Using Information Systems in Pharmacovigilance

Promotion of Adverse Drug Reaction Reporting

Doctoral Program in Clinical and Health Services Research

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Abbreviations

ATC	-	Anatomical Therapeutic Chemical classification system.
ADR	-	Adverse Drug Reaction(s)
AERS	-	Adverse Events Reporting Systems
AE	-	Adverse Events
ARIMA	-	Autoregressive Integrated Moving Average
CDSS	-	Clinical Decision Support Systems
CIDES	-	Health Information and Decision Sciences Department
CINTESIS	-	Centre for Research in Health Technologies and Information Systems
CPARA	-	Catálogo Português de Alergias e Reações Adversas (*Portuguese catalog of allergies and adverse reactions*)
EHR	-	Electronic Health Record(s)
EPR	-	Electronic Patient Record(s)
EMA	-	European Medicines Agency
FMUP	-	Faculdade de Medicina da Universidade do Porto *(Faculty of Medicina, University of Porto)*
FDA	-	Food and Drug Administration
FIOCRUZ	-	Oswaldo Cruz Foundation
GEDII	-	Grupo de Estudo da Doença Inflamatória Intestinal *(Study Group of Inflammatory Bowel Disease)*
HL7	-	Health Level Seven
INFARMED	-	Autoridade Nacional do Medicamento e Produtos de Saúde, IP *(National Authority of Medicines and Health Products, IP)*
IS	-	Information Systems
ISO	-	International Organisation for Standardisation
MA	-	Marketing authorization
PPV	-	Positive Predictive Value
RAM	-	Reações Adversas a Medicamentos *(adverse drug reactions)*
SIRAI	-	Sistema de Informação de Reações Adversas e Incidentes *(Information System for Adverse Reactions and Incidents)*
TTA	-	Time to causality assessment
ULSM	-	Unidade Local de Saúde de Matosinhos *(Health Local Unit of Matosinhos)*
UFN	-	Unidade de Farmacovigilância do Norte (*Northern Pharmacovigilance Centre*)
USA	-	United States of America
VPP	-	Valor Positivo Preditivo *(Positive Predictive Value)*
WHO	-	World Health Organisation

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To Clara and João, the two most extraordinary projects I have ever started!

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Resumo da tese

As decisões na área da segurança do medicamento são tomadas através de revisões regulares, baseadas sobretudo na informação disponibilizada pelos sistemas de farmacovigilância que assentam fundamentalmente na notificação espontânea de Reações Adversas a Medicamentos (RAM). Estas notificações são feitas de forma voluntária pelos profissionais de saúde e pelos utentes. O sistema de notificação espontânea de RAM tem a enorme mais-valia da deteção precoce dos problemas de segurança dos medicamentos, mas sofre da grande limitação decorrente da sub-notificação. Estima-se que apenas cerca de 10% das reações adversas que ocorrem sejam efetivamente notificadas às Autoridades Reguladoras, nos países desenvolvidos. Para combater este problema, os sistemas de farmacovigilância têm desenvolvido várias estratégias, devendo os sistemas de informação ser encarados como uma oportunidade nesta área, uma vez que constituem uma presença central no nosso quotidiano, nomeadamente ao nível das instituições de saúde.

O objetivo desta tese é investigar estratégias para promover a notificação de RAM utilizando os sistemas de informação para facilitar o processo. Esta investigação é constituída por seis estudos, com os seguintes objetivos individualizados: 1) estabelecer o estado da arte sobre o uso de sistemas de informação na notificação espontânea de RAM; 2) comparar diferentes estratégias de promoção da notificação de RAM, determinando o seu custo/efetividade; 3) promover a notificação espontânea de RAM entre os profissionais de saúde que exercem atividade em hospitais, através de *hyperlinks* diretos para o formulário de notificação *online*; 4) implementar e avaliar o consumo de um *webservice* por um registo clínico eletrónico habitualmente utilizado por um grupo que participa num estudo multicêntrico na área da gastroenterologia; 5) aperfeiçoar o processo de avaliação de causalidade das notificações de RAM utilizando um modelo de apoio à decisão; 6) criar a área pessoal do notificador no *website* da unidade de farmacovigilância, tornando a notificação de RAM uma atividade motivadora e informativa.

Para estabelecer o estado da arte sobre o tema em estudo, foi elaborada uma revisão sistemática (**Capítulo 2**) sobre a utilização dos sistemas de informação em farmacovigilância, através das bases de dados bibliográficas das áreas científicas da saúde e das tecnologias de informação. De um total de 3865 artigos selecionados na pesquisa inicial, 33 artigos foram incluídos na análise, descrevendo 29 projetos diferentes. Foi efetuada uma meta-análise com 7 dos 29 projetos, para calcular a medida agregada do aumento da notificação de RAM,

obtendo-se o valor de 2.1 (significando que as intervenções duplicaram o número de RAM notificadas).

