and statically significance (Table 17,

model 2). In four 4-months periods the intervention is not more statically significance (RR=2.77; p= 0.35).

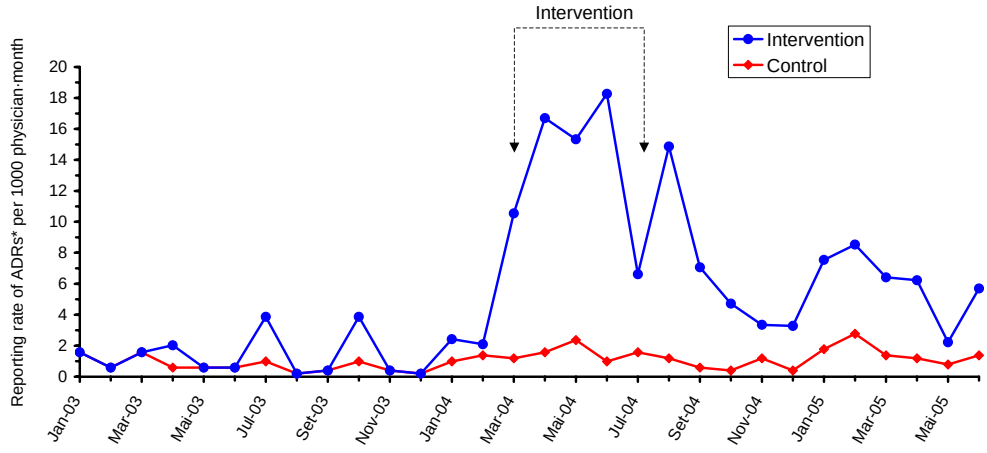

Figure 24. Reporting rate of ADR per 1000 physician-month (between January 2003 and June of 2005)

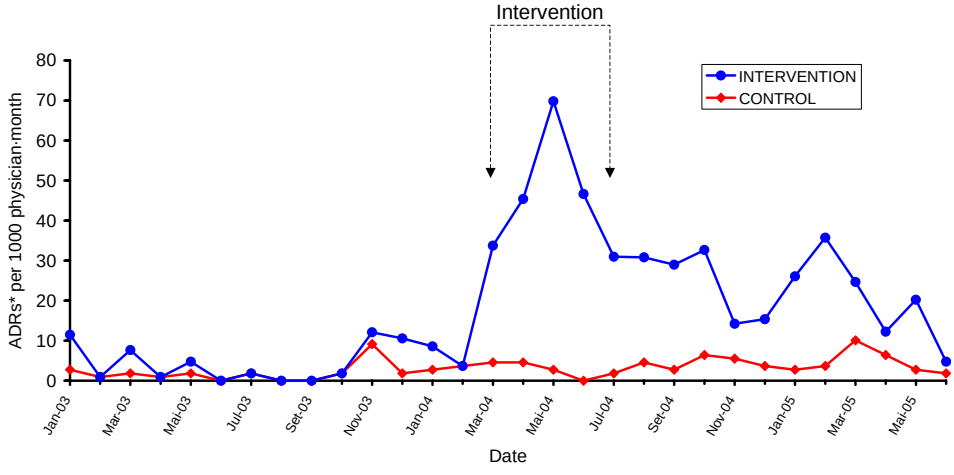

Figure 25. Reporting rate of ADR per 1000 pharmacists-month (between January 2003 and June of 2005)

The figures (Figure 26 and Figure 27) show the effect of the intervention on the reporting of serious, unexpected, with defined or probable causality, and on new drugs ADR for 1000

physician-month and 1000 pharmacist-month respectively. In Figure 26 (a, b, c, d) could be observed that the intervention multiplies by 6-fold (RR=6.07; p=0.001) the serious ADR reporting; by 8-fold (RR=8.47; p<0.001) the ratio of report ADR the defined or probable causality; in 32-fold (RR=32.60; p<0.001) the ratio to report ADR unexpected and finally increase in 8-fold the ratio of reporting ADR to the new medicines (RR=8.24; p=0.002).

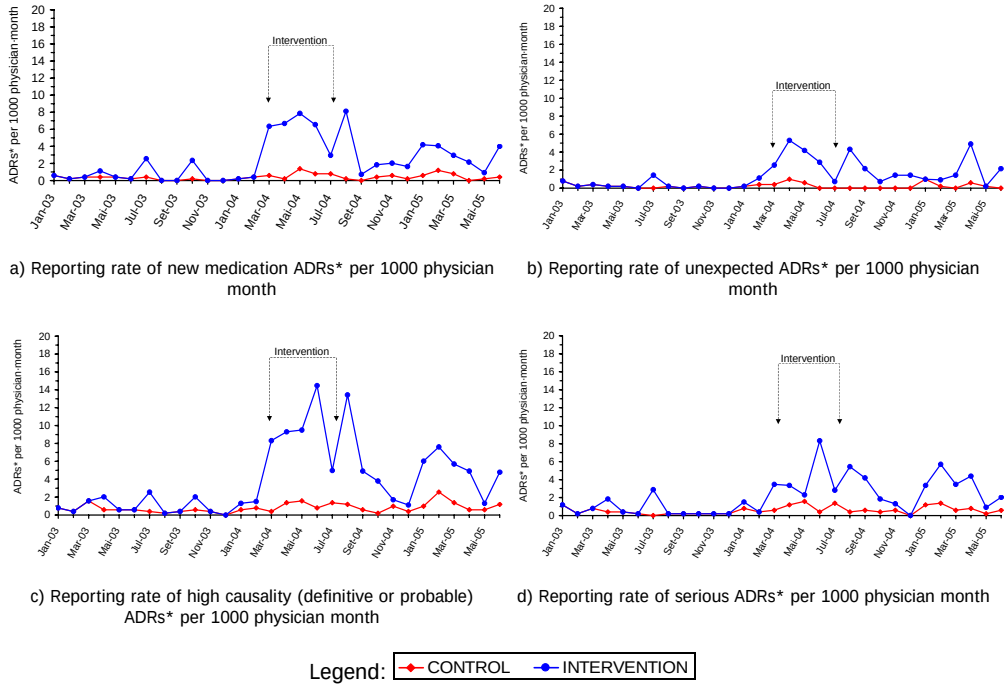

Figure 26. Reporting rate of ADR per 1000 physician-month (serious, highly probability, unexpected and new medicines).

In Figure 27 (a, b, c, d) could be observed that the intervention multiplies by 10-fold (RR=9.79; p=0.002) the serious ADR reporting; by 9-fold (RR=8.67; p=0.002) the ratio of report ADR the defined or probable causality; in 4-fold (RR=4.41; p=0.04) the ratio to report ADR unexpected and finally increase in 9-fold the ratio of reporting ADR to the new medicines (RR=9.33; p<0.001)).

In Table 16 it is possible observed the effect of the intervention in the report ratios, adjusted by baseline values and the speciality and workplace for physicians. Intervention increase total report ratios about 10-fold (RR=9.65; p<0.0001) during the pos-intervention period (see Table 16, model 1).

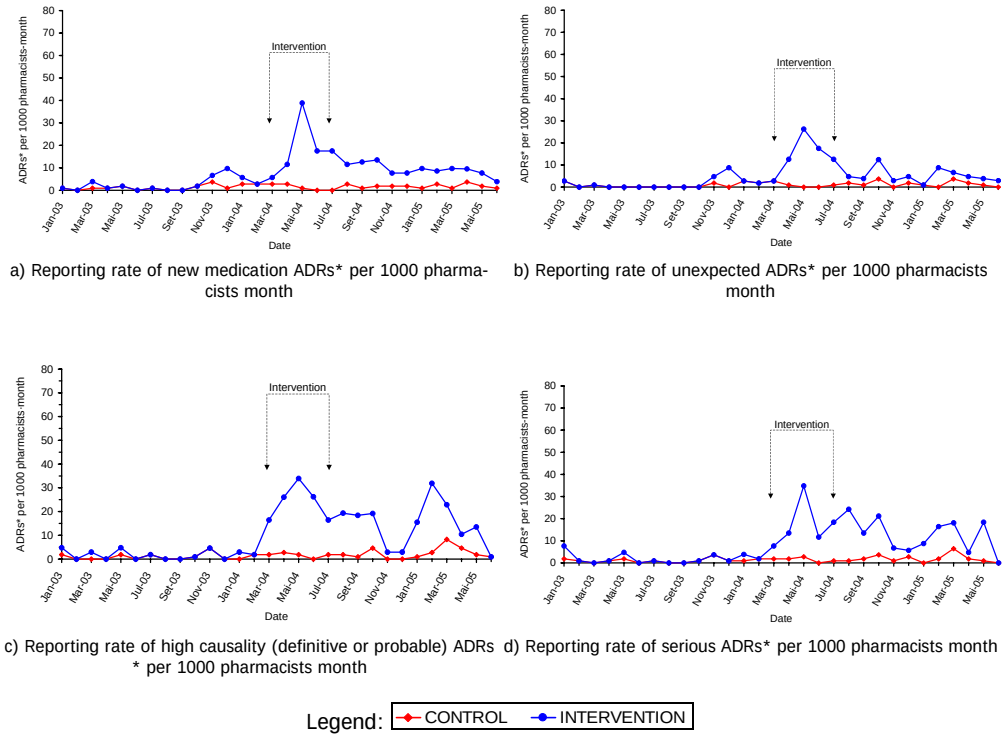

Figure 27. Reporting rate of ADR per 1000 pharmacist-month (serious, highly probability, unexpected and new medicines).

In Table 17 it is possible observed the effect of the intervention in the report ratios, adjusted by baseline values and workplace for pharmacists. Intervention increase total report ratios about 6-fold (RR=5.87; p=0.001) during the pos-intervention period (see Table 17, model 1).

It is observed that the yellow card administered during the intervention increases in more than 3-fold the effectiveness of the intervention that without yellow card (15.3 vs. 4.5), and this effect is maximum in first 4 months and disappear in the following months. The distribution of purple card during the intervention not influenced the effectiveness of the same. Our results present an RR=5.9, when the purple card is distributed during the intervention and a RR=4.2, when the purple card is not distributed during the intervention.

Finally, in models it is possible see that exist a very small cross-contamination effect between groups; for example control group only increase 29% the total reports ratio (RR=1.29; p=0.30) during the pos-intervention period for physicians and 63% for pharmacists (RR=1.63;

p=0.13). The baseline differences between groups are not relevant for all dependent variables (the statistic significance for *group* variable is always higher than 0.5), although the models show results adjusted by these differences.

Table 16. Effect of intervention over ADR reporting of physicians. Evaluation of the effect of the report form and duration of the effect.

Models		Results	
Model description with dependent variable	**Independent variables**	**RR (IC95%)**	**P-Value**
Model 1. Effect of intervention on total number of ADR reported[a]	Period	1.29 (0.80-2.08)	0.30
	Group	0.72 (0.27-1.98)	0.53
	Period x Group	9.65 (3.63 -25.68)	<0.0001
Model 2. Effect of time (in 4-month periods) since intervention on total number of ADR reported	4-month period 1º	1.15 (0.55 – 2.41)	0.71
	4-month period 2º	1.15 (0.55 -2.41)	0.71
	4-month period 3º	1.52 (0.78 – 2.95)	0.22
	4-month period 4º	1.31 (0.45 – 3.83)	0.62
	Group	0.75 (0.31 – 1.83)	0.53
	Group x 4-month period 1°	23.27 (7.42 – 72.95)	<0.001
	Group x 4-month period 2º	6.61 (1.90 – 22.99)	0.003
	Group x 4-month period 3º	5.02 (1.50 – 16.73)	0.009
	Group x 4-month period 4º	4.73 (0.94 – 23.71)	0.06
Model 3. Effect of intervention on serious ADR reporting[a]	Period	1.33 (0.76 – 2.27)	0.30
	Group	0.74 (0.28 – 1.94)	0.53
	Period x Group	6.07 (2.04 -18.02)	0.001
Model 4. Effect of intervention on definitive-probable ADR reporting[a]	Period	1.55 (0.94-2.57)	0.09
	Group	0.78 (0.30-2.05)	0.63
	Period x Group	8.47 (2.98-24.05)	<0.001
Model 5. Effect of intervention on unexpected ADR reporting[a]	Period	0.52 (0.19-1.41)	0.20
	Group	0.48 (0.09-2.51)	0.39
	Period x Group	32.60 (4.94-215.20)	<0.001
Model 6. Effect of intervention on new drug ADR reporting[a]	Period	1.46 (0.70-3.02)	0.31
	Group	1.13 (0.35-3.68)	0.84
	Period x Group	8.24 (2.20- 30.83)	0.002
Model 7. Effect of report form on total number of ADR reported[a]	Period	1.28 (0.79-2.07)	0.31
	Intervention without RF[b]	1.08 (0.30-3.88)	0.91
	Intervention with RF[b]	0.42 (0.12-1.40)	0.16
	Intervention without RF[b] x Period	4.46 (1.14-17.47)	0.03
	Intervention with RF[b] x Period	15.29 (4.26-54.94)	<0.001
Model 8. Effect of time (in 4-month periods) since intervention and of report form on total number of ADR reported	4-month period 1º	1.15 (0.55-2.41)	0.71
	4-month period 2º	1.15 (0.55-2.41)	0.71
	4-month period 3º	1.52 (0.78-2.95)	0.22
	4-month period 4º	1.31 (0.45-3.83)	0.63
	Intervention without RF[b]	1.56 (0.47-5.25)	0.47
	Intervention with RF[b]	0.50 (0.15-1.66)	0.26
	Without RF x 4-month period 1°	6.27 (1.23-31.93)	0.03
	Without RF x 4-month period 2º	5.22 (0.98-27.89)	0.05
	Without RF x 4-month period 3º	1.58 (0.21-12.01)	0.66
	Without RF x 4-month period 4º	8.01 (1.01-65.17)	0.05
	With RF x 4-month period 1°	39.86 (9.74-163.13)	<0.001
	With RF x 4-month period 2º	8.16 (1.72-38.70)	0.008
	With RF x 4-month period 3º	8.38 (1.92-36.64)	0.004
	With RF x 4-month period 4º	4.74 (0.67-33.48)	0.12

Period: Months before intervention =0, months after intervention =1.
Group: Control group=0, intervention group=1
4-month period: Reference category: Months before intervention

a. During all post-intervention period (median of 13 months following)
b. Reference category: control group

Table 17. Effect of intervention over ADR reporting of pharmacists. Evaluation of the effect of the report form and duration of the effect.

Models		Results	
Model description with dependent variable	**Independent variables**	**RR (IC95%)**	**P-Value**
Model 1. Effect of intervention on total number of ADR reported[a]	Period	1.63 (0.87-3.06)	0.13
	Group	1.52 (0.35-6.68)	0.58
	Period x Group	5.87 (1.98-17.39)	0.001
Model 2. Effect of time (in 4-month periods) since intervention on total number of ADR reported	4-month period 1º	0.85 (0.27-2.69)	0.78
	4-month period 2º	1.98 (0.86-4.56)	0.11
	4-month period 3º	2.26 (1.02-5.03)	0.05
	4-month period 4º	1.06 (0.20-5.51)	0.95
	Group	1.54 (0.35-6.75)	0.58
	Group x 4-month period 1°	20.21 (4.60-88.87)	<0.0001
	Group x 4-month period 2º	4.80 (1.31-17.57)	0.02
	Group x 4-month period 3º	3.27 (0.88-12.05)	0.08
	Group x 4-month period 4º	2.77 (0.33-23.35)	0.35
Model 3. Effect of intervention on serious ADR reporting[a]	Period	1.30 (0.59-2.84)	0.51
	Group	1.08 (0.18-6.37)	0.93
	Period x Group	9.79 (2.24-42.66)	0.002
Model 4. Effect of intervention on definitive-probable ADR reporting[a]	Period	1.82 (0.87-3.81)	0.11
	Group	1.15 (0.20-6.47)	0.88
	Period x Group	8.67 (2.12-35.42)	0.002
Model 5. Effect of intervention on unexpected ADR reporting[a]	Period	1.68 (0.74-3.80)	0.22
	Group	1.24 (0.37-4.18)	0.73
	Period x Group	4.41 (1.11-17.53)	0.04
Model 6. Effect of intervention on new drug ADR reporting[a]	Period	1.05 (0.50-2.16)	0.90
	Group	0.80 (0.26-2.51)	0.71
	Period x Group	9.33 (2.53-34.40)	<0.001
Model 7. Effect of report form on total number of ADR reported[a]	Period	1.63 (0.87-3.06)	0.13
	Intervention without RF[b]	1.22 (0.04-36.76)	0.91
	Intervention with RF[b]	1.53 (0.35-6.75)	0.57
	Intervention without RF[b] x Period	4.24 (0.13-135.24)	0.41
	Intervention with RF[b] x Period	5.98 (1.97-18.21)	0.002
Model 8. Effect of time (in 4-month periods) since intervention and of report form on total number of ADR reported	4-month period 1º	0.85 (0.26-2.68)	0.78
	4-month period 2º	1.98 (0.86-4.56)	0.11
	4-month period 3º	2.26 (1.02-5.03)	0.05
	4-month period 4º	1.06 (0.20-5.51)	0.95
	Intervention without RF[b]	1.30 (0.04-39.14)	0.88
	Intervention with RF[b]	1.54 (0.35-6.86)	0.57
	Without RF x 4-month period 1°	14.20 (0.31-646.52)	0.17
	Without RF x 4-month period 2º	2.03 (0.02-189.27)	0.76
	Without RF x 4-month period 3º	1.78 (0.02-164.53)	0.80
	Without RF x 4-month period 4º	7.78 (0.07-902.59)	0.40
	With RF x 4-month period 1°	20.67 (4.60-92.78)	<0.0001
	With RF x 4-month period 2º	5.00 (1.33-18.76)	0.02
	With RF x 4-month period 3º	3.38 (0.89-12.78)	0.07
	With RF x 4-month period 4º	2.58 (0.29-22.80)	0.39

Period: Months before intervention =0, months after intervention =1.
Group: Control group=0, intervention group=1
4-month period: Reference category: Months before intervention

a. During all post-intervention period (median of 13 months following)
b. Reference category: control group

6 DISCUSSION

6.1 Discussion Method

6.1.1 Case-Control study

This is a case-control study which means that the subjects participating in the study were separated according to a yes/no variable that known priori (report of ADR in this study), needs different fraction of each sample group, for example for physician group 100% for cases and about 10% for controls. However, it lacks longitudinal character, since the expositions, were not measured previously to the appearance of the effect, bell that in the cases if carries through a time that this occurred. This would be an inconvenience for studies of etiologist causing pathologies, where the risk factor could be affected by the appearance of the pathology. In studies where attitudes and personal characteristic of subjects were analysed (gender, education, etc.) it can be assumed that a transversal or posterior measure to the effect is as valid as one carried out retrospectively, since these are characteristics with high stability along time. In this study, only variable "*I do not know how the information reported in the yellow/purple card is used*", might have been influenced by the reporter condition, since when an ADR is reported the Northern Pharmacovigilance Unit gets in touch with the reporter, thus increasing its knowledge about the system functioning.

The spontaneous report of ADR program is focussed in several health professionals such as physicians, pharmacists, dentists and nurses. Nevertheless, the health professionals included in the studies were only physicians and pharmacists. It is important to note that Northern Pharmacovigilance Unit just star working in the beginning of 2001 (although a few reports arrived during December 2000).

The data collection selection method was based on the following criteria: (1) need of time and human and material resources; (2) geographical covering of the North region of Portugal; and (3) quality of answers. The auto-fulfilling questionnaires represent a limitation when they are sent to the population in general, in people with a lower or middle cultural level, and the quality of the reply in this situation can be poor. In the present study, the population to the questionnaire was sent is a population of university degree, which means that is

probably not a problem. Due to three previously characteristics it was opted by an auto-fulfilling questionnaire, sent by mail. This possibly represents a limitation, and the answer ratio expected is lower than if a personal interview was adopted.

The calculation of the sample size in epidemiologic studies is complex[162] being in the reality the efficiency criteria that really condition it. In this study, all the subjects that filled the condition of case established in the beginning of the study had been included and were compared with a number approximately eight times superior of controls (due to the very reduced number of cases) although a ratio of one to four is more efficient from a statistical point of view. The stratification by sub-regions, was carried out to get a homogenous geographically distribution of the controls sample. It was used this variable as base because it was the only one that in reality could be used, since the databases did not contain information concerning other variables.

The questionnaire is the instrument for measurement of the data; if it presents low reproducibility, the results are limited. The limitations of the method of data collection, are inherent to any the other type of method based on opinion studies. Thus, the possibility of collected answers was not adjusted to reality for the following reasons:

(1) Treatment of complacency on the part of those questioned, answering with what they believe is expected of them.

(2) Similar phenomena, but at a corporate level, answering with what they believe society expects that a "good professional" thinks, so that the image of the groups is not affected.

(3) The existence of an identification number in each questionnaire (essential for re-sending of questionnaires to those that had not answered). Despite the letter of introduction guaranteeing absolute confidentiality, the possibility of the opinions of the questioned subjects to be not totally trusted, thus revealing opinions which have the intention to safeguard the image of "good professional", before possible auditing.

The topics above limit, to a certain extent, the validity of the method of data acquisition; however, an anonymous questionnaire is the only possible way to collect information on the enclosed aspects in this study. To measure the validity of the questionnaire the only possible method was the opinion of experts. The pilot test demonstrates high reproducibility for all the 15 statements, as can be observed in the results chapter.

The internal validity of this study is determined by the non-agreement between the theoretical and the real sample, because the participation of the subjects is not of 100%. From the 731 physicians who could have answered, only 397 answered it what represents 54.3% of the total. In relation to the pharmacists, the results are more interesting, because from the 295 that could have answered, 256 had returned the filled questionnaire, which means 86.8% of the total. Analyzing these data by the condition of being case or control, we verify that the percentage of cases that reply is higher than in controls. These differences of participation can be attributed to: (1) a bigger motivation of the cases in relation to the ADR, the same motivation that took them to fill the questionnaire; (2) the professionals who already had participated in the system of ADR report are familiarised to the system, having a less cautious attitude when filling the questionnaire.

The reply level was significantly more raised in the pharmacists than in physicians, possibly because these have a more fixed workplace than physicians (when specialising, physicians circulate between several services) and more availability of time.

An important aspect to have into account is that the controls that had participated in the study possibly are inside the group of non-reporters, the most motivated for the subject of the ADR.

6.1.2 Cluster Randomized Trial

Our study presents several strengths and limitations. The use of control group allowed the negation of other potential source of bias and confounding such as seasonal variation or "outbreak of reports" (like produced in year 2000 in UK in meningococcal by group C conjugate vaccines).[163] This potential effect makes “before and after” comparisons difficult to interpret.[21,39,49,50]

This is a randomized study and because that avoids the potential selection biased of participants based on its greater or smaller probability of potential answer to the intervention; and when making the distribution by cluster diminishes the risk of contamination between groups. However it increases the risk of which the groups are left unbalanced by baseline values mainly, when the number of clusters is small as it is the case of our study. We eliminated this effect fitting in the statistical analysis the variables that have been unbalanced after the randomization and by the baseline values of the dependent variables[164] and comparing the values before the intervention, the changes before and after the intervention and control group.[165]

Most cluster-randomized trials allocate approximate equal numbers of clusters to experimental and controls groups. This is the most statistically efficient randomization ratio, but this may not be the most economically efficient.[152] When the intervention under evaluation have an important cost difference respect control group, may be more economically efficient to randomize fewer clusters to the intervention group than the control group.[152] Therefore, we carried out an unequal randomization,[153,154] that allows that with the same resources increase the statistically power of the study, since we could increase the size of the control group sample without any cost in the intervention.

Statistically analysis of clusters randomized trial must take into account the clustering effects, otherwise values are likely to be to small and confidence intervals too narrow (the chances of spuriously significant findings are increased). Consequently, standard statistical techniques as applied to individual-level data are not appropriate.[166] The analysed by means of multilevel/hierarchical regression modelling techniques that allow for the clustering and permit both individual level and group characteristics to be taken into account. A recent study published demonstrated in a simulation study[161] that the performance of penalized quasi-likelihood method (the same we used in our study) is superior for analysis of clustered exponential family observations. An additional problem in cluster randomized trial design is that carrying out the cluster random distribution (not by individuals) implies that the statistical analysis needs to take care of the cluster effect (the intra-cluster correlation is higher than the inter-cluster).

A possible limitation is that only half of the physicians of intervention group went to the formation, although this number is similar to that other study[103] with group sessions. To reach the other half of physicians it might be needed active search strategies by means of one-to-one interventions that present a greater percentage of participation. In order to avoid that the percentage of participation produces a slant equivalent to the one of selection (possibly the physicians who attended are motivated in subjects of ADR), a statistical analysis by "intention to treat"[159] was carried out: all the physicians of intervention clusters were included in the statistical analysis although they did not go to the intervention. This approach infra-considers the effectiveness of the intervention, but it provides a measurement more close to the effectiveness of the intervention. For pharmacists the results are very different, 80.7% of intervention group went to the formation, mainly because we went to each communitarian pharmacies the strategy was of one-to-one interventions that present a greater percentage of participation, nevertheless, the efficiency of pharmacists interventions to improve

the ADR reporting were lower compared with physicians results in our study, this effect is similar to other study[104] that showed that the small group face-to-face intervention did not appear to offer bigger impacts over large seminars in improving the appropriate use of drugs.[104]

6.2 Discussion of Results

6.2.1 Case-Control studies

When in 1992, the National System of Pharmacovigilance was created, and consequently the Program of Spontaneous Report of ADR, already its main limitation was known. Thus the experience accumulated in other countries and regions indicated a low level of participation of the professionals where the system of Pharmacovigilance is based.[22,36,38,39]

In Portugal in the end of 2000, beginning of 2001, had been created the regional units of pharmacovigilance, among others things, with the intention to bring the system closer to those who contribute to it, and also to diminish the problem of under-reporting. In the beginning of this study, the number of medical reporters was of 88 (final ones of 2002) and of pharmacists was of 34 (2003 middle).

The number of spontaneous ADR reports in the Northern Pharmacovigilance Unit in the first 3 years of functioning was of 445 (146 in 2001, 165 in 2002 and 134 in 2003). The number of national reports (including health professional and pharmaceutical industry) started with 9 reporters in 1992 and was growing very slowly. In 2001, the national totals of reports had been 1342, in 2002 of 1263, in 2003 decreasing of 1100 reports.[31]

The north region of Portugal, has an extension above 20.000Km² and about 3.7 millions of person (50% of them live in the metropolitan zone of Porto), 14% have more than 65 years old. The numbers of physicians that work for the Regional Health Administration in North of Portugal are about approximately 7000 physicians and the number of pharmacists about 1400 (work in hospitals and communitarian pharmacies). In 2001 the Northern Pharmacovigilance Unit received only 114 spontaneous reports from physicians and 19 from pharmacists. The ratios of report are very low compared to values collected in different bibliographical sources.[36,78,120] Pharmacist's reporters ploughs less than physicians in Portugal, the value is less than study performed in Netherlands.[30]

In these circumstances, it was judged important to carry through a study whose objectives are: (1) to analyze the factors that condition the low level of participation of the physician and pharmacists population of north Portugal and (2) to intervention in this group of professionals to increase its participation in the spontaneous report ADR system.

6.2.1.1 Personal and Professional characteristics related with ADR reporting

In relation to the personal and professional characteristics of the physicians who had answered to the questionnaire, we verify that in relation to gender, the probability to notify is bigger in women then in men. However, this characteristic loses meant when we adjust to the remaining variables.[36] Nevertheless, in the bibliography, some studies exhibit differences in the probability to notify in relation to gender.[25,41] In relation to the age it is not verified in this study, such as in others,[36,41] influence of the age in the probability of notifying. Our dates indicate that, acts and to gender to appear you have in influence on pharmacist's reporting. [46]

About relation to "the number of patients seen to per day", we could think that it would have influence in the probability to notify, but in this study, it was observed that the average of patients received per day is very similar between reporters (16.5) and no reporters (15.8), such as in other study.[41] Another study[36] points out that this variable only has influence on the ADR report when the number of patients consulted per day is superior to 20.

In relation to "the number of prescriptions written to per day" in our work, the reporters carried out a slightly higher number of prescriptions (25.0) than non reporters (21.9), however it can not be determined any influence of this variable in the report. Additionally, it is important to note that in the group of reporters there are a higher percentage of general practitioners that are physicians who usually prescribe a bigger number of drugs. In other studies, this variable presents influence in the report, but only for average prescription values of 15 or higher.[36,41] This might be due to fact that when there are more prescriptions the probability of ADR detection increases and, simultaneously, the probability of reporting.[36] In relation to the pharmacists the following question was placed in the questionnaire "Approximately, how many drugs dispense, in average, per day", but it was eliminated from the results because in relation to the hospital pharmacists it is difficult and non-objective to answer to it.

It is well known that ADR have a strong impact in hospital practice; indeed, some studies state that >6%[9,52,56] of all hospital admissions are due to ADR, while others report that >30% of hospitalised patients suffer from ADR[8,9,56] thereby leading to increased costs[5,6] and excess

mortality.[59] Nevertheless, in Portugal, physicians who work in hospitals are seven times less likely to report ADR than physician's who work in primary care. These findings are similar to other studies conducted in Spain,[41] Germany,[114] the US[70] and UK.[45] It might be thought that the reason for this is that there are some hospital-based specialities that are associated with a low number of prescriptions, yet our study reveals that this effect remains and indeed increases when adjustment is made for speciality and number of prescriptions. We observed that reporting probability is lower among surgical and medical-surgical specialities, a finding that is in agreement with other studies[42,43] and one that is perhaps due to differences in post-graduate education.[93]

The inclusion of pharmacovigilance subjects in under and post-graduate degree syllabuses is vital for medical knowledge.[80,91] However, this varies significantly, not only between countries but also between different universities in same country.[68,79] In view of the lower probability of reporting in hospital environments, it could, therefore, be important to give priority to hospital interventions when these are designed.[167,168]

Among Portuguese pharmacists, however, reporting is twenty times higher in a hospital than a community setting, a finding in line with other study.[169] Setting-related differences in reporting, albeit of a diametrically opposed nature, have also been observed among medical practitioners, both in Portugal[51] and elsewhere.[41,42,68] Such workplace-related differences might be due to a several factors, namely: hospitals pharmacists are better informed as regards pharmacovigilance and clinical pharmacy subjects;[82] constant contact with serious ADR;[47] and a close relationship with physicians[47] who sometimes delegate ADR report to hospital pharmacists. The finding of a lower reporting probability among community pharmacists could be great interest when it comes to designing educational programs, since this would indicate the need to assign priority to educational interventions addressing this segment.[34,50,106]

6.2.1.2 Knowledge and attitudes related with ADR reporting

The results shown that differences in terms of knowledge, attitudes or opinions are those conditioned the reporter character of physicians and pharmacists. In 1976, Inman proposed the "seven deadly sins" (initially he had proposed seven reasons,[37] but later added an eight[69]) as reasons for under-reporting, though in so doing he had medical practitioners in mind. It is conceivable however, that many of the reasons could be common to medical practitioners and pharmacists alike. These reasons could be divided into two different groups:[76] (i) three

linked to attitudes relating to professional activity (financial incentives, legal aspects and ambition to publish); and (ii) five linked to ADR-related attitudes and knowledge (complacency, insecurity, diffidence, indifference, and ignorance).

Our data indicate that Portuguese physicians and pharmacists do not see any need for additional financial recompense, the following statement intent to represent this "I should be financially reimbursed for providing the ADR service", the *payment of a fee* it was describe by Inman in addition to not reporting, because the physicians are pay for example[69] for the pharmaceutical companies to participate in clinical trials for example in majority of studies we could observed that this is not appointed as an reason to not reporting[36,41,46,114] but in literature appear two articles that appoint for the stimulation of ADR reporting with financial recompense.[136,137] The physicians and pharmacists think that reporting is their duty "I have a professional obligation to report ADR".[36,41] Portuguese pharmacists and physicians that can in no way compromise their professional liability "Reporting ADR puts my career at risk", these results are in line with studies conducted in Europe addressing the same topic[44-46,68,114] but are different from other studies involving US physicians[37,39,138] perhaps because the health system are different. Inman[37] described the *fear* of possible involvement in litigation or investigation of prescribing costs by the Health departments, as a cause to not reporting. Another proposed reason was the *ambition* to collect and publish a personal series of cases;[37] that appear in the questionnaire as this "I think that the most correct way to report ADR is in medical/pharmaceutical literature", nevertheless this does not seem to be an important factor for Portuguese physicians and pharmacists, e.g. a bibliographic review found a reference to few Portuguese paper on ADR reporting in MEDLINE review indices (key words: adverse drug reaction or events, Portugal; in June the 2005). This is in line with European study[68] that included Portuguese physician's, we observed that none of Inman's reasons connected with professional activity displayed any influence on ADR reporting and we could observed the same in another European study[45] and in an Chinese study.[125]

The first reason linked to ADR-related attitudes and knowledge, proposed by Inman[37] was the *complacency*, designed for the encouraged by one-side drug promotion and the belief that only safe drugs are allowed on the market, in our study this statement is "Really serious adverse drug reaction is well documented by the time a drug is marketed". It might be concluded that majority of Portuguese physicians and pharmacists in this study are those who are more in agreement with this statement, like in other studies.[39,41,68] Our study[51] indicated that this attitude is statistically associated with probability to notify an increment equivalent

to the interquartile range could lead to a rise in report probability of 87% for physicians and 223% for pharmacists, which implies a huge importance of the effect. Comparison of the present study with other studies is difficult, since only a few of these used the same type of visual analogical scale. Nevertheless, some studies carried out in Spain,[41] UK[44] and US[36] also exhibit statically significant differences.

Other reason for under-reporting is the *insecurity*; in our questionnaire the statement is "It is nearly impossible to determine whether a drug is responsible for a particular adverse reaction". The majority of pharmacists (median 4.5) and physicians (median 3.0) are disagreement with this question. This question is statically significant for our physicians, increased the probability to notify in 20% for one-unit decrease on the visual analogical scale. It is of interest that the opinion of physicians in our survey was similar to those previously reported from physicians in the US,[36] UK,[44] Netherlands[42] and Spain.[41] This statement is not statistically significant for pharmacists; however, it is interesting to note that in a UK study[46] where pharmacists start to notify since 1997, where one question placed in a questionnaire was "level of clinical knowledge makes it difficult to decide whether or not an ADR has occurred" and one third of inquired agrees that this factor discourage pharmacists from reporting ADR.

Inman[37] recognises that the afraid of ridiculous for reporting an ADR suspicion that is *diffidence* as one of the causes that determine the fulfilment and the sent of the report card to authorities. The question placed in the questionnaire was "I that one would only report an adverse drug reaction if I was sure that it was related to the use of a particular drug". The majority of pharmacists and physicians might be in agreement with this assertion because perhaps they think that only are accepted forms that demonstrate a causal relation. These results are similar to a study[68] carried out in several European countries where the Portuguese physicians answering to the questionnaire present a higher percentage of agreement answers with this statement (10.8% of the responders), in other study performed in Sweden[43] physicians, referee this assertion as an cause for under-reporting as in a study assemble in US[39] and in German.[114] This statement in our study is statistically significant for both professional's, for physicians[21,41,125] the interquartile range of these measure indicate that a change from 75th to the 25th percentile would lead to reporting probability rising by 143% and for pharmacists the value is 240%. Other studies found significant statistically for similar statement like as a study carried out in the US,[47] from the 235 pharmacists that answered to the questionnaire 32.3% considered that this is a cause for non-reporting. A study performed in

UK,[46] shown that pharmacists were more likely to report if there was a degree of certainty that the drug had caused an ADR (82.4% of 280) and a lack of confidence in the diagnosis of an ADR[46,47,48] was important for pharmacists, they more likely report ADR when they are more confident about the ADR. This is a consistent finding from all surveys, and may reflect the anxieties of reporters "not to appear foolish", a sentiment that needs to be dispelled through communications from regulatory agencies and education.

It seems evident that the opinion of a single physician might substantially influence the knowledge of several other colleagues, as for instance the Mc Bride[170] case, the Australian physician that with a single letter to the director of a medical journal, allows the finding of the association between thalidomide and a teratogenicity reaction. The opinion related to "The one case an individual physicians might see could not contribute to medical knowledge", that, according to Inman[37] represents the *indifference* on the part an individual physician to his essential role as a clinical investigator who should be contributing to the general advancement of medical knowledge and is one of the seven causes for under-reporting. In our study pharmacists and physicians disagree mostly with this statement (median 4.0). In a study carried out in US[36] it was verified that physicians that answered to the questionnaire disagree mostly with this assertion, but there were no major differences between reporters and non-reporters. This question has a significant statically in our study only for physicians, the probability of notify increase about 20%, when a one-unit decrease on the visual analogical scale, in other studies[36,41,44] where this statement were present the significance statically were observed too. For pharmacists the statement not presented significance statistically. This statement could be related with other assertion present in the questionnaire "when I read medical/pharmaceutical literature I am interested in articles about ADR", mostly pharmacists and physicians agreement with this declaration (median respective 9.0 and 8.0), nevertheless this statement did not have significance for pharmacist sample that answered the questionnaire.

The last reason linked to ADR-related attitudes and knowledge, proposed by Inman[37] was the *ignorance* of the Committee's requirements for reporting. The spontaneous report of ADR program was designed to detect all types of undesirable effects that might be associated to each drug, thus including severe and less severe reactions. Consequently the following question is placed in the questionnaire "It is only necessary to report serious or unexpected ADR". Our study found that the mostly physicians and pharmacists disagree with is statement (median 2.0). The lack of knowledge bout the functioning of system of spontaneous re-

port of ADR by physicians and pharmacists is presented in several studies.[21,42,43,46,47,114] According to our data, potential changes equivalent to the interquartile range could lead to a rise in reporting probability of 71% for physicians and 316% for pharmacists, other studies realized with pharmacists in UK[46] and US[47] and physicians[21,42,44,45,125] present significance statistically for this statement. In Portugal, the program of spontaneous report of ADR is such in other countries, for reporting of all kinds of ADR but is especially dedicated to severe and unexpected ones. In some countries, as UK besides that, special attention is devoted new drugs in market (less than 5 years).

After these five reasons, others statements related with reporting system: as possible complexity or unknown of the use of information was answered (1) "I would be more likely to report ADR if there were an easier method" and (2) "I do not know how the information reported in the report card is used". In relation to these statements, the answers from pharmacists and physicians are quite different; for the first statement the majority of physicians agree (median 7.5) and pharmacists are in the middle (median 5.0). To the second question about this issue the position from to professional groups are very different, mostly physicians agree with the affirmation (median 6.5) nevertheless, pharmacist disagree with this statement (median 3.5). These results could demonstrate that Portuguese pharmacists know better than physicians what happen with this information, and the importance of that for pharmacovigilance system. It is comprehensible that if potentially reporters ignore the utility of the information that they could introduce in the system and the cards reports contain information about the report and the patient, even guarantying confidentiality, is logical that those who do not know the system are more reticent to report ADR, because they does not like report confidential information, this problem was refereed in several studies. [41,44,45,48,120]

The both statement are significantly for physicians, the probability of notify increase about 25%, when a one-unit decrease on the visual analogical scale, nevertheless only the first question has significance for pharmacists, about 16%. In others studies[41,42,44,114] physicians referee as significantly reason not to report the bureaucratic of the system.

This questionnaire has two questions regarding the time necessary to report an ADR. *Lethargy* was classified as "don't' have time" and the questions that represent this concept are: (1) "I do not have time to complete the report card" and (2) "I do not have time to think about the involvement of the drug or the other causes in ADR". Our results show that both professional's disagree with first statement, the median for pharmacist is 1.5 and for physicians 3.5. In numerous studies the physicians and pharmacists appoint this as one cause to not re-

port.[21,42,46,48] Other studies found similar results for this statement like as.[36,39,41] For the second question the median (2.5) are the same for both, the majority of physicians and pharmacists that answer to the questionnaire disagree with this statement, nevertheless the pharmacist's agreement with this statement increase compared with first question of time, perhaps because the lack of time to actively look for ADR while in clinical practice.[46] In our study the two statements are statistically significance for physicians, like in other studies[21,41,42] however for pharmacists only the second question is significantly.[46]

The last question placed in the questionnaire is related to the relation between health professionals and the pharmaceutical industry, and the statement was "I talk with pharmaceutical companies about possible ADR with their drugs". In the current study this point is not statically significant for physicians neither for pharmacists when an ADR is reported. Nevertheless, the majority of physicians agree with this affirmation (median 8.5) to contrary of pharmacists that are in the middle (median 5.5). This question is difficult to compare with other studies, because normally the statements in other studies is about the sent of the reports card to pharmaceutical company as in US,[47] this situation occurred in countries did not have the same system as the major European countries. In the majority European countries like in Portugal, to avoid economical interests, the health professionals, should report ADR directly through the spontaneous reporting system to regional pharmacovigilance centres (these centres belong to the Pharmacovigilance Department of Healthy Ministry) and the pharmaceutical companies must have a Pharmacovigilance Department too and should informed the Healthy Authorities about the security of them products, accordingly with the law.

To the five ADR-related reasons proposed by Inman's for physicians we are the first to find association with all of them, in contrast with others that have found only one, two, three or four of these. [41,43,44,114,121] For pharmacists we found association with the complacency,[47] ignorance[46,47] and diffidence[46,48] these factors seem to be associated with the lower reporting probability, comparing these results to those of other studies is difficult since this is the first study to examine the link between pharmacists' attitudes and reporting; indeed, relating it to similar studies undertaken on medical practitioners proved scarcely feasible. We believe that the discrepancies between our and other published results could be due to our use of a visual analogue scale. This scale would be able to detect small, albeit relevant, differences in medical and pharmacists' attitudes that are not discernible when using a categorical-type scale with three or four categories. Moreover, thanks to this scale[41,51] we have detected a strong association between attitudes and reporting. With respect to the results of pharmacists, it is

important to refer that from the methodological point of view the sample is smaller than for physicians and that confidence intervals are bigger although significant. For the attitudes complacency, diffidence and ignorance they are less accurate.

Pharmacists can play an important role in pharmacovigilance, both in community practice and in a hospital setting. In both settings, co-operation among pharmacists and medical practitioners is important. Pharmacists can contribute considerably to the quantity and quality of ADR reporting, normal their reports are well documented.[171] Nevertheless is interest referee that pharmacist's reports more often concern external organs systems such as disorders of the skin and the eyes.[30] Until now, nothing has been known about which factors induced and which inhibited pharmacists vis-à-vis reporting. Hence, the results of our study may well constitute an important contribution, since they indicate which ADR attitudes are strongly associated with reporting. It therefore follows that modifying such attitudes could greatly reduce ADR under-reporting.

This strong association between knowledge/attitudes and under-reporting may well indicated that educational interventions purpose-designed to change such knowledge/attitudes could bring about important improvements in reporting [i.e. *knowledge-attitudes-practices* model].[76] However, in order for this to occur it is also important that these educational strategies enhance the degree of balance between medical and pharmacists practitioners, their environment (patients, colleagues, health system administration and pharmaceutical industry: needs satisfaction theory)[76] and their ADR-related motivation. Not only must such education be undertaken by institutions involved in this field, such as universities, pharmacovigilance units and other health system professionals having a duty to ensure that it becomes an activity that forms an integral part of their daily routines. To the end, pharmacists' and physicians' ADR education[80,81,87] must be improved, possibly through the implementation of educational programs focusing on altering attitudes identified by the study as being associated with under-reporting. We feel that this study could provide a good basis for designing interventions studies aimed at decreasing under-reporting, and creating a "reporting culture" among health professionals.

6.2.2 Cluster Randomized Trial

In this large, controlled, cluster randomized trial the physicians multiply by more than 9-fold and the pharmacists multiply by more than 5-fold the number of report card notifications during the year following to the educative intervention of one hour of duration. The effect is

maximum, 20-folds in the first 4-month period (for physicians and pharmacists) and for physicians the effect remains about 5-fold during more than one year after the intervention. For pharmacists the results remained about 3.0-fold higher than control group, in the second and third 4-months period. Also an improvement in the quality (relevance) of the reports has been observed because an increase of serious, unexpected, new drugs and imputation of high causality ADR reporting occurs. The results of this study might be very important from both educational and public health point of views, since it indicates educative strategies that might significantly improve ADR vigilance.

The magnitude of the effect found in our study not very often has been observed in the alterations of health professional's performance.[93,100,101,103] The revisions on the effectiveness of interventions to improve the provider behaviour already consider as "moderately important" improvements of 20%[172] while in our case the improvements were in the order of 900% for physicians and 500% for pharmacists. These improvements were maintained during more than one year after the intervention. The factors that can explain these magnitudes of effect in professional behaviour change are multiple: the target of the intervention,[100] the type of intervention (outreach visit),[103] the number of interventions,[100,173] the organising organism of the intervention,[98] inexistence of barriers,[100,174] the existence of incentives,[136,137] degree of interactivity of the interventions,[174] and its design from gaps detected in the health professionals. [100]

The target of the intervention may also account for the high effect magnitudes reported by other authors who addressed this same topic; a study realized in UK (Dublin)[21], over 3 months, the greater availability of yellow cards and reminders about reporting ADRs led to an approximate five-fold increase in reports but reporting declined rapidly thereafter when verbal reminders were withdrawn, despite continued ready availability of cards suggesting that making cards available alone does not significantly increase reporting, another study performed in US (Rhode Island)[39] present more than 17-fold increase in reports submitted by physicians, after intervention. A teaching hospital in Puerto Rico[49] implemented a new policy for reporting ADR. After the first year, the number of ADR reported per year increased from an average of 32 ADR/year to 167/year, during the second year, 274 ADR were reported for a 750% increase. This significant improvement is the result of an effective educational campaign, a simplified reporting method, and a more complete definition of an ADR. In this study suspected ADRs were reported to pharmacy: (1) direct observation and reporting by health professionals; (2) reports by quality assurance and (3) by laboratory service, the form

is signed by the person making the report and sent to pharmacy for evaluation by a clinical pharmacy. A program was created to stimulate reporting of ADRs in US (Mississippi) included both institutional and community based health care facilities located in urban and rural settings. Pharmacists had the expertise and responsibility to assume a more active role in the reporting of ADRs. The intervention included a promotional packet outlining the pilot project plus ADR reporting guidelines. There had been follow-up mailings to reinforce the program goals in addition the publication of the Department responsible for the program included several articles related to ADR reporting. Methods used in this project increased the monthly average of reported ADRs from 3.94 to 16.5 (318%).[50]

By comparing pharmacists with physicians, it can be observed that the latter show better results. Some of the factors that might justify these differences are: (1) the educative intervention was designed based on the results of study 1 that was itself designed based on knowledge and attitudes derived from the Imann's seven signs planned for physicians was also used for pharmacists with some adaptations; (2) in study 1 the differences for pharmacists are smaller than for physicians both in number of attitudes and in the magnitude of the found effect; (3) there are also some differences in interventions and participants; therefore, the background of the professional, the interaction between participants and the size of the target group is important.[104,175] In our study the professionals' physicians and pharmacist have different background, the size of the group and consequently the interaction between participants during the intervention are different too. The intervention in pharmacists was more individual in each communitarian pharmacy, this difficult the interaction between participants.

Possibly one of the factors that can explain this so important effect is the subject of our intervention. Our results as well as those from other authors[21,39] on the same subject found a very important answer to the intervention for improve the reporting. It has been described that for some objectives of intervention (like changes in the prescription, use of diagnostic tests, reporting ADR) not all the changes in the knowledge and attitudes of the professionals produce changes in health care outcomes due to multiple barriers[100] like the expectations of the patient, or administrative ties like the lack of time.[174] We thought that unlike others, our intervention has the advantage to present few barriers, and those detected – the need of much time to reporting or the absence of the report card were explicitly covered during the intervention.

It has also been described that educative interventions to improve health professional's performance are more effective when multiple interventions were carried out. The other studies to improve the notification use multiple interventions (mailings,[39,50] newsletters,[39,50] and oral presentations,[39,50] articles in staff newsletters,[39,50] advertisement,[39] and cooperation with hospital pharmacy[39]) whereas our single study consisted of only one session of one hour of duration, accompanied by an informative leaflet and a report card for each professional. It has been described that the availability of the report card could improve the notification of ADR about 50%.[40] In Portugal report card is distributed every year through a medicine formulary, in all formation about this issue and replaced if there is a reporting, and that is possible to report without the report card (through internet, telephone or fax). When the Northern Pharmacovigilance Unit was created in 2001 were sent to health centre directors and hospital clinical directors report cards and are still sent whenever requested. We feel that the report form may be construed as a cointervention which can act both as a facilitating factor and as a remainder[40] and which, by virtue of its low cost, ought to accompany all educational interventions aimed at improving reporting.

Another factor that can influence in the effectiveness of the intervention is its design. The revisions on the subject indicate that the more interactive the materials and the presentations the more effective they are.[174] Our intervention was designed to be the most interactive possible with respect to the presentation, the discussion and the leaflet. Another point that can explain the effectiveness of our intervention is that it was designed specifically from gaps of education detected in phase I of our study. This allows the elaboration of specific and concrete messages, and therefore more efficient.[100] In addition, these messages were given by an academic and independent organising organism ("detail academy"), which can increase the effectiveness of the intervention.[176] Unlike interventions made by the national systems of health, that can be based on the negotiation,[136,137] our intervention is based on the persuasion that derives from the authority and credibility of the educator, and of the evidence that can contribute when coming from a university organization.

The observed efficiency of the intervention could also be attributed to the low departure level.[30] Thus, one might think that the levels of the departure reporting of Portugal were very low, and that therefore the magnitude of the effect found in our study is not applicable to other cases in which the numbers of under-reporting are not so low. Nevertheless, when we consider the direct reports of physicians we observed that in Portugal the number of notifications is approximately of 70 by million inhabitants, inferior to the European average but su-

perior to countries like Germany, Italy, Greece, US and Canada. For pharmacists, Spain and France had values higher than Portugal (19 pharmacists' report/million habitants) but in Italy the report ratio is lower than in Portugal. In both situations we talk about directly reports from health professionals, and are from 2001.[30]

One of the possible limitations of the educative interventions is that its effect can be limited in time. Nevertheless, there are only a few studies of continuing medical education methods that evaluate the duration of changes in clinical practices,[177] the existing studies indicate that the effect of the continuing medical education diminishes with time, but that can be maintained between nine months[103,178] and two years.[178,179] Our data indicate that the effect is maxim in the first months, but it remains stable, at least one year after the intervention. We don't have long-term data but we believe that in order to maintain the interest of the physicians and pharmacists in the system, it could be of interest to make repeated and regular interventions. Our data show that it could be sufficient to make these interventions with an annual interval. In addition, we think that the successive interventions should not be centred again in the initial message, and could be based on practical factors that have been very effective to improve the behaviour of physicians and pharmacists to fulfil the report card.

6.3 Policy Implications

ADR is a persistent and important public health problem in terms of morbidity, mortality, and cost and the under-reporting is the principal limitation of ADR reporting systems in all countries. We detect during this study that health professionals had inadequate knowledge about ADR and about the pharmacovigilance system and that these attitudes/knowledge are associated with ADR reporting. These results should encourage health political leaders to design continuing educational strategies for physicians and pharmacists in order to generate a reporting culture. This is especially true presently since in the last years we could observe a medicine safety crisis with the withdrawal of a series of drugs from the market,[180-182] mainly in countries where the pharmacovigilance systems are based in data provided from pharmaceutical industry. The establishment of a reporting culture in health professionals will allow data acquisition with no bias that could detect earlier medicine safety problems and also increase the motivation and involvement of health professionals in the pharmacovigilance process.

From gaps detected in the attitudes/knowledge study we design an educative intervention with approximately one hour that proved to be extremely effective in increasing the quantity and quality of ADR reporting. Since the results were effective during more than one year after the intervention, it indicates that health professionals respond well to this type of interventions. If these results can be replicated over time in other settings, it might well indicate that many countries could substantially enhance ADR reporting in terms of both volume and relevance by means of educational strategies purpose-designed to meet professionals' training needs. This would enable the role of health professionals in pharmacovigilance to be enhanced and ADRs to be detected earlier and more reliably, thus making for substantial improvements in drug safety monitoring. To keep the effect it will probably be necessary reminding interventions that, ideally, should be oriented to more practical questions, for instance workshops that will allow the continuation of the interest. Additionally other types of interventions are described such as mailings, phone calls, leaflets, bulletins, etc., but have proven to be less efficient.

7 CONCLUSION

- Factors socio-demographic and personal related with under-reporting of ADR found in our study for physicians were: type of medical specialization and workplace; for pharmacists this factor was the workplace.

- Knowledge-attitudes –based in "seven deadly sins"of Inman– related with under-reporting of ADR were for physicians: *complacency, insecurity, diffidence, indifference*, and *ignorance* and for pharmacists the found related with under-reporting were: *complacency*, *ignorance*, and *diffidence*.

- Educative intervention increases the quantity and quality (relevance) of spontaneous report of ADR. In terms of quantity, the spontaneous report increased about 10-fold for physicians and 6-fold for pharmacist during more of one year after intervention. In terms of relevance quality: (1) for physicians the intervention multiplies by 6-fold the serious ADR reporting; by 8-fold the ratio of report ADR the defined or probable causality; in 32-fold the ratio to report ADR unexpected and finally increase in 8-fold the ratio of reporting ADR to the new medicines; and (2) for pharmacists the intervention multiplies by 10-fold the serious ADR reporting; by 9-fold the ratio of report ADR the defined or probable causality; in 4-fold the ratio to report ADR unexpected and finally increase in 9-fold the ratio of reporting ADR to the new medicines.

- For physicians the duration of effect remains about 5-fold higher than control group, in the second, third and fourth 4-months period. For pharmacists the duration of effect remains about 3.0-fold higher than control group, in the second and third 4-months period, in four 4-months period the intervention is not more statically significance.

- It is observed that the yellow card (physicians) administered during the intervention increases in more than 3-fold the effectiveness of the intervention that without report form, and this effect is maximum in first 4 months and disappear in the following months. For pharmacist the distribution of purple card during the intervention not influenced the effectiveness of the same.

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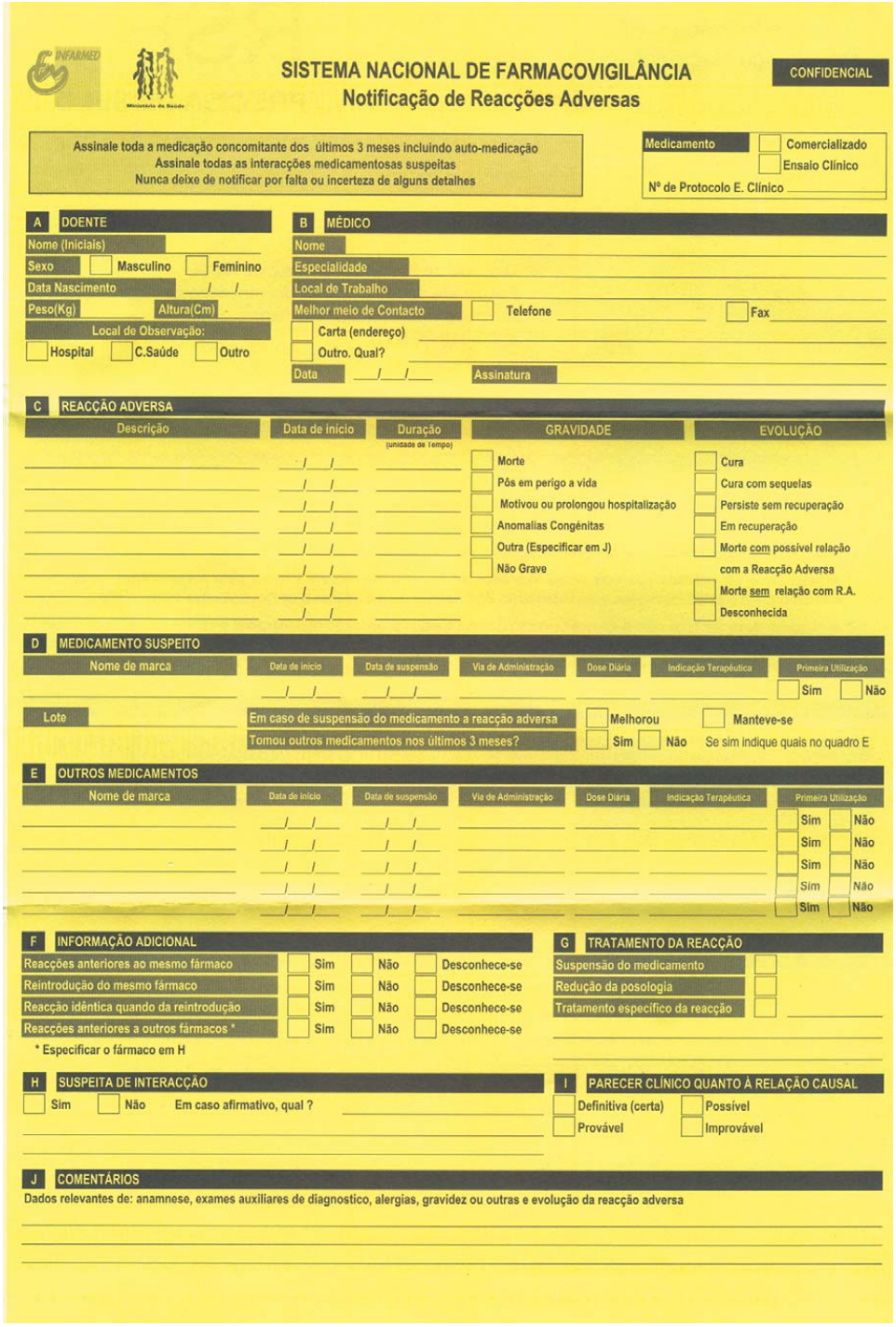
APPENDIXES

APPENDIX A

Report Forms: yellow form (physicians); purple form (pharmacists) and white form (nurses).



INFARMED

Ministério da Saúde

SISTEMA NACIONAL DE FARMACOVIGILÂNCIA
Notificação de Reacções Adversas

CONFIDENCIAL

Assinale toda a medicação concomitante dos últimos 3 meses incluindo auto-medicação
Assinale todas as interacções medicamentosas suspeitas
Nunca deixe de notificar por falta ou incerteza de alguns detalhes

Medicamento ☐ Comercializado ☐ Ensaio Clínico
Nº de Protocolo E. Clínico _____

A DOENTE

Nome (Iniciais) _____
Sexo ☐ Masculino ☐ Feminino
Data Nascimento ___/___/___
Peso(Kg) _____ Altura(Cm) _____
Local de Observação:
☐ Hospital ☐ C.Saúde ☐ Outro

B MÉDICO

Nome _____
Especialidade _____
Local de Trabalho _____
Melhor meio de Contacto ☐ Telefone _____ ☐ Fax _____
☐ Carta (endereço) _____
☐ Outro. Qual? _____
Data ___/___/___ Assinatura _____

C REACÇÃO ADVERSA

Descrição	Data de início	Duração (unidade de tempo)
	___/___/___	
	___/___/___	
	___/___/___	
	___/___/___	
	___/___/___	
	___/___/___	
	___/___/___	
	___/___/___	

GRAVIDADE
☐ Morte
☐ Pós em perigo a vida
☐ Motivou ou prolongou hospitalização
☐ Anomalias Congénitas
☐ Outra (Especificar em J)
☐ Não Grave

EVOLUÇÃO
☐ Cura
☐ Cura com sequelas
☐ Persiste sem recuperação
☐ Em recuperação
☐ Morte com possível relação com a Reacção Adversa
☐ Morte sem relação com R.A.
☐ Desconhecida

D MEDICAMENTO SUSPEITO

Nome de marca	Data de início	Data de suspensão	Via de Administração	Dose Diária	Indicação Terapêutica	Primeira Utilização
	___/___/___	___/___/___				☐ Sim ☐ Não

Lote _____
Em caso de suspensão do medicamento a reacção adversa ☐ Melhorou ☐ Manteve-se
Tomou outros medicamentos nos últimos 3 meses? ☐ Sim ☐ Não Se sim indique quais no quadro E

E OUTROS MEDICAMENTOS

Nome de marca	Data de início	Data de suspensão	Via de Administração	Dose Diária	Indicação Terapêutica	Primeira Utilização
	___/___/___	___/___/___				☐ Sim ☐ Não
	___/___/___	___/___/___				☐ Sim ☐ Não
	___/___/___	___/___/___				☐ Sim ☐ Não
	___/___/___	___/___/___				☐ Sim ☐ Não
	___/___/___	___/___/___				☐ Sim ☐ Não

F INFORMAÇÃO ADICIONAL

Reacções anteriores ao mesmo fármaco	☐ Sim	☐ Não	☐ Desconhece-se
Reintrodução do mesmo fármaco	☐ Sim	☐ Não	☐ Desconhece-se
Reacção idêntica quando da reintrodução	☐ Sim	☐ Não	☐ Desconhece-se
Reacções anteriores a outros fármacos *	☐ Sim	☐ Não	☐ Desconhece-se

* Especificar o fármaco em H

G TRATAMENTO DA REACÇÃO

Suspensão do medicamento ☐
Redução da posologia ☐
Tratamento específico da reacção ☐ _____

H SUSPEITA DE INTERACÇÃO

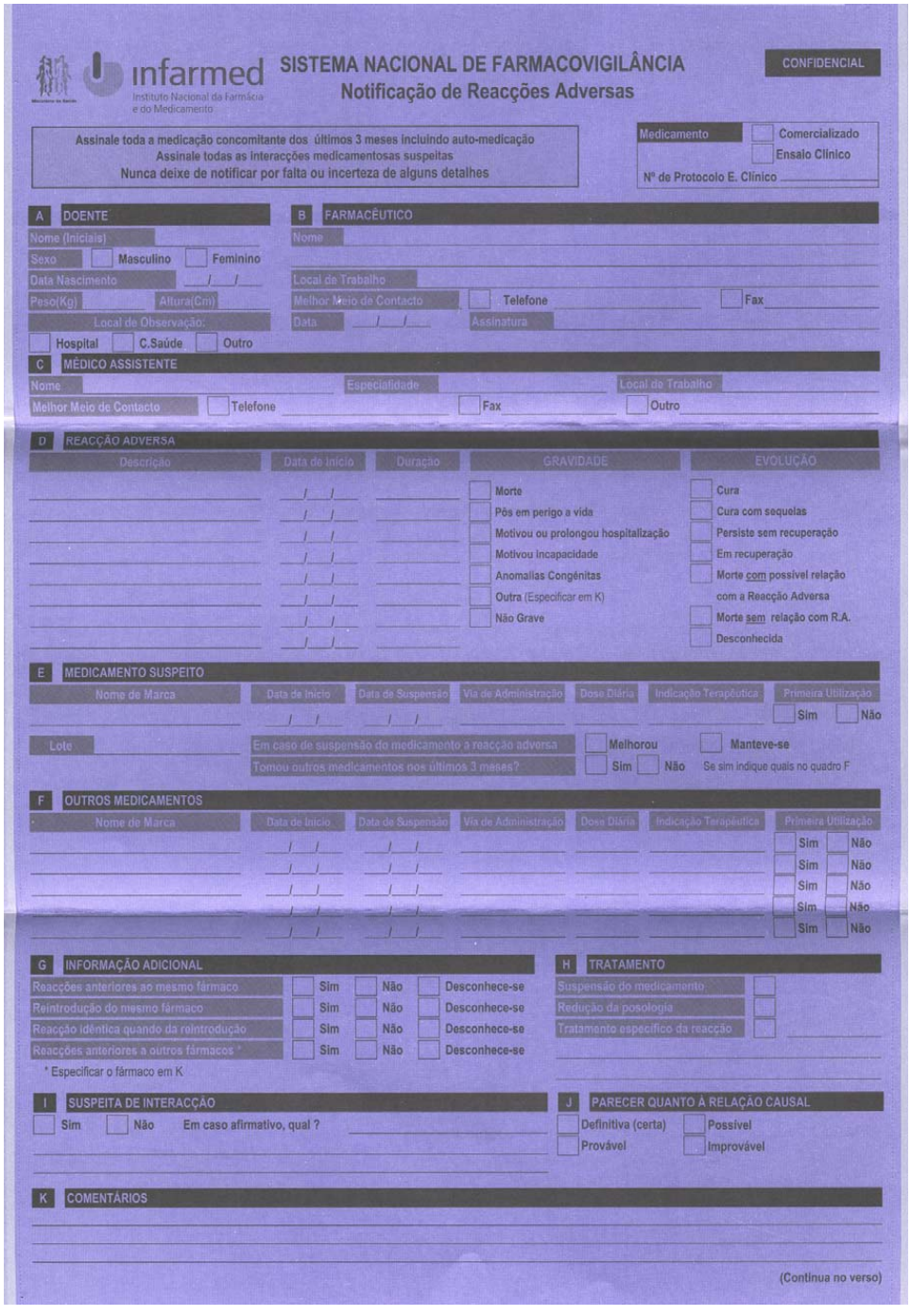
☐ Sim ☐ Não Em caso afirmativo, qual ? _____

I PARECER CLÍNICO QUANTO À RELAÇÃO CAUSAL

☐ Definitiva (certa) ☐ Possível
☐ Provável ☐ Improvável

J COMENTÁRIOS

Dados relevantes de: anamnese, exames auxiliares de diagnostico, alergias, gravidez ou outras e evolução da reacção adversa



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Instituto Nacional da Farmácia e do Medicamento

SISTEMA NACIONAL DE FARMACOVIGILÂNCIA
Notificação de Reacções Adversas

CONFIDENCIAL

Assinale toda a medicação concomitante dos últimos 3 meses incluindo auto-medicação
Assinale todas as interacções medicamentosas suspeitas
Nunca deixe de notificar por falta ou incerteza de alguns detalhes

Medicamento ☐ Comercializado ☐ Ensaio Clínico
Nº de Protocolo E. Clínico

A DOENTE
Nome (Iniciais)
Sexo ☐ Masculino ☐ Feminino
Data Nascimento ___/___/___
Peso(Kg) Altura(Cm)
Local de Observação:
☐ Hospital ☐ C.Saúde ☐ Outro

B FARMACÊUTICO
Nome
Local de Trabalho
Melhor Meio de Contacto ☐ Telefone ☐ Fax
Data ___/___/___ Assinatura

C MÉDICO ASSISTENTE
Nome Especialidade Local de Trabalho
Melhor Meio de Contacto ☐ Telefone ☐ Fax ☐ Outro

D REACÇÃO ADVERSA

Descrição	Data de Início	Duração	GRAVIDADE	EVOLUÇÃO
	___/___/___		☐ Morte	☐ Cura
	___/___/___		☐ Pôs em perigo a vida	☐ Cura com sequelas
	___/___/___		☐ Motivou ou prolongou hospitalização	☐ Persiste sem recuperação
	___/___/___		☐ Motivou incapacidade	☐ Em recuperação
	___/___/___		☐ Anomalias Congénitas	☐ Morte com possível relação
	___/___/___		☐ Outra (Especificar em K)	com a Reacção Adversa
	___/___/___		☐ Não Grave	☐ Morte sem relação com R.A.
	___/___/___			☐ Desconhecida

E MEDICAMENTO SUSPEITO

Nome de Marca	Data de Início	Data de Suspensão	Via de Administração	Dose Diária	Indicação Terapêutica	Primeira Utilização
	___/___/___	___/___/___				☐ Sim ☐ Não

Lote
Em caso de suspensão do medicamento a reacção adversa ☐ Melhorou ☐ Manteve-se
Tomou outros medicamentos nos últimos 3 meses? ☐ Sim ☐ Não Se sim indique quais no quadro F

F OUTROS MEDICAMENTOS

Nome de Marca	Data de Início	Data de Suspensão	Via de Administração	Dose Diária	Indicação Terapêutica	Primeira Utilização
	___/___/___	___/___/___				☐ Sim ☐ Não
	___/___/___	___/___/___				☐ Sim ☐ Não
	___/___/___	___/___/___				☐ Sim ☐ Não
	___/___/___	___/___/___				☐ Sim ☐ Não
	___/___/___	___/___/___				☐ Sim ☐ Não

G INFORMAÇÃO ADICIONAL

Reacções anteriores ao mesmo fármaco	☐ Sim	☐ Não	☐ Desconhece-se
Reintrodução do mesmo fármaco	☐ Sim	☐ Não	☐ Desconhece-se
Reacção idêntica quando da reintrodução	☐ Sim	☐ Não	☐ Desconhece-se
Reacções anteriores a outros fármacos *	☐ Sim	☐ Não	☐ Desconhece-se

* Especificar o fármaco em K

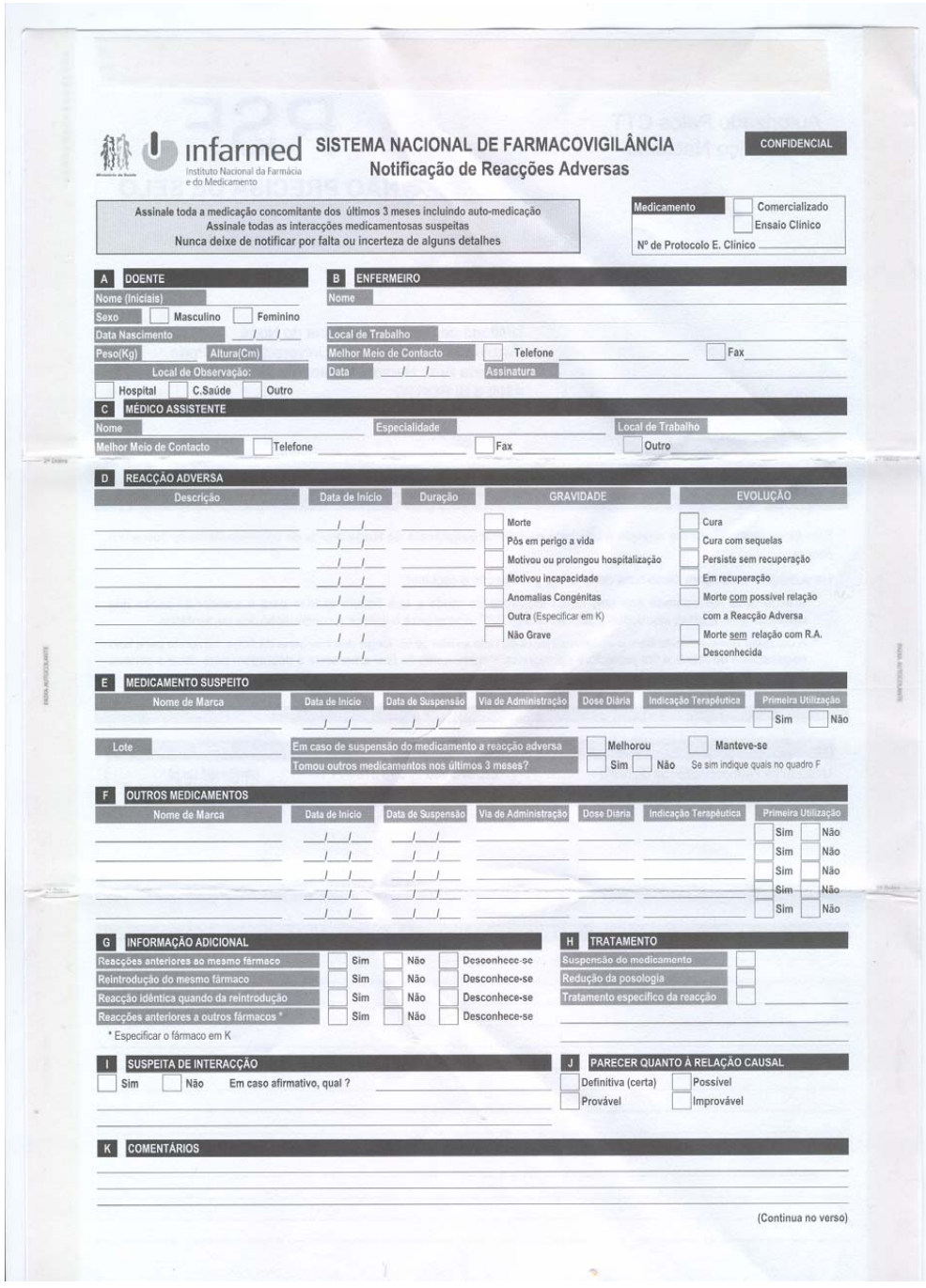
H TRATAMENTO
Suspensão do medicamento ☐
Redução da posologia ☐
Tratamento específico da reacção ☐

I SUSPEITA DE INTERACÇÃO
☐ Sim ☐ Não Em caso afirmativo, qual ?

J PARECER QUANTO À RELAÇÃO CAUSAL
☐ Definitiva (certa) ☐ Possível
☐ Provável ☐ Improvável

K COMENTÁRIOS

(Continua no verso)



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Instituto Nacional da Farmácia e do Medicamento

SISTEMA NACIONAL DE FARMACOVIGILÂNCIA
Notificação de Reacções Adversas

CONFIDENCIAL

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Assinale todas as interacções medicamentosas suspeitas
Nunca deixe de notificar por falta ou incerteza de alguns detalhes

Medicamento ☐ Comercializado ☐ Ensaio Clínico
Nº de Protocolo E. Clínico

A DOENTE
Nome (Iniciais)
Sexo ☐ Masculino ☐ Feminino
Data Nascimento __/__/__
Peso(Kg) Altura(Cm)
Local de Observação:
☐ Hospital ☐ C.Saúde ☐ Outro

B ENFERMEIRO
Nome
Local de Trabalho
Melhor Meio de Contacto ☐ Telefone ☐ Fax
Data __/__/__ Assinatura

C MÉDICO ASSISTENTE
Nome Especialidade Local de Trabalho
Melhor Meio de Contacto ☐ Telefone ☐ Fax ☐ Outro

D REACÇÃO ADVERSA

Descrição	Data de Início	Duração	GRAVIDADE	EVOLUÇÃO
	__/__/__		☐ Morte	☐ Cura
	__/__/__		☐ Pôs em perigo a vida	☐ Cura com sequelas
	__/__/__		☐ Motivou ou prolongou hospitalização	☐ Persiste sem recuperação
	__/__/__		☐ Motivou incapacidade	☐ Em recuperação
	__/__/__		☐ Anomalias Congénitas	☐ Morte com possível relação
	__/__/__		☐ Outra (Especificar em K)	com a Reacção Adversa
	/ /		☐ Não Grave	☐ Morte sem relação com R.A.
	__/__/__			☐ Desconhecida

E MEDICAMENTO SUSPEITO

Nome de Marca	Data de Início	Data de Suspensão	Via de Administração	Dose Diária	Indicação Terapêutica	Primeira Utilização
	__/__/__	__/__/__				☐ Sim ☐ Não

Lote
Em caso de suspensão do medicamento a reacção adversa ☐ Melhorou ☐ Manteve-se
Tomou outros medicamentos nos últimos 3 meses? ☐ Sim ☐ Não Se sim indique quais no quadro F

F OUTROS MEDICAMENTOS

Nome de Marca	Data de Início	Data de Suspensão	Via de Administração	Dose Diária	Indicação Terapêutica	Primeira Utilização
	__/__/__	__/__/__				☐ Sim ☐ Não
	__/__/__	__/__/__				☐ Sim ☐ Não
	__/__/__	__/__/__				☐ Sim ☐ Não
	__/__/__	__/__/__				☐ Sim ☐ Não
	__/__/__	__/__/__				☐ Sim ☐ Não

G INFORMAÇÃO ADICIONAL

Reacções anteriores ao mesmo fármaco	☐ Sim	☐ Não	☐ Desconhece-se
Reintrodução do mesmo fármaco	☐ Sim	☐ Não	☐ Desconhece-se
Reacção idêntica quando da reintrodução	☐ Sim	☐ Não	☐ Desconhece-se
Reacções anteriores a outros fármacos *	☐ Sim	☐ Não	☐ Desconhece-se

* Especificar o fármaco em K

H TRATAMENTO
Suspensão do medicamento ☐
Redução da posologia ☐
Tratamento específico da reacção ☐

I SUSPEITA DE INTERACÇÃO
☐ Sim ☐ Não Em caso afirmativo, qual ?

J PARECER QUANTO À RELAÇÃO CAUSAL
☐ Definitiva (certa) ☐ Possível
☐ Provável ☐ Improvável

K COMENTÁRIOS

(Continua no verso)

APPENDIX B

Questionnaires

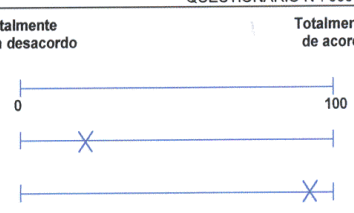
Physician's questionnaire (original)

Sistema Nacional Farmacovigilância
infarmed
Instituto Nacional da Farmácia e do Medicamento
Unidade de Farmacovigilância do Norte

QUESTIONÁRIO Nº: 000

INSTRUÇÕES DE PREENCHIMENTO.

Na coluna da esquerda encontram-se os comentários que serão objecto da sua avaliação e na coluna da direita apresenta-se uma **escala gradual** em que deverá marcar com uma X o lugar que, na sua opinião, representa o seu **grau de acordo** com o comentário do texto. Se está totalmente em desacordo, assinale no extremo esquerdo, e conforme aumente o seu grau de acordo com a afirmação do texto, marque para a direita.



NOTIFICAÇÃO DE REACÇÕES ADVERSAS

		Totalmente em desacordo — Totalmente de acordo
1.	As reacções adversas realmente graves já se encontram descritas, antes da entrada do medicamento no mercado.	
2.	É-me praticamente impossível determinar se um medicamento é responsável por uma reacção adversa em particular.	
3.	Só notifico uma reacção adversa, se estiver seguro de que esta está relacionada com algum medicamento.	
4.	Uma reacção adversa a um medicamento, notificada por um único médico, não pode trazer muita informação ao conhecimento científico.	
5.	Quando consulto revistas científicas, interesso-me por artigos sobre reacções adversas a medicamentos.	
6.	Notificaria mais reacções adversas, se o sistema de notificação fosse mais simples.	
7.	Penso que a maneira mais adequada de notificar uma reacção adversa é através da publicação em revistas médicas.	
8.	Os médicos que participam na notificação de reacções adversas deverão ser compensados economicamente.	
9.	Do ponto de vista profissional, tenho a obrigação de notificar as reacções adversas a medicamentos.	
10.	Se notifico uma reacção adversa, torno-me mais susceptível a futuras implicações legais.	
11.	Só devo notificar reacções adversas graves e inesperadas.	
12.	Não disponho de tempo para preencher a ficha amarela.	
13.	Não disponho de tempo para ponderar o envolvimento do medicamento ou de outras causas na reacção adversa.	
14.	Desconheço a utilização que se dá à informação fornecida na ficha amarela.	
15.	Comento com representantes da Indústria Farmacêutica possíveis reacções adversas dos seus medicamentos.	

PROGRAMA DE NOTIFICAÇÃO ESPONTÂNEA DE REACÇÕES ADVERSAS
(FICHA AMARELA)

■ **Desde Janeiro de 2001:**

1. Em alguma ocasião, teve a intenção de notificar reacções adversas e **não dispunha** da ficha amarela? Sim ☐ Não ☐
2. Alguma vez teve a suspeita de uma reacção adversa, mas **não chegou a preencher** a ficha amarela, mesmo dispondo dela? Sim ☐ Não ☐
3. Alguma vez preencheu as fichas amarelas, que **não chegou a enviar** por causas distintas? Sim ☐ Não ☐

PARA FINALIZAR, ALGUMAS PERGUNTAS DE CARÁCTER GERAL

Que idade tem? __ __ anos **Sexo:** F ☐ M ☐

Qual é a sua especialidade?

_____

Que tipo/s de actividade/s desempenha?

Medicina Privada ☐
Medicina Pública ☐
Ambas ☐

em meio:

Hospitalar ☐
Ambulatório ☐
Ambos ☐

Aproximadamente, quantos pacientes recebe, em média, por dia?

1ª Consulta ___ ___
Consulta de seguimento ___ ___

Aproximadamente, quantos medicamentos prescreve em média, por dia?

___ ___

Aproximadamente, que percentagem de pacientes toma mais de um medicamento por dia?

___ ___%

Em que percentagem, foram esses medicamentos prescritos por si, desde o início do tratamento?

___ ___%

SUGESTÕES QUE GOSTARIA DE FAZER SOBRE O PROGRAMA DE NOTIFICAÇÃO ESPONTÂNEA DE REACÇÕES ADVERSAS

MUITO OBRIGADO PELA SUA COLABORAÇÃO

Instituto Nacional de Farmácia e do Medicamento
Ministério da Saúde

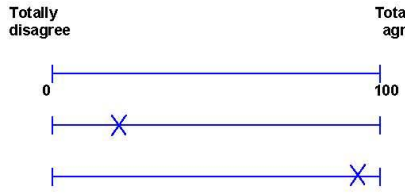
Physician's questionnaire (translation)

Sistema Nacional Farmacovigilância
infarmed
Instituto Nacional da Farmácia e do Medicamento
Unidade de Farmacovigilância do Norte

QUESTIONNAIRE Nº:

FILLING INSTRUCTIONS.

In the left column are questions that will be the subject of your evaluation and in the right column there is a **gradual scale** where you should mark with a X the place where, accordingly to your opinion represents your **agreement** with the text comment. If you are totally in disagreement, you should place a cross at the left end, and as your agreement increases you should move the cross to the right.



ADVERSE DRUG REACTIONS

		Totally disagree — Totally agree
1.	Really serious adverse drug reaction is well documented by the time a drug is marketed.	
2.	It is nearly impossible to determine whether a drug is responsible for a particular adverse reaction.	
3.	I would only report an adverse drug reaction if I was sure that it was related to the use of a particular drug.	
4.	The one case an individual physician might see could not contribute to medical knowledge.	
5.	When I read medical literature I am interested in articles about adverse drug reactions.	
6.	I would be more likely to report ADR if there were an easier method.	
7.	I think that the most correct way to report ADR is in medical literature.	
8.	I should be financially reimbursed for providing the ADR service.	
9.	I have a professional obligation to report ADR.	
10.	Reporting ADR puts my career at risk.	
11.	It is only necessary to report serious or unexpected ADR.	
12.	I do not have time to complete the yellow card.	
13.	I do not have time to think about the involvement of the drug or the other causes in ADR.	
14.	I do not know how the information reported in the yellow card is used.	
15.	I talk with pharmaceutical companies about possible ADR with their drugs.	

ADVERSE DRUG REACTION REPORTING PROGRAM
(YELLOW CARD)

■ **Since January 2001:**

1.	Did you ever want to report an ADR and you **do not have** the purple card.	Yes ☐	No ☐
2.	Did you ever have an ADR suspicious but you **do not fill** the purple card even having it.	Yes ☐	No ☐
3.	Did you ever fill the yellow card but you **do not send it** by any reason.	Yes ☐	No ☐

SOME GENERAL QUESTIONS

How old are you? __ __ years **Gender:** F ☐ M ☐

What is your speciality?

_ _ _ _ _ _ _ _ _ _ _ _ _ _

What type of activity?

Private medicine ☐
Public medicine ☐
Both ☐

In which workplace?

Hospital ☐
Primary care ☐
Both ☐

Approximately, what is the number of patients seen per day?

1st Consult ___ ___
Following consult ___ ___

Approximately, what is the number of prescriptions written per day?

___ ___

Approximately, which percentage of patients uses more than one drug a day?

___ ___%

In which percentage were those drugs prescript by you since the beginning of the treatment?

___ ___%

SOME SUGESTIONS THAT YOU LIKE TO DO ABOUT THE ADVERSE DRUG REACTION REPORTING PROGRAM

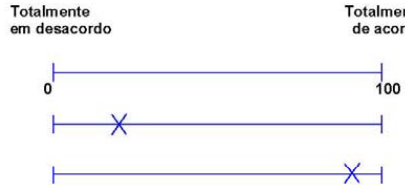
THANK YOU VERY MUCH FOR YOUR COOPERATION

Pharmacist's questionnaire (original)

QUESTIONÁRIO Nº:

INSTRUÇÕES DE PREENCHIMENTO.

Na coluna da esquerda encontram-se os comentários que serão objecto da sua avaliação e na coluna da direita apresenta-se uma **escala gradual** em que deverá marcar com uma X o lugar que, na sua opinião, representa o seu **grau de acordo** com o comentário do texto. Se está totalmente em desacordo, assinale no extremo esquerdo, e conforme aumente o seu grau de acordo com a afirmação do texto, marque para a direita.



NOTIFICAÇÃO DE REACÇÕES ADVERSAS

		Totalmente em desacordo — Totalmente de acordo
1.	As reacções adversas realmente graves já se encontram descritas, antes da entrada do medicamento no mercado.	
2.	É-me praticamente impossível determinar se um medicamento é responsável por uma reacção adversa em particular.	
3.	Só notifico uma reacção adversa, se estiver seguro de que esta está relacionada com algum medicamento.	
4.	Uma reacção adversa a um medicamento, notificada por um único farmacêutico, não pode trazer muita informação ao conhecimento científico.	
5.	Quando consulto revistas científicas, interesso-me por artigos sobre reacções adversas a medicamentos.	
6.	Notificaria mais reacções adversas, se o sistema de notificação fosse mais simples.	
7.	Penso que a maneira mais adequada de notificar uma reacção adversa é através da publicação em revistas farmacêuticas.	
8.	Os farmacêuticos que participam na notificação de reacções adversas deverão ser compensados economicamente.	
9.	Do ponto de vista profissional, tenho a obrigação de notificar as reacções adversas a medicamentos.	
10.	Se notifico uma reacção adversa, torno-me mais susceptível a futuras implicações legais.	
11.	Só devo notificar reacções adversas graves e inesperadas.	
12.	Não disponho de tempo para preencher a ficha roxa.	
13.	Não disponho de tempo para ponderar o envolvimento do medicamento ou de outras causas na reacção adversa.	
14.	Desconheço a utilização que se dá à informação fornecida na ficha roxa.	
15.	Comento com representantes da Indústria Farmacêutica possíveis reacções adversas dos seus medicamentos.	

PROGRAMA DE NOTIFICAÇÃO ESPONTÂNEA DE REACÇÕES ADVERSAS (FICHA ROXA)

■ **Desde Janeiro de 2001:**

1.	Em alguma ocasião, teve a intenção de notificar reacções adversas e **não dispunha** da ficha roxa.	Sim ☐	Não ☐
2.	Alguma vez teve a suspeita de uma reacção adversa, mas **não chegou a preencher** a ficha roxa, mesmo dispondo dela.	Sim ☐	Não ☐
3.	Alguma vez prencheu as fichas roxas, que **não chegou a enviar** por causas distintas.	Sim ☐	Não ☐

PARA FINALIZAR, ALGUMAS PERGUNTAS DE CARÁCTER GERAL

Que idade tem? __ __ anos **Sexo:** F ☐ M ☐

Que tipo/s de actividade/s desempenha?

Privada ☐
Pública ☐
Ambas ☐

em:
- Farmácia Hospitalar
  - Director de Serviço ☐
  - Outro ☐
- Farmácia de Oficina
  - Director Técnico ☐
  - Farmacêutico Adjunto ☐
  - Outro ☐

Aproximadamente, quantos medicamentos dispensa, em média, por dia?

___ ___

Aproximadamente, que percentagem de pacientes toma mais de um medicamento por dia?

___ ___%

Quantos funcionários trabalham na farmácia?

- Farmacêuticos___ ___
- Técnicos de farmácia ___ ___ (farmácia hospitalar)
- Ajudantes Técnicos ___ ___ (farmácia de oficina)
- Outros___ ___

SUGESTÕES QUE GOSTARIA DE FAZER SOBRE O PROGRAMA DE NOTIFICAÇÃO ESPONTÂNEA DE REACÇÕES ADVERSAS

MUITO OBRIGADO PELA SUA COLABORAÇÃO

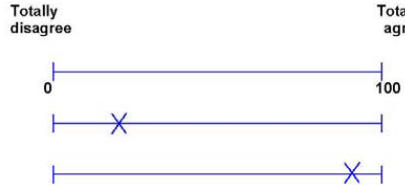
Instituto Nacional de Farmácia e do Medicamento
Ministério da Saúde

Pharmacist's questionnaire (translation)

QUESTIONNAIRE Nº:

FILLING INSTRUCTIONS.

In the left column are questions that will be the subject of your evaluation and in the right column there is a **gradual scale** where you should mark with a X the place where, accordingly to your opinion represents your **agreement** with the text comment. If you are totally in disagreement, you should place a cross at the left end, and as your agreement increases you should move the cross to the right.



ADVERSE DRUG REACTIONS

		Totally disagree — Totally agree
1.	Really serious adverse drug reaction is well documented by the time a drug is marketed.	
2.	It is nearly impossible to determine whether a drug is responsible for a particular adverse reaction.	
3.	I would only report an adverse drug reaction if I was sure that it was related to the use of a particular drug.	
4.	The one case an individual pharmacist might see could not contribute to pharmaceutical knowledge.	
5.	When I read pharmaceutical literature I am interested in articles about ADR.	
6.	I would be more likely to report ADR if there were an easier method.	
7.	I think that the most correct way to report ADR is in pharmaceutical literature.	
8.	I should be financially reimbursed for providing the ADR service.	
9.	I have a professional obligation to report ADR.	
10.	Reporting ADR puts my career at risk.	
11.	It is only necessary to report serious or unexpected ADR.	
12.	I do not have time to complete the purple card.	
13.	I do not have time to think about the involvement of the drug or the other causes in ADR.	
14.	I do not know how the information reported in the purple card is used.	
15.	I talk with pharmaceutical companies about possible ADR with their drugs.	

ADVERSE DRUG REACTION REPORTING PROGRAM
(PURPLE CARD)

■ **Since January 2001:**

1.	Did you ever want to report an ADR and you **do not have** the purple card.	Yes ☐	No ☐
2.	Did you ever have an ADR suspicious but you **do not fill** the purple card even having it.	Yes ☐	No ☐
3.	Did you ever fill the purple card but you **do not send it** by any reason.	Yes ☐	No ☐

SOME GENERAL QUESTIONS

How old are you? __ __ years **Gender:** F ☐ M ☐

What type of activity?

Private ☐
Public ☐
Both ☐

in:
- Hospital pharmacy
  - Service director ☐
  - Other ☐
- Communitarian pharmacy
  - Technical director ☐
  - Auxiliary pharmacist ☐
  - Other ☐

Approximately, how many drugs do you dispense in one day?

___ ___

Approximately, which percentage of patients uses more than one drug a day?

___ ___%

How many employees are in the pharmacy?

- Pharmacists___ ___
- Pharmacy technicians ___ ___ (hospital pharmacy)
- Technical auxiliaries ___ ___ (communitarian pharmacy)
- Others___ ___

SOME SUGESTIONS THAT YOU LIKE TO DO ABOUT THE ADVERSE DRUG REACTION REPORTING PROGRAM

THANK YOU VERY MUCH FOR YOUR COOPERATION

Instituto Nacional de Farmácia e do Medicamento
Ministério da Saúde

APPENDIX C

Expert's opinion (validity)

1. National Pharmacovigilance Department of INFARMED

Questionnaire is balanced (questions nº, fulfill time, etc.). Questions are very well elaborated in sense to identify the causes of under reporting in Portugal by health professionals.

2. Northern Pharmacovigilance Unit

Questionnaire is balanced (questions nº, fulfill time, etc.). Questions are very well elaborated in sense to identify the causes of under reporting in Portugal by health professionals.

In relation to the scale it could be better if has a middle division with 50 value or 3 divisions with values 25, 50 and 75.

3. Pharmacology Department of the Pharmacy Faculty, University of Coimbra, (Professor Margarida Carmona)

Questionnaire is balanced (questions nº, fulfill time, etc.). Questions are very well elaborated in sense to identify the causes of under reporting in Portugal by health professionals.

In relation to the scale it could be difficult the answer form because pharmacists did not know this type of scale.

4. Pharmacology Department of the Pharmacy Faculty, University of Porto (Professor Jorge Oliveira)

Questionnaire is balanced (questions nº, fulfill time, etc.). Questions are very well elaborated in sense to identify the causes of under reporting in Portugal by health professionals.

In relation to the scale could be happen some problems with fulfil of the questionnaire and with analyse. The scale could be better has individual values between 0 and 10.

5. Institute Superior of Health Sciences of North (Professor Jorge Proença)

Questionnaire is balanced (questions nº, fulfill time, etc.). Questions are very well elaborated in sense to identify the causes of under reporting in Portugal by health professionals. In relation to the scale it could be better if has a middle division with 50 value.

6. Pharmacoepidemiology Studies Centre of National Association of Pharmacies (Prof. Ana Martins)

Questionnaire is balanced (questions nº, fulfill time, etc.). Questions are very well elaborated in sense to identify the causes of under reporting in Portugal by health professionals.

The scale could be better has individual values between 0 and 10. Communitarian pharmacists could have problems to know how many medicines dispense in middle per day it could be better establishing a range of 1 week for example.

APPENDIX D

Introduction letter (Case-Control Study)

First physician's letter

Sistema Nacional Farmacovigilância
infarmed
Instituto Nacional da Farmácia e do Medicamento
Unidade de Farmacovigilância do Norte

Porto, 3 de Dezembro de 2002

Caro colega

Após dez anos de funcionamento do Programa de Notificação Espontânea de Reacções Adversas a Medicamentos (RAM), através da Ficha Amarela, vamos realizar um estudo farmacoepidemiológico[1] com o objectivo de identificar e avaliar as atitudes e opiniões dos profissionais de saúde, de forma a corrigir deficiências no seu funcionamento e melhorar o grau de participação dos médicos na notificação de RAM.

Como sabe, a Notificação Espontânea de RAM, por parte dos profissionais de saúde, constitui o método farmacoepidemiológico mais usado e universalmente aceite, para a detecção de RAM de medicamentos, recentemente comercializados e de RAM inesperadas ou raras. Por isso, o seu valor é inestimável, no seio de um sistema de saúde moderno, por contribuir para uma maior segurança e eficácia no uso terapêutico dos fármacos.

O universo deste estudo é formado por uma amostra representativa de 800 médicos inscritos na ARS-Norte, seleccionados de maneira aleatória e por um procedimento informático.

Do ponto de vista metodológico, é fundamental que haja uma participação completa e com uma elevada qualidade das respostas. Por isso, é de importância vital que dedique cinco minutos do seu precioso tempo ao questionário que juntamos, desenhado a pensar num rápido e fácil preenchimento.

Garantimos a confidencialidade absoluta dos dados. O código numérico do questionário utilizar-se-á mantendo o anonimato, para resolver o problema das "não respostas". A informação recolhida só será apresentada de maneira agrupada e utilizada unicamente para fins científico-académicos. Comprometemo-nos desde já enviar os artigos a que der lugar este estudo.

No cabeçalho do questionário, encontrará as instruções para o seu correcto preenchimento, que agradecemos leia atentamente. Quando terminar de preencher o questionário, coloque-o dentro do envelope franquiado e envia-o pelo correio. Se tiver alguma dúvida ou problema durante o preenchimento do questionário, pode telefonar para o número 225573990.

Agradecendo antecipadamente a sua colaboração, enviamos os melhores cumprimentos.

Prof. Doutor Jorge Polónia
Coordenador da UFN

Mestre Teresa Herdeiro
Prof. Coord. Equip. IPSN

Insistimos novamente na importância do preenchimento cuidadoso do questionário, pois disso dependerá a validade do estudo.

[1]com a colaboração da Universidade de Santiago de Compostela.

Second physician's letter

Porto, 5 de Fevereiro de 2003

Caro colega

Como se recordará, no passado mês de Dezembro, enviámos um questionário com o objectivo de identificar e avaliar as atitudes e opiniões dos profissionais de saúde, sobre o Programa de Notificação Espontânea de Reacções Adversas a Medicamentos (RAM) através da Ficha Amarela. O estudo tem como finalidade corrigir as eventuais deficiências do Programa de Notificação de RAM, assim como motivar e melhorar o grau de participação dos médicos na notificação de RAM.

Como resultado do envio anterior obteve-se um elevado nível de respostas. Contudo, solicitamos de novo a sua colaboração, dado que o nosso interesse está em que o estudo seja um reflexo fiel da opinião de todos os médicos inscritos na ARS-Norte.

Para efeito, remetemos um novo questionário e agradecemos desde já a sua valiosa colaboração, melhores

cumprimentos.

Prof. Doutor Jorge Polónia
Coordenador da UFN

Mestre Teresa Herdeiro
Prof. Coord. Equip. IPSN

Se não recebermos noticias suas em breve, entraremos em contacto consigo para resolver qualquer dúvida que possa ter.

Third physician's letter

Sistema Nacional Farmacovigilância
infarmed
Instituto Nacional da Farmácia e do Medicamento
Unidade de Farmacovigilância do Norte

Porto, 4 de Abril de 2003

Caro colega

Como sabe, estamos a realizar um estudo com o objectivo de conhecer as atitudes e opiniões dos médicos inscritos na ARS-Norte, sobre distintos aspectos do Programa de Notificação Espontânea de Reacções Adversas a Medicamentos (RAM), depois de 10 anos de funcionamento.

Até agora enviamos por duas vezes o questionário, obtendo um nível de resposta satisfatório; contudo para conseguir a **validade metodológica** adequada somos obrigados a insistir de novo na necessidade de participação. Para isso, enviamos de novo o questionário, que foi desenhado pensando num rápido e fácil preenchimento (**apenas cinco minutos**), por sermos conhecedores das limitações de tempo na nossa profissão.

Solicitamos que o envie tão depressa quanto possível, já que cada questionário recebido contribui grandemente para aumentar a validade final do estudo. Por isso, **a sua colaboração é muito importante**.

Ao mesmo tempo que insistimos na **confidencialidade absoluta** dos dados, aproveitamos para agradecer a valiosa colaboração.

Melhores cumprimentos.

Prof. Doutor Jorge Polónia
Coordenador da UFN

Mestre Teresa Herdeiro
Prof. Coord. Equip. IPSN

Para qualquer esclarecimento, não hesite em contactar-nos para o telefone 225573990.

Fourth physician's letter

Sistema Nacional Farmacovigilância
infarmed
Instituto Nacional da Farmácia e do Medicamento
Unidade de Farmacovigilância do Norte

Porto, 2 de Junho de 2003

Caro colega

Como sabe, estamos a realizar um estudo com o objectivo de conhecer as atitudes e opiniões dos médicos inscritos na ARS-Norte, sobre distintos aspectos do Programa de Notificação Espontânea de Reacções Adversas a Medicamentos (RAM), depois de 10 anos de funcionamento.

Até agora enviamos três questionários, alcançando um nível de participação satisfatório; contudo para conseguir a **validade metodológica** adequada somos obrigados a insistir de novo na necessidade de participação. Para isso, enviamos de novo o questionário, que foi desenhado pensando num rápido e fácil preenchimento (**somente cinco minutos**), por sermos conhecedores das limitações de tempo na nossa profissão.

Solicitamos que o envie tão depressa quanto possível, já que cada questionário recebido contribui grandemente para aumentar a validade final do estudo. Por isso, **a sua colaboração é muito importante**.

Ao mesmo tempo que insistimos na **confidencialidade absoluta** dos dados, aproveitamos para agradecer a valiosa colaboração.

Melhores cumprimentos.

Prof. Doutor Jorge Polónia
Coordenador da UFN

Mestre Teresa Herdeiro
Prof. Coord. Equip. IPSN

Junto com o questionário enviamos uma **Ficha Amarela**, para o caso de necessitar.

First pharmacist's letter

Sistema Nacional Farmacovigilância
infarmed
Instituto Nacional da Farmácia e do Medicamento
Unidade de Farmacovigilância do Norte

Porto, 5 de Junho de 2003

Cara colega

Após dez anos de funcionamento do Programa de Notificação Espontânea de Reacções Adversas a Medicamentos (RAM), através da Ficha Roxa, vamos realizar um estudo farmacoepidemiológico[1] com o objectivo de identificar e avaliar as atitudes e opiniões dos profissionais de saúde, de forma a corrigir deficiências no seu funcionamento e melhorar o grau de participação dos farmacêuticos na notificação de RAM.

Como sabe, a Notificação Espontânea de RAM, por parte dos profissionais de saúde, constitui o método farmacoepidemiológico mais usado e universalmente aceite, para a detecção de RAM de medicamentos, recentemente comercializados e de RAM inesperadas ou raras. Por isso, o seu valor é inestimável, no seio de um sistema de saúde moderno, por contribuir para uma maior segurança e eficácia no uso terapêutico dos fármacos.

O universo deste estudo é formado por uma amostra representativa de 300 farmacêuticos que exercem a sua profissão na área geográfica da Administração Regional de Saúde do Norte, seleccionados de maneira aleatória e por um procedimento informático.

Do ponto de vista metodológico, é fundamental que haja uma participação completa e com uma elevada qualidade das respostas. Por isso, é de importância vital que dedique cinco minutos do seu precioso tempo ao questionário que juntamos, desenhado a pensar num rápido e fácil preenchimento.

Garantimos a confidencialidade absoluta dos dados. O código numérico do questionário utilizar-se-á mantendo o anonimato, para resolver o problema das "não respostas". A informação recolhida só será apresentada de maneira agrupada e utilizada unicamente para fins científico-académicos. Comprometemo-nos desde já enviar os artigos a que der lugar este estudo.

No cabeçalho do questionário, encontrará as instruções para o seu correcto preenchimento, que agradecemos leia atentamente. Quando terminar de preencher o questionário, coloque-o dentro do envelope franquiado e envia-o pelo correio. Se tiver alguma dúvida ou problema durante o preenchimento do questionário, pode telefonar para o número 225573990.

Agradecendo antecipadamente a sua colaboração, enviamos os melhores cumprimentos.

Mestre Teresa Herdeiro
Prof. Coord. Equip. IPSN

Prof. Doutor Jorge Polónia
Coordenador da UFN

Junto com o questionário enviamos uma **Ficha Roxa**, para o caso de necessitar.
Insistimos novamente na importância do preenchimento cuidadoso do questionário, pois disso dependerá a validade do estudo.

[1]com a colaboração da Universidade de Santiago de Compostela.

Second pharmacist's letter

Porto, 3 de Agosto de 2003

Cara colega

Como se recordará, no passado mês de Julho, enviámos um questionário com o objectivo de identificar e avaliar as atitudes e opiniões dos profissionais de saúde, sobre o Programa de Notificação Espontânea de Reacções Adversas a Medicamentos (RAM) através da Ficha Roxa. O estudo tem como finalidade corrigir as eventuais deficiências do Programa de Notificação de RAM, assim como motivar e melhorar o grau de participação dos farmacêuticos na notificação de RAM.

Como resultado do envio anterior obteve-se um elevado nível de respostas. Contudo, solicitamos de novo a sua colaboração, dado que o nosso interesse está em que o estudo seja um reflexo fiel da opinião de todos os farmacêuticos que exercem a sua profissão na área geográfica da ARS-Norte.

Para efeito, remetemos um novo questionário e agradecemos desde já a sua valiosa colaboração.

Melhores cumprimentos.

Mestre Teresa Herdeiro
Prof. Coord. Equip. IPSN

Prof. Doutor Jorge Polónia
Coordenador da UFN

Se não recebermos noticias suas em breve, entraremos em contacto consigo para resolver qualquer dúvida que possa ter.

Third physician's letter

Sistema Nacional Farmacovigilância
infarmed
Instituto Nacional da Farmácia e do Medicamento
Unidade de Farmacovigilância do Norte

Porto, 4 de Outubro de 2003

Cara colega

Como sabe, estamos a realizar um estudo com o objectivo de conhecer as atitudes e opiniões dos farmacêuticos que exercem a sua profissão na área geográfica da ARS-Norte, sobre distintos aspectos do Programa de Notificação Espontânea de Reacções Adversas a Medicamentos (RAM), depois de 10 anos de funcionamento.

Até agora enviamos por duas vezes o questionário, obtendo um nível de resposta satisfatório; contudo para conseguir a **validade metodológica** adequada somos obrigados a insistir de novo na necessidade de participação. Para isso, enviamos de novo o questionário, que foi desenhado pensando num rápido e fácil preenchimento (**apenas cinco minutos**), por sermos conhecedores das limitações de tempo na nossa profissão.

Solicitamos que o envie tão depressa quanto possível, já que cada questionário recebido contribui grandemente para aumentar a validade final do estudo. Por isso, **a sua colaboração é muito importante**.

Ao mesmo tempo que insistimos na **confidencialidade absoluta** dos dados, aproveitamos para agradecer a valiosa colaboração.

Melhores cumprimentos.

Mestre Teresa Herdeiro
Prof. Coord. Equip. IPSN

Prof. Doutor Jorge Polónia
Coordenador da UFN

Se não recebermos noticias suas em breve, entraremos em contacto consigo para resolver qualquer dúvida que possa ter.

Fourth physician's letter

Sistema Nacional Farmacovigilância
infarmed
Instituto Nacional da Farmácia e do Medicamento
Unidade de Farmacovigilância do Norte

Porto, 2 de Dezembro de 2003

Cara colega

Como sabe, estamos a realizar um estudo com o objectivo de conhecer as atitudes e opiniões dos farmacêuticos que exercem a sua profissão na área geográfica da ARS-Norte, sobre distintos aspectos do Programa de Notificação Espontânea de Reacções Adversas a Medicamentos (RAM), depois de 10 anos de funcionamento.

Até agora enviamos três questionários, alcançando um nível de participação satisfatório; contudo para conseguir a **validade metodológica** adequada somos obrigados a insistir de novo na necessidade de participação. Para isso, enviamos de novo o questionário, que foi desenhado pensando num rápido e fácil preenchimento (**somente cinco minutos**), por sermos conhecedores das limitações de tempo na nossa profissão.

Solicitamos que o envie tão depressa quanto possível, já que cada questionário recebido contribui grandemente para aumentar a validade final do estudo. Por isso, **a sua colaboração é muito importante**.

Ao mesmo tempo que insistimos na **confidencialidade absoluta** dos dados, aproveitamos para agradecer a valiosa colaboração.

Melhores cumprimentos.

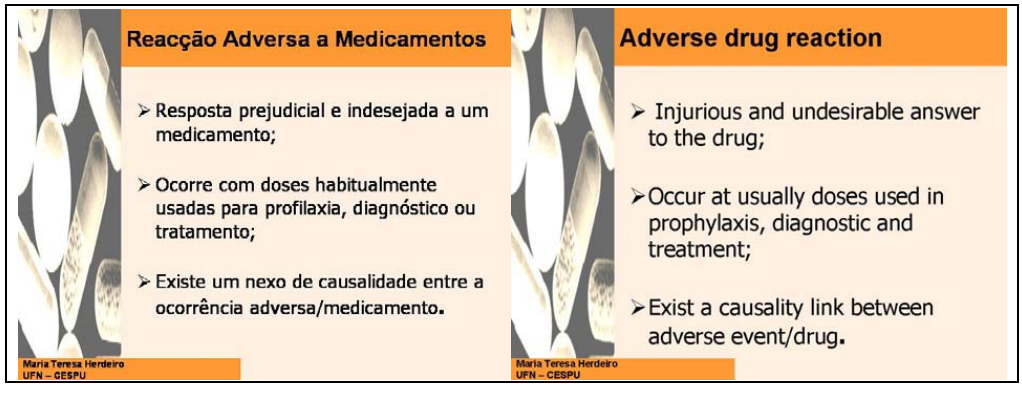
Mestre Teresa Herdeiro
Prof. Coord. Equip. IPSN

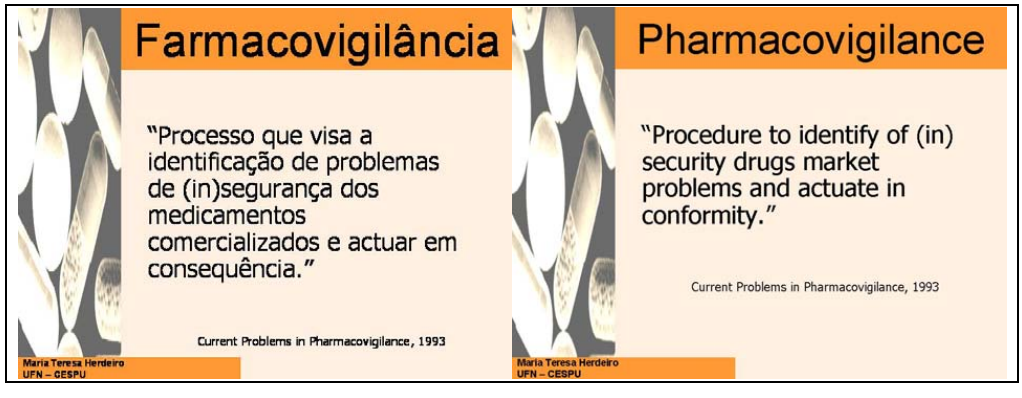
Prof. Doutor Jorge Polónia
Coordenador da UFN

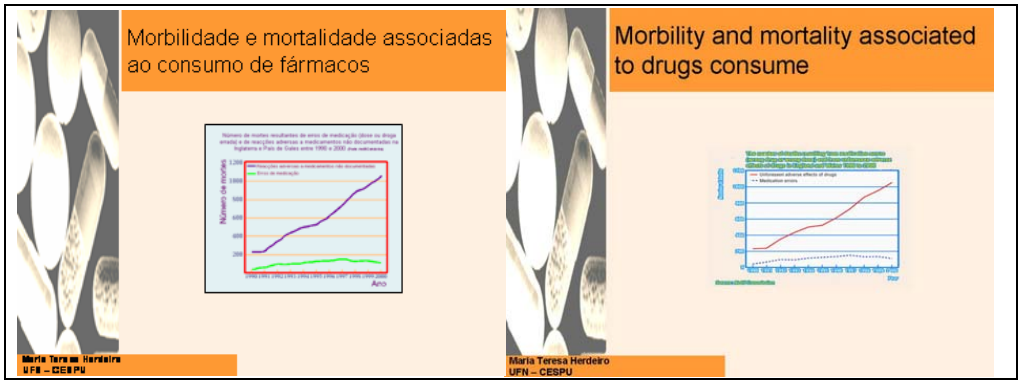
APPENDIX E

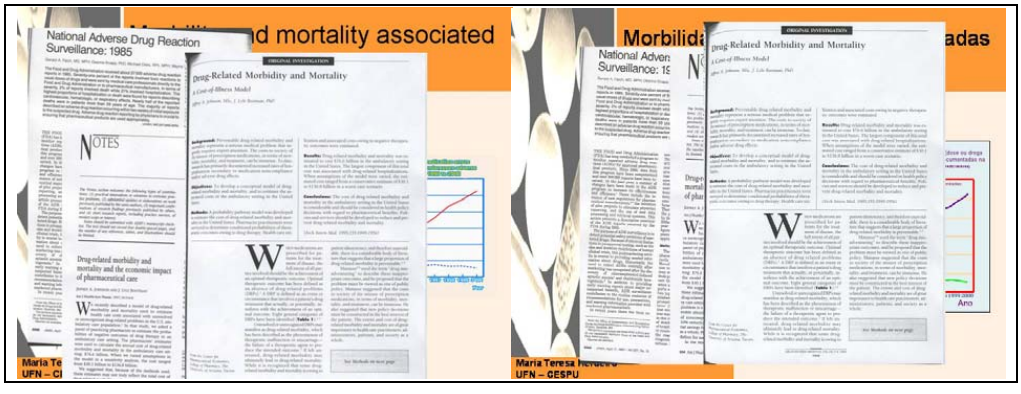
Presentation in PowerPoint

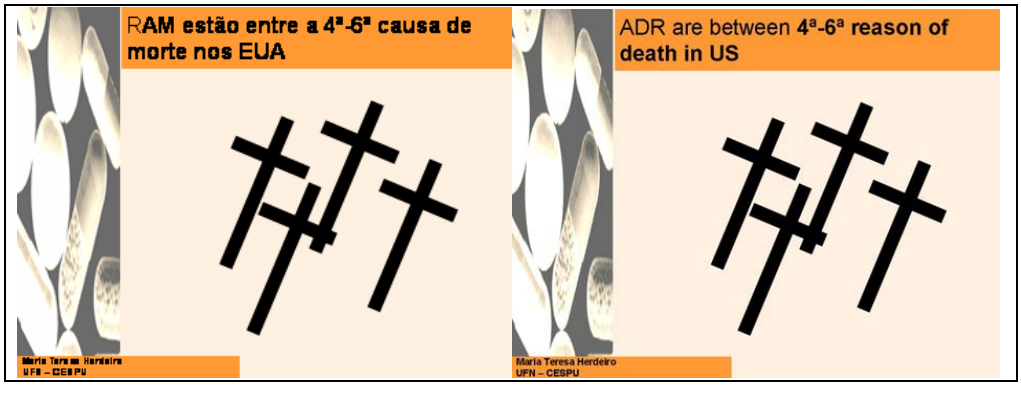
Physician presentation (original and translation)

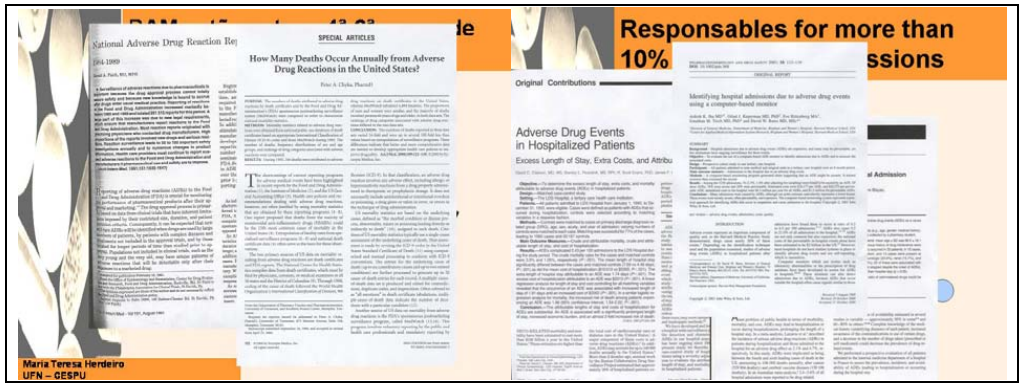


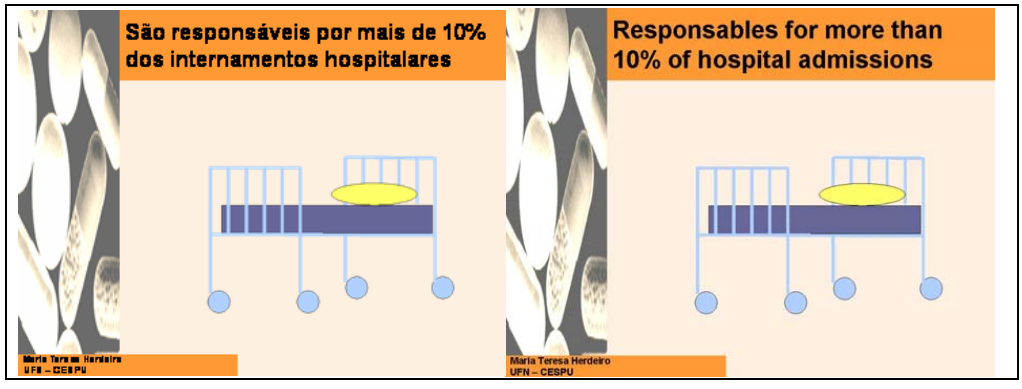


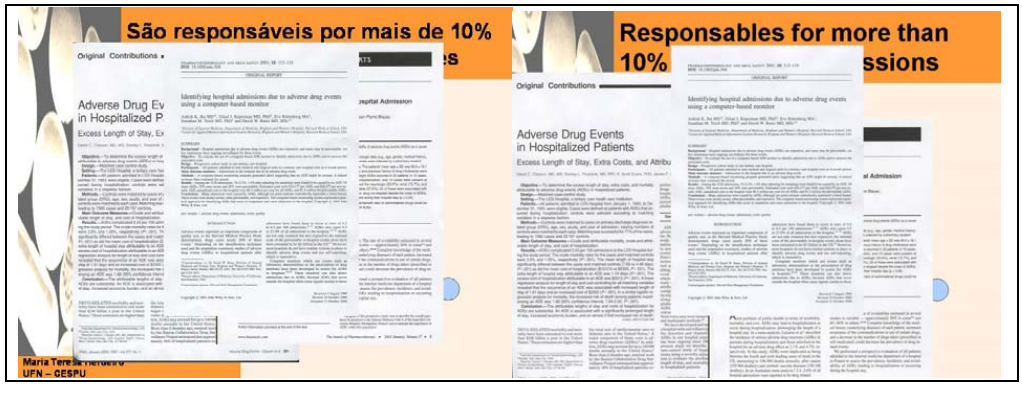

Morbilidade e mortalidade associadas ao consumo de fármacos
Maria Teresa Herdeiro
UFN – CESPU
Morbility and mortality associated to drugs consume
Maria Teresa Herdeiro
UFN – CESPU


National Adverse Drug Reaction Surveillance: 1985
Drug-Related Morbidity and Mortality
Drug-related morbidity and mortality and the economic impact of pharmaceutical care
Maria Teresa Herdeiro
UFN – CESPU


RAM estão entre a 4ª-6ª causa de morte nos EUA
Maria Teresa Herdeiro
UFN – CESPU
ADR are between 4ª-6ª reason of death in US
Maria Teresa Herdeiro
UFN – CESPU


How Many Deaths Occur Annually from Adverse Drug Reactions in the United States?
Responsables for more than 10%
Adverse Drug Events in Hospitalized Patients
Maria Teresa Herdeiro
UFN – CESPU


São responsáveis por mais de 10% dos internamentos hospitalares
Responsables for more than 10% of hospital admissions
Maria Teresa Herdeiro
UFN – CESPU


São responsáveis por mais de 10%
Responsables for more than 10%
Adverse Drug Events in Hospitalized Patients
UFN – CESPU

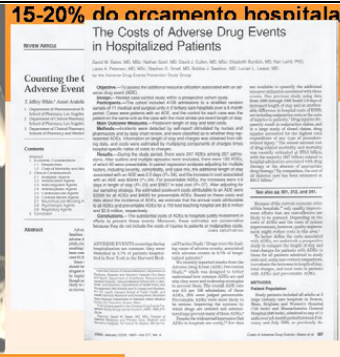
15-20% do orçamento hospitalar são gastos na resolução de complicações provocadas por fármacos

Maria Teresa Herdeiro
UFN – CESPU

15-20% of hospital budget are spent in the resolution of complications caused by drugs

Maria Teresa Herdeiro
UFN – CESPU

15-20% do orçamento hospitalar



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UFN – CESPU

15-20% of hospital budget are spent in the resolution of complications cause

Métodos usados

- Estudo epidemiológico (coortes, caso-controlo)
- **Notificação Espontânea**
- Monitorização de prescrição-evento
- Estudo de bases de dados de doentes

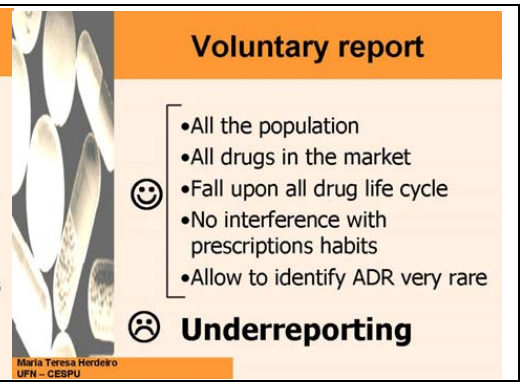
Maria Teresa Herdeiro
UFN – CESPU

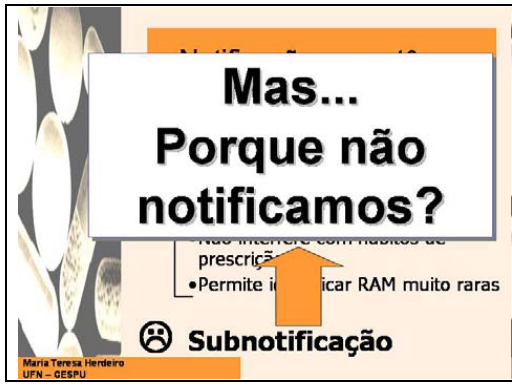
Methods

- Epidemiological study (cohorts, case-control)
- **Voluntary report**
- Monitorization of prescription-event
- Patients data base studies

Maria Teresa Herdeiro
UFN – CESPU


Notificação espontânea
•Envolve **toda a população**
•Abrange **todos os medicamentos no mercado**
•Incide sobre **todo o ciclo de vida do medicamento**
•Não interfere com hábitos de prescrição
•Permite identificar RAM muito raras
Subnotificação
Maria Teresa Herdeiro
UFN – CESPU


Voluntary report
•All the population
•All drugs in the market
•Fall upon all drug life cycle
•No interference with prescriptions habits
•Allow to identify ADR very rare
Underreporting
Maria Teresa Herdeiro
UFN – CESPU


Mas...
Porque não notificamos?
Subnotificação
Maria Teresa Herdeiro
UFN – CESPU


BUT...
Why we don't report?
Maria Teresa Herdeiro
UFN – CESPU

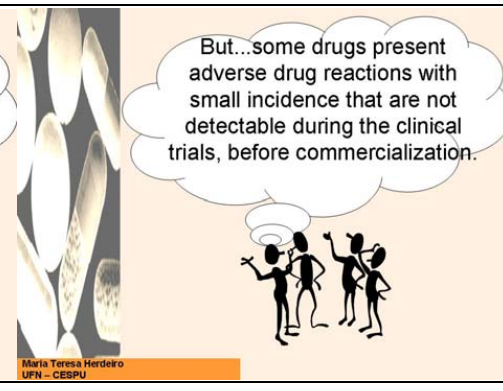

Todas as reacções adversas graves a medicamentos são conhecidas ?
Maria Teresa Herdeiro
UFN – CESPU

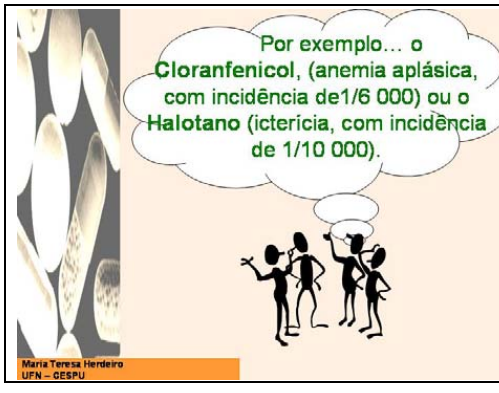

All adverse serious drug reactions are known ?
Maria Teresa Herdeiro
UFN – CESPU

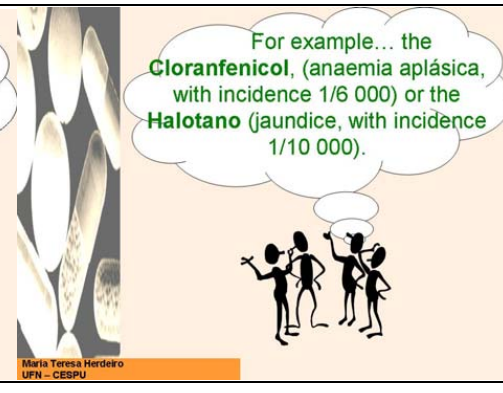

Sim. A indústria Farmacêutica faz ensaios pré-clínicos e clínicos antes do medicamento entrar no mercado.
Maria Teresa Herdeiro
UFN – CESPU


Yes. Pharmaceutical companies realized pre-clinics and clinical trials before the drug penetrate the market.
Maria Teresa Herdeiro
UFN – CESPU


Mas...por vezes há fármacos que apresentam Reacções Adversas de baixa incidência que não são detectadas durante os ensaios clínicos, de pré-comercialização.
Maria Teresa Herdeiro
UFN – CESPU


But...some drugs present adverse drug reactions with small incidence that are not detectable during the clinical trials, before commercialization.
Maria Teresa Herdeiro
UFN – CESPU


Por exemplo... o Cloranfenicol, (anemia aplásica, com incidência de1/6 000) ou o Halotano (icterícia, com incidência de 1/10 000).
Maria Teresa Herdeiro
UFN – CESPU

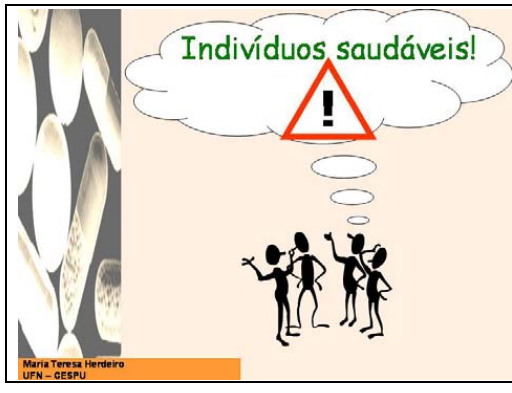

For example... the Cloranfenicol, (anaemia aplásica, with incidence 1/6 000) or the Halotano (jaundice, with incidence 1/10 000).
Maria Teresa Herdeiro
UFN – CESPU


Populações seleccionadas !
Maria Teresa Herdeiro
UFN – CESPU


Selected populations !
Maria Teresa Herdeiro
UFN – CESPU


Ensaios de Curta duração!
Maria Teresa Herdeiro
UFN – CESPU


Short duration trials!
Maria Teresa Herdeiro
UFN – CESPU


Indivíduos saudáveis!
Maria Teresa Herdeiro
UFN – CESPU


Healthy person!
Maria Teresa Herdeiro
UFN – CESPU


Tamanho da amostra limitado!
Maria Teresa Herdeiro
UFN – CESPU
Limited size of sample!
Maria Teresa Herdeiro
UFN – CESPU


Quando é que notifica?
Maria Teresa Herdeiro
UFN – CESPU
When do I report?
Maria Teresa Herdeiro
UFN – CESPU

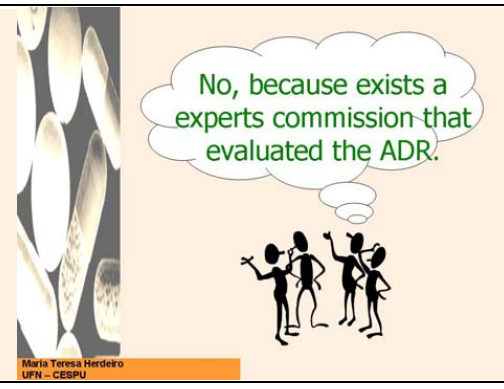

Notifico, quando consigo determinar se um medicamento é responsável por uma reacção adversa em particular.
Maria Teresa Herdeiro
UFN – CESPU
I report, when I determine when a drug is responsible for a particular adverse reaction
Maria Teresa Herdeiro
UFN – CESPU


Notifico só se estiver seguro que reacção adversa está relacionada com um medicamento específico.
Maria Teresa Herdeiro
UFN – CESPU
I would only report an adverse drug reaction if I were sure that it was related to the use of a particular drug .
Maria Teresa Herdeiro
UFN – CESPU


Eu acho que sempre que temos uma suspeita devemos notificar.
Maria Teresa Herdeiro
UFN – CESPU
I think that we must report always we have a suspicious.
Maria Teresa Herdeiro
UFN – CESPU


Mas... Não corremos o risco de gerar falsos alarmes?
Maria Teresa Herdeiro
UFN – CESPU
But... there are risks of false alarms?
Maria Teresa Herdeiro
UFN – CESPU


Não, porque existe uma comissão de peritos que avalia as RAM.
Maria Teresa Herdeiro
UFN – CESPU


No, because exists a experts commission that evaluated the ADR.
Maria Teresa Herdeiro
UFN – CESPU


A minha notificação será importante?
Maria Teresa Herdeiro
UFN – CESPU

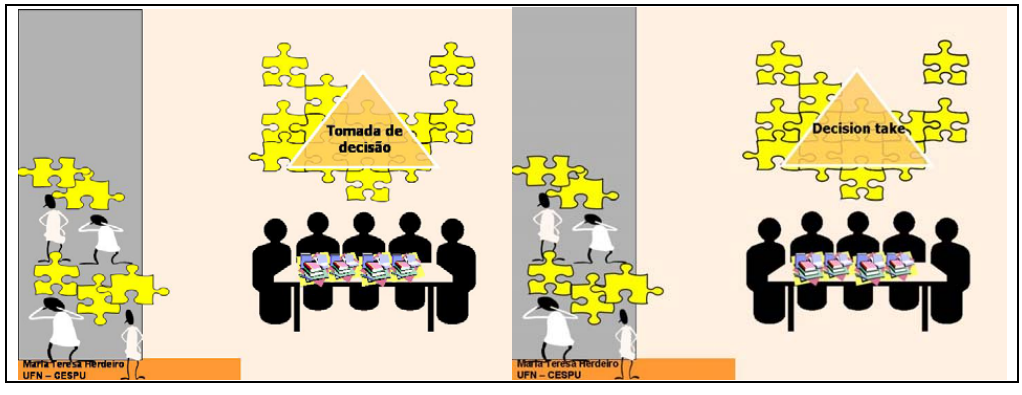

Is my report important?
Maria Teresa Herdeiro
UFN – CESPU


A minha notificação será importante?
Maria Teresa Herdeiro
UFN – CESPU


Is my report important?
Maria Teresa Herdeiro
UFN – CESPU

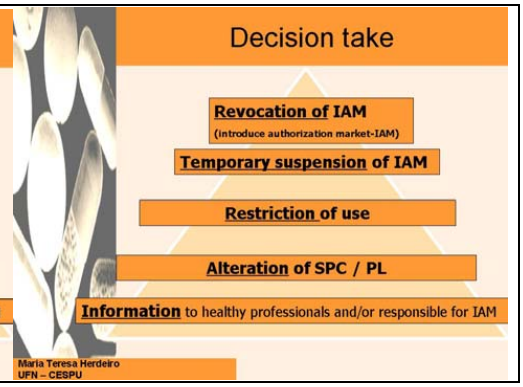

Que RAM devo notificar?
Todas as Minhas suspeitas
Graves e não graves
Inesperadas e esperadas
Maria Teresa Herdeiro
UFN – CESPU
What ADR should I report?
All my suspicions
Serious and no serious
Unexpected and expected
Maria Teresa Herdeiro
UFN – CESPU


Todas !!
Todas as Minhas suspeitas
Graves e não graves
Inesperadas e esperadas
Maria Teresa Herdeiro
UFN – CESPU
All !!
All my suspicions
Serious and no serious
Unexpected and expected
Maria Teresa Herdeiro
UFN – CESPU


Tomada de decisão
Maria Teresa Herdeiro
UFN – CESPU
Decision take
Maria Teresa Herdeiro
UFN – CESPU

y


Tomada de Decisão
Revogação da AIM
Suspensão temporária da AIM
Restrição da utilização
Alteração do RCM / FI
Informação aos profissionais de saúde e/ou titulares de AIM
Maria Teresa Herdeiro
UFN – CESPU


Decision take
Revocation of IAM
(introduce authorization market-IAM)
Temporary suspension of IAM
Restriction of use
Alteration of SPC / PL
Information to healthy professionals and/or responsible for IAM
Maria Teresa Herdeiro
UFN – CESPU

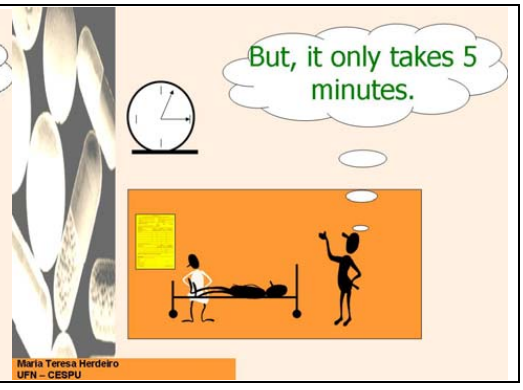

Bem... mas muitas vezes não tenho tempo para preencher a Ficha Amarela...
Maria Teresa Herdeiro
UFN – CESPU


Well... Sometimes I do not have time to fulfill the yellow card...
Maria Teresa Herdeiro
UFN – CESPU

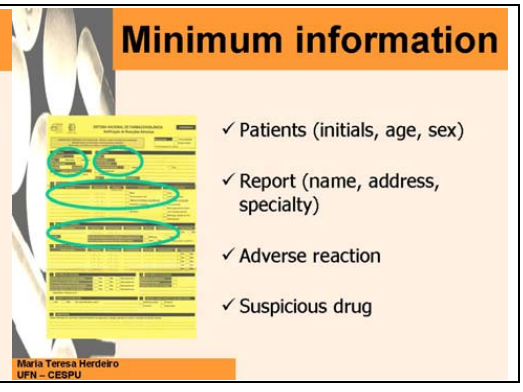

Mas, só precisa de 5 minutos.
Maria Teresa Herdeiro
UFN – CESPU

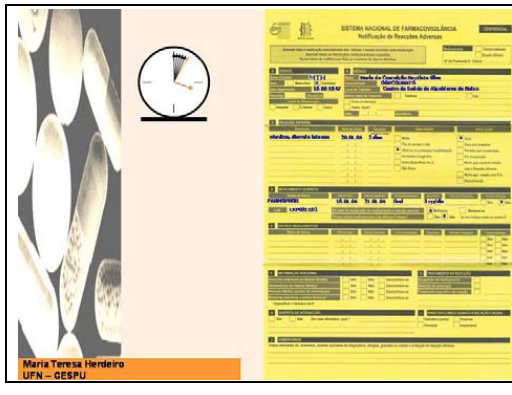

But, it only takes 5 minutes.
Maria Teresa Herdeiro
UFN – CESPU

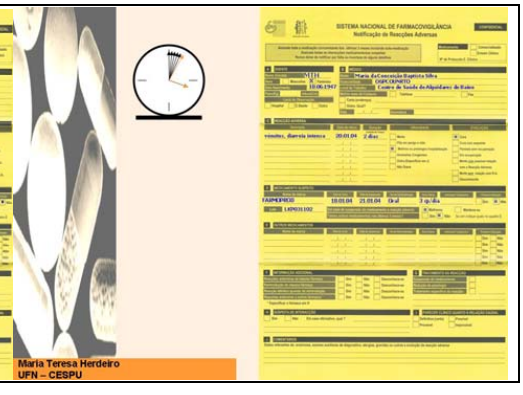

Mas, só precisa de 5 minutos.
Maria Teresa Herdeiro
UFN – CESPU


But, it only takes 5 minutes.
Maria Teresa Herdeiro
UFN – CESPU

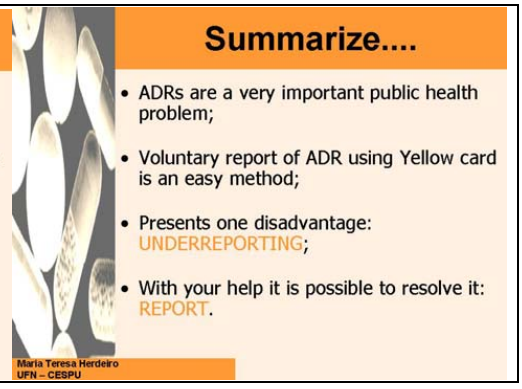

Informação mínima
✓ Doente (iniciais, idade, sexo)
✓ Notificador (nome, morada, especialidade)
✓ Reacção adversa
✓ Medicamento suspeito
Maria Teresa Herdeiro
UFN – CESPU


Minimum information
✓ Patients (initials, age, sex)
✓ Report (name, address, specialty)
✓ Adverse reaction
✓ Suspicious drug
Maria Teresa Herdeiro
UFN – CESPU


Maria Teresa Herdeiro
UFN – CESPU


Maria Teresa Herdeiro
UFN – CESPU


Resumindo....
• As RAM são um problema importante de saúde pública;
• A notificação espontânea de RAM através da ficha amarela é um método de fácil utilização;
• Apresenta uma desvantagem a SUBNOTIFICAÇÃO;
• Com a ajuda de todos é possível de resolver NOTIFIQUE.
Maria Teresa Herdeiro
UFN – CESPU


Summarize....
• ADRs are a very important public health problem;
• Voluntary report of ADR using Yellow card is an easy method;
• Presents one disadvantage: UNDERREPORTING;
• With your help it is possible to resolve it: REPORT.
Maria Teresa Herdeiro
UFN – CESPU

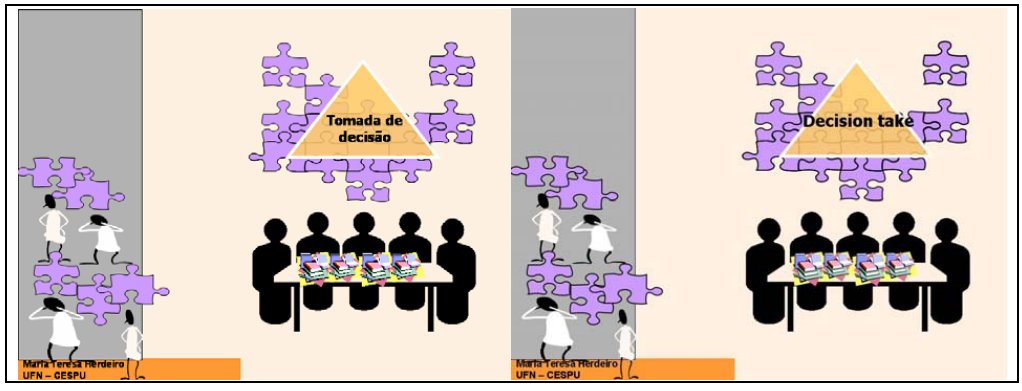

Unidade de Farmacovigilância do Norte
✓Telefone: 225 573 990
✓Fax: 225 573 971
✓E-mail: ufn@med.up.pt
✓Internet: http://ufn.med.up.pt
✓Correio: Unidade de Farmacovigilância do Norte
Faculdade de Medicina da Universidade do Porto
Alameda Prof. Hernâni Monteiro
4200-319 - PORTO
Maria Teresa Herdeiro
UFN – CESPU

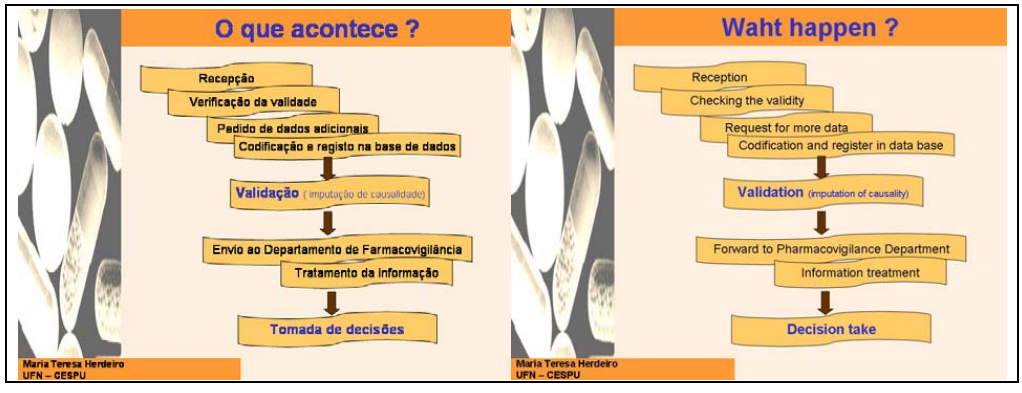

North Pharmacovigilance Unit
✓Phone: 225 573 990
✓Fax: 225 573 971
✓E-mail: ufn@med.up.pt
✓Internet: http://ufn.med.up.pt
✓Mail: North Pharmacovigilance Unit, Faculty of Me
University of Porto
Alameda Prof. Hernâni Monteiro
4200-319 - PORTO
Maria Teresa Herdeiro
UFN – CESPU


Muito Obrigado pela atenção
Maria Teresa Herdeiro
UFN – CESPU

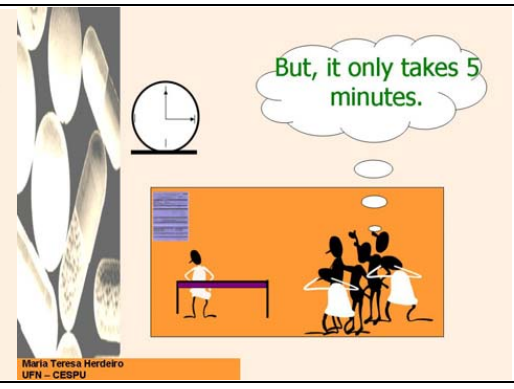

Thank you for your attention
Maria Teresa Herdeiro
UFN – CESPU

Pharmacist's presentation (different slides)





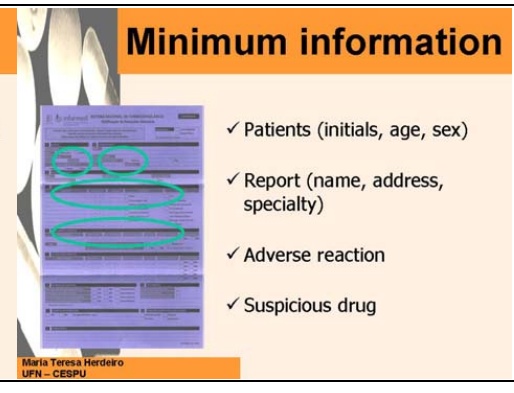

Mas, só precisa de 5 minutos.
Maria Teresa Herdeiro
UFN – CESPU

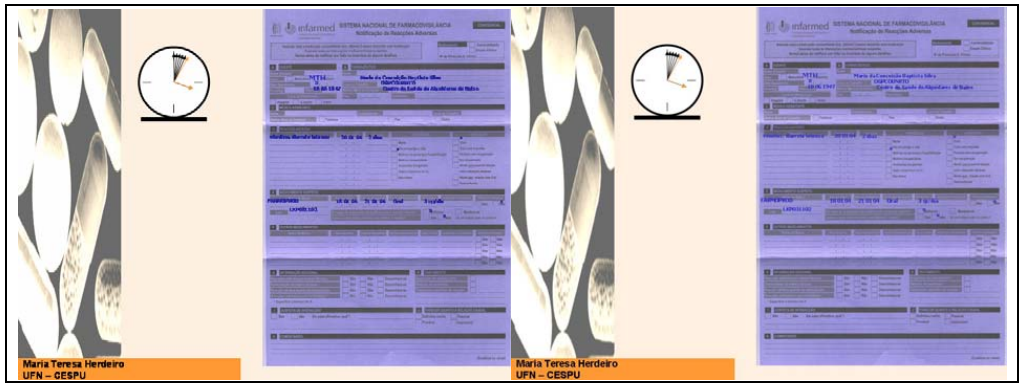

But, it only takes 5 minutes.
Maria Teresa Herdeiro
UFN – CESPU


Só precisas de 5 minutos.
Maria Teresa Herdeiro
UFN – CESPU


But, it only takes 5 minutes.
Maria Teresa Herdeiro
UFN – CESPU


Informação mínima
✓ Doente (iniciais, idade, sexo)
✓ Notificador (nome, morada, especialidade)
✓ Reacção adversa
✓ Medicamento suspeito
Maria Teresa Herdeiro
UFN – CESPU


Minimum information
✓ Patients (initials, age, sex)
✓ Report (name, address, specialty)
✓ Adverse reaction
✓ Suspicious drug
Maria Teresa Herdeiro
UFN – CESPU


Maria Teresa Herdeiro
UFN – CESPU
Maria Teresa Herdeiro
UFN – CESPU

APPENDIX F

Letter of introduction (Cluster-Randomized Trial)

Hospital letter

Hospital Distrital de Macedo de Cavaleiros
Direcção Clínica
Dra. Maria Manuela Adrião Garrido Viana
Rua Dr. Urze Pires
5340-263 Macedo de Cavaleiros

data: 2004/02/19

Assunto: **Acção de formação em Farmacovigilância**

A Unidade de Farmacovigilância do Norte tem vindo a realizar um estudo farmacoepidemiológico desde 2002, com colaboração da ARS-Norte. Este estudo teve como primeiro objectivo identificar e avaliar as atitudes e opiniões dos profissionais de saúde (médicos e farmacêuticos), sobre a notificação espontânea de Reacções Adversas a Medicamentos (RAM). Com base nos resultados obtidos no primeiro estudo, iremos começar a realizar acções de formação, em hospitais/centros de saúde pertencentes às zonas seleccionadas aleatoriamente, com o objectivo de ajudar estes profissionais a diminuir a sub-notificação e se possível criar uma "cultura de notificação".

Gostaríamos de realizar, na Vossa instituição acções de formação, sobre o assunto em epígrafe, pelo que sugeríamos a marcação de uma reunião com a brevidade possível, para agendarmos a formação (data/local).

Com os melhores cumprimentos,

Prof. Doutor Jorge Polónia
Coordenador da UFN

Mestre Teresa Herdeiro
Prof. Coord. Equip. IPSN

1

Health Centre letter

Sistema Nacional Farmacovigilância
infarmed
Instituto Nacional da Farmácia e do Medicamento
Unidade de Farmacovigilância do Norte

Director do Centro de Saúde de Ribeira de Pena
Dr Paulino Rodrigues
Lugar de Salvador
4870-151 – Ribeira de Pena

Data: 2004/02/28
Assunto: **Acção de formação em Farmacovigilância**

A Unidade de Farmacovigilância do Norte encontra-se a realizar um estudo farmacoepidemiológico desde 2002, com a colaboração da ARS-Norte. Este estudo teve como primeiro objectivo identificar e avaliar as atitudes e opiniões dos profissionais de saúde (médicos e farmacêuticos), sobre a notificação espontânea de Reacções Adversas a Medicamentos. Com base nos resultados obtidos no primeiro estudo, propomo-nos a realizar acções de formação com o objectivo de ajudar os profissionais de saúde a diminuir a sub-notificação e se possível criar uma "cultura de notificação".

Gostaríamos de realizar, na Vossa instituição acções de formação, sobre o assunto em epígrafe, pelo que sugeríamos a marcação de uma reunião com a brevidade possível, para agendarmos a formação (data/local).

Com os melhores cumprimentos

Prof. Doutor Jorge Polónia
Coordenador da UFN

Mestre Teresa Herdeiro
Prof. Coord. Equip. IPSN

Communitarian Pharmacists

Farmácia Cortes Pinto
Dra. Alexandra Cortes Pinto
Rua João Pedro Ribeiro, 841
4000-308 – Porto

Data: 2004/03/8
Assunto: **Acção de formação em Farmacovigilância**

A Unidade de Farmacovigilância do Norte encontra-se a realizar um estudo farmacoepidemiológico desde 2002, com a colaboração da ARS-Norte. Este estudo teve como primeiro objectivo identificar e avaliar as atitudes e opiniões dos profissionais de saúde (médicos e farmacêuticos), sobre a notificação espontânea de Reacções Adversas a Medicamentos. Com base nos resultados obtidos no primeiro estudo, propomo-nos a realizar acções de formação com o objectivo de ajudar os profissionais de saúde a diminuir a sub-notificação e se possível criar uma "cultura de notificação".

Gostaríamos de realizar, na sua farmácia acções de formação, sobre o assunto em epígrafe, pelo que sugeríamos a marcação de uma reunião com a brevidade possível, para agendarmos a formação (data/local).

Com os melhores cumprimentos

Mestre Teresa Herdeiro
Prof. Coord. Equip. IPSN

Prof. Doutor Jorge Polónia
Coordenador da UFN

APPENDIX G

Letter for Regional Health Administration of North (Cluster-Randomized Trial)

Sistema Nacional Farmacovigilância
infarmed
Instituto Nacional da Farmácia e do Medicamento
Unidade de Farmacovigilância do Norte

Administração Regional de Saúde

Rua Santa Catarina, 1288
4447 - Porto

vossa ref.:
data:

nossa ref.: UFN/**02.39**
data: 2004/03/08

Assunto: **Avaliação do conhecimento e atitudes dos profissionais de saúde face à notificação espontânea de reacções adversas a medicamentos**

Na sequência da nossa carta sobre o assunto em epígrafe enviada em Janeiro de 2002, vimos pela presente dar-vos conhecimento da actual situação do estudo que estamos a realizar na Unidade de Farmacovigilância do Norte, Faculdade de Medicina da Universidade do Porto.

A primeira fase do estudo que tinha como objectivo realizar uma revisão bibliográfica exaustiva, recolher e analisar através de um questionário, as opiniões e atitudes dos médicos e farmacêuticos da Região Norte, no que diz respeito ao programa de notificação e identificar por sua vez os factores que estão associados à notificação de reacções adversas a medicamentos (RAM), encontra-se terminada.

Estamos neste momento a iniciar a segunda fase do estudo ou seja uma vez identificados os factores associados à notificação RAM, preparamos uma intervenção educativa para melhorar a Notificação Espontânea. Vamos assim dar início às acções de formação nos Centros de Saúde, Hospitais e farmácias seleccionadas, pelo que agradecemos a Vossa colaboração.

Com os nossos melhores cumprimentos.

Prof. Doutor Jorge Polónia

Coordenador da Unidade de Farmacovigilância do Norte

APPENDIX H

Confirmation letter (Cluster-Randomized Trial)

Confirmation letter

Director do Centro de Saúde de Ribeira de Pena
Dr Paulino Rodrigues
Lugar de Salvador
4870-151 – Ribeira de Pena

Data: 2004/03/5
Assunto: **Acção de formação em Farmacovigilância**

De acordo com reunião tida esta semana, confirmamos a acção de formação acima descrita para o dia 18 de Março do corrente ano, às 17 horas, no centro de saúde de Ribeira de Pena.

Agradecíamos o envio do nome dos médicos do centro de saúde para assim prepararmos os certificados de participação a entregar no dia da acção de formação. A lista poderá ser enviada para o fax 225573971.

Com os melhores cumprimentos

Prof. Doutor Fernando Ramos
Coordenador da UFN

Mestre Teresa Herdeiro
Prof. Coord. Equip. IPSN

APPENDIX I

Pamphlets

Physician pamphlet (original)

Notificação Espontânea de Reacções Adversas a Medicamentos

Sempre que tiver a suspeita de uma reacção adversa seja ela grave ou não grave, esperada ou inesperada, preencha a Ficha Amarela.
O preenchimento não demora mais de 5 minutos. Experimente!
Para que a sua notificação seja válida basta que preencha os dados seguintes:
(1) *doente;*
(2) *médico;*
(3) *reacção adversa;*
(4) *medicamento suspeito.*

Não deixe de notificar por dúvidas relativamente à causalidade. Em caso de dúvidas, por favor contacte-nos. Estamos sempre à sua espera.

Conte connosco, nós contamos consigo!

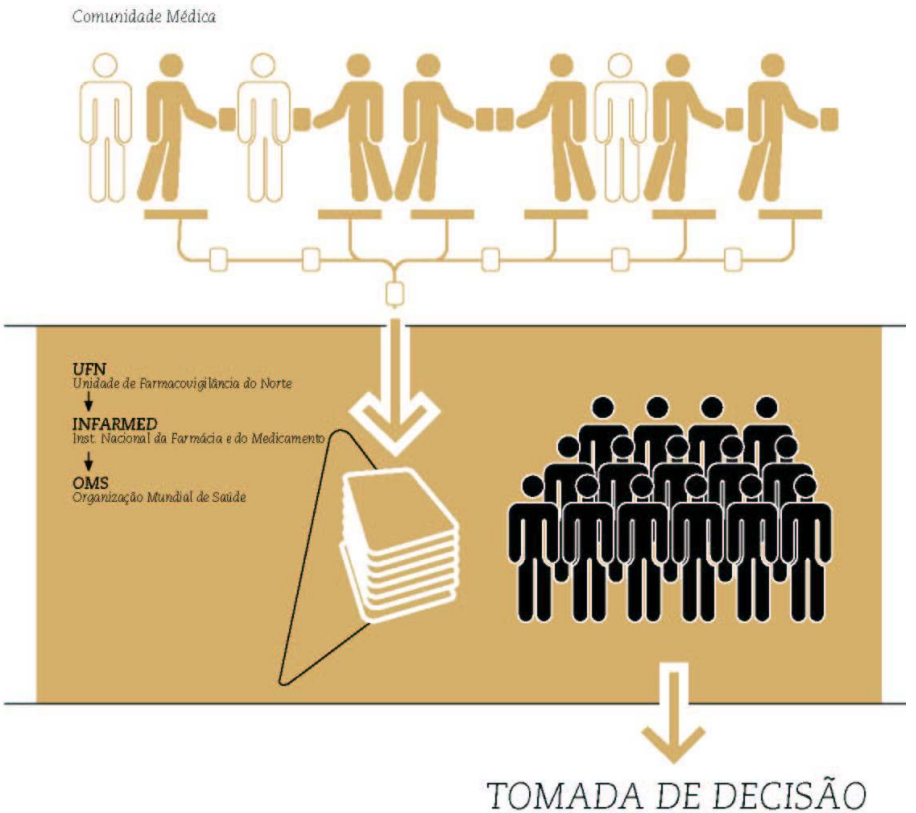
UNIDADE DE FARMACOVIGILÂNCIA DO NORTE
Faculdade de Medicina da Universidade do Porto
Alameda Prof. Hernâni Monteiro
4200-319 Porto

Telf: 22 5573990
Fax: 22 5573971
E-mail: ufn@med.up.pt
Internet:http://ufn.med.up.pt

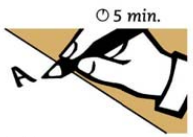
Notificação Espontânea de Reacções Adversas a Medicamentos

"A Farmacovigilância tem como objectivo identificar os problemas de insegurança dos medicamentos e actuar em consequência."
Current Problems in Pharmacovigilance, 1993

*A **notificação espontânea de reacções adversas a medicamentos** é um dos métodos mais utilizados em Farmacovigilância cujo sucesso depende da participação dos profissionais de saúde. A sua maior limitação reside na* **SUBNOTIFICAÇÃO.** *É esta limitação que nós queremos contrariar, mas para isso* **PRECISAMOS de SI.** *Ajude-nos a tornar os medicamentos mais* **SEGUROS.**



Spontaneous reporting of Adverse Drug Reactions



Every time that you have an adverse drug reaction suspicious wherever it is serious or not, expected or unexpected, please fill the yellow card.
The fulfilment only takes 5 minutes. Please try!
In order to validate your report please fill the following data:
(5) patient
(6) physicians
(7) adverse reaction
(8) suspicious medicine

Report even if you have any doubts about causality. If you have any question please contact us.
We are waiting for you.

Count on us
we count on you!

UNIDADE DE FARMACOVIGILÂNCIA DO NORTE
Faculdade de Medicina da Universidade do Porto
Alameda Prof. Hernâni Monteiro
4200-319 Porto

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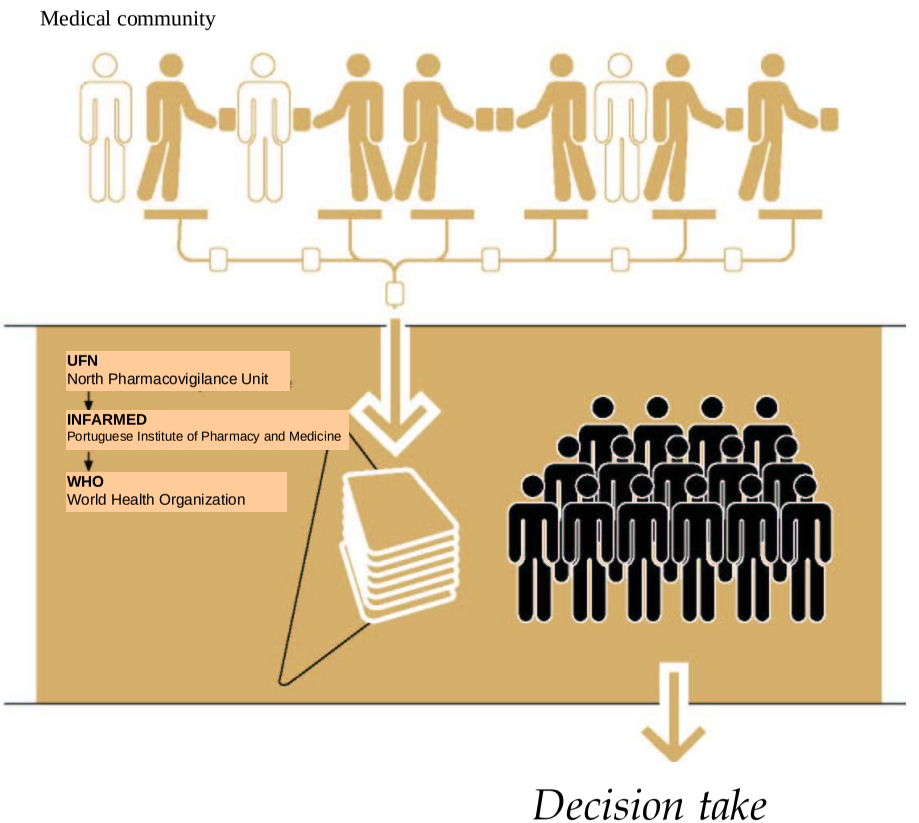
E-mail: ufn@med.up.pt
Internet:http://ufn.med.up.pt

Spontaneous Reporting of Adverse Drug Reactions

"Pharmacovigilance has the objective of identify safety problems of drugs and act accordingly"
Current problems in pharmacovigilance A993

The spontaneous reporting of adverse drug reactions is one of the available methods used in pharmacovigilance. Its success depends on the participation of health professionals. Its main limitation is UNDER REPORTING. It is this limitation that we intend to change. To do that, WE NEED YOU. Help us making drugs SAFIER.



Pharmacist pamphlet (original)

Notificação Espontânea de Reacções Adversas a Medicamentos

Sempre que tiver a suspeita de uma reacção adversa seja ela grave ou não grave, esperada ou inesperada, preencha a Ficha Roxa.
O preenchimento não demora mais de 5 minutos. Experimente!
Para que a sua notificação seja válida basta que preencha os dados seguintes:
(1) doente;
(2) farmacêutico;
(3) reacção adversa;
(4) medicamento suspeito.

Não deixe de notificar por dúvidas relativamente à causalidade. Em caso de dúvidas, por favor contacte-nos. Estamos sempre à sua espera.

5 min.

Conte connosco, nós contamos consigo!

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Alameda Prof. Hernâni Monteiro
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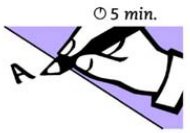
Spontaneous reporting of Adverse Drug Reactions



Every time that you have an adverse drug reaction suspicious wherever it is serious or not, expected or unexpected, please fill the purple card.
The fulfilment only takes 5 minutes. Please try!
In order to validate your report please fill the following data:
(1) patient
(2) pharmacist
(3) adverse reaction
(4) suspicious medicine

Report even if you have any doubts about causality. If you have any question please contact us.
We are waiting for you.

Count on us
we count on you!

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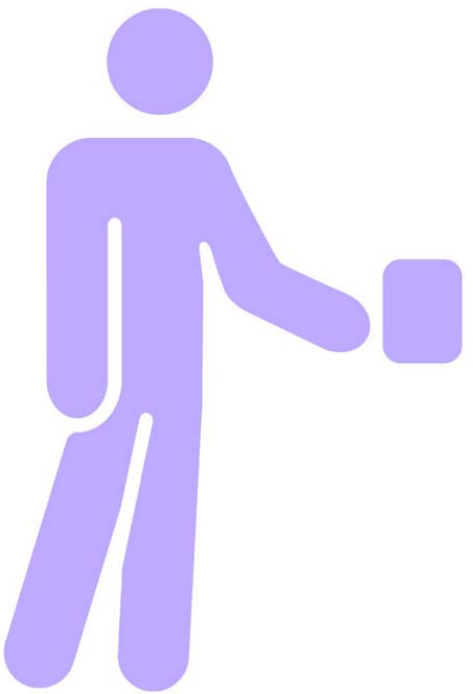

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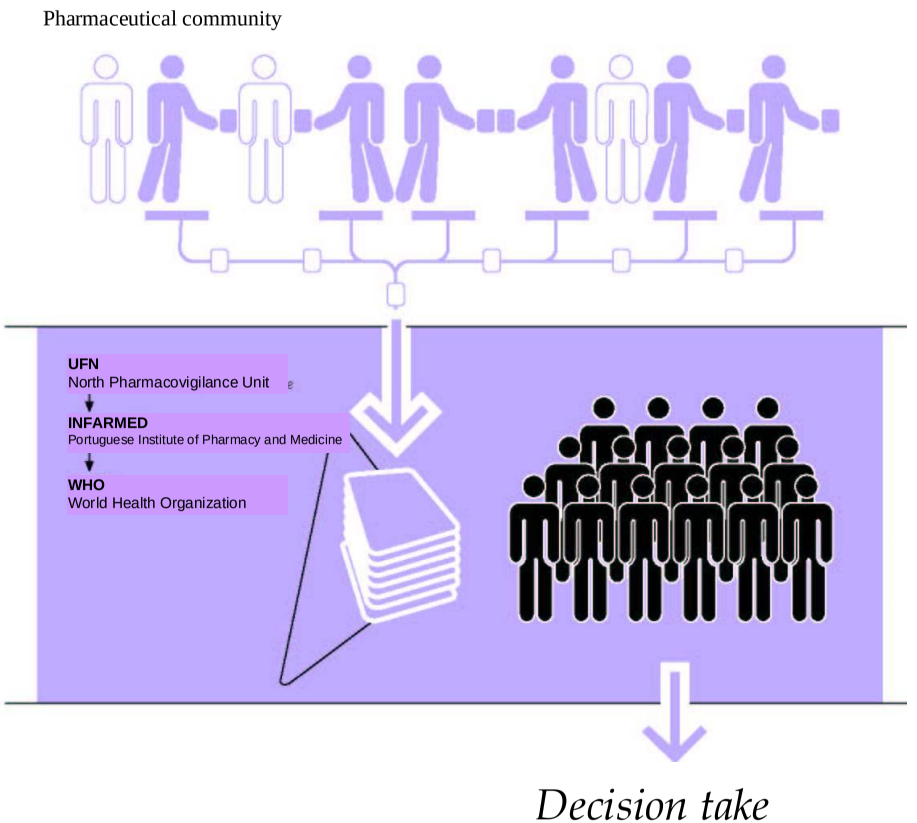

APPENDIX J

Participation certificate

Original

Translation