No **Capítulo 3**, são analisadas e descritas as várias estratégias que têm sido adotadas na Unidade de Farmacovigilância do Norte no sentido de promover a notificação de RAM, no que diz respeito ao número e relevância das notificações de RAM obtidas e aos custos envolvidos. Os custos da notificação de RAM foram calculados adicionando os custos iniciais de implementação da estratégia com os custos de manutenção da mesma (para cada estratégia analisada). Este custo global foi dividido pelo número de notificações de RAM obtidas por cada intervenção, para determinar o seu custo/efetividade. Todas as estratégias aumentaram o número de notificações de RAM. O maior aumento foi verificado com os protocolos estabelecidos com departamentos hospitalares (321 notificações de RAM obtidas, com o custo de 1.96€ cada uma), seguido da intervenção educativa (265 notificações de RAM obtidas, a 20.31€ cada uma) e pela inclusão de *hyperlinks* (135 notificações de RAM, com o custo de 15.59€ cada uma). Relativamente às RAM graves, os protocolos foram a intervenção mais eficiente (2.29€ cada notificação), seguido da inclusão de *hyperlinks* (30.28€ cada notificação, sem custos de manutenção). Os protocolos obtiveram o melhor resultado relativamente à notificação de RAM inesperadas (5.12€ cada notificação), seguido da intervenção educativa (38.79€ por notificação).

O **Capítulo 4** descreve um estudo ecológico desenvolvido durante o período de 2006-2011 na região Norte de Portugal, que consistiu na inclusão de *hyperlinks* diretos para o formulário *online* de notificação de RAM nos registos clínicos eletrónicos e/ou nos ambientes de trabalho dos profissionais de saúde dos hospitais desta região. A mediana mensal das notificações de RAM (total e *online*) e respetivos âmbitos foram analisados antes e depois da intervenção em todos os hospitais neste estudo. Dezasseis centros hospitalares entraram no estudo (27 hospitais), sendo que onze centros (18 hospitais) incluíram o *hyperlink*. Considerando os hospitais que colocaram o *hyperlink* no registo clínico eletrónico, a mediana mensal de notificação de RAM aumentou significativamente, de duas (âmbito 0-12) para cinco notificações (âmbito 1-17). A mediana mensal de notificação de RAM através do formulário *online* também aumentou significativamente, de uma notificação (âmbito 0-5) antes da intervenção para duas notificações (âmbito 1-17) depois da intervenção. Além disso, a notificação de RAM graves aumentou 3 vezes, e a notificação de RAM inesperadas aumentou 4.5 vezes. Nenhum destes aumentos significativos foi observado nos hospitais que não incluíram o *hyperlink*. Também se observou um aumento significativo das visitas diárias ao

website da Unidade de Farmacovigilância do Norte, de 10 visitas diárias antes da intervenção para 27 depois da intervenção ($p<0.001$).

No **Capítulo 5** encontra-se detalhado o processo de desenvolvimento de um serviço informático – chamado *webservice* – que foi implementado num registo clínico eletrónico em utilização por um grupo de gastroenterologistas. Foi feito um estudo entre 2013 e 2015, para analisar a tendência de notificação de RAM e o tipo de RAM notificadas por esse grupo de médicos. De abril de 2013 a fevereiro de 2015, foram enviadas 167 notificações de RAM para a Unidade de Farmacovigilância do Norte, através deste *webservice*, significando 10% do total de RAM recebidas no mesmo período. Destas 167 notificações, 118 eram casos graves (1 deles colocou a vida do doente em risco). Para medir o impacto da intervenção, foram considerados apenas os médicos do grupo que pertencem à região Norte de Portugal. Estes médicos notificaram 9 RAM durante os 23 meses anteriores à implementação do *webservice* e 121 RAM nos 23 meses posteriores à sua implementação, significando um aumento de 81%.

Para aperfeiçoar o processo de avaliação de causalidade das notificações de RAM, foi desenvolvida uma rede Bayesiana - descrita no **Capítulo 6** - baseada na avaliação que tinha sido feita pelo avaliador especialista da Unidade de Farmacovigilância do Norte, ao longo de 12 anos, às notificações de RAM recebidas nesta Unidade. Os resultados desta rede foram comparados com os resultados da introspeção global, com base numa coorte de validação independente, para sensibilidade, valor preditivo positivo (VPP) e tempo de avaliação de causalidade. A causalidade foi classificada, de acordo com os graus de causalidade definidos pela Organização Mundial de Saúde, como: Definitiva, Provável, Possível ou Condicional. A coorte de derivação era constituída por 593 notificações de RAM (10.1% classificadas com o grau Definitiva, 58.4% com o grau Provável, 25.6% com o grau Possível e 5.9% com o grau Condicional) e a coorte de validação por 463 notificações (7.5% classificadas com o grau Definitiva, 79.5% com o grau Provável, 9.5% com o grau Possível e 2.8% com o grau Condicional). Foi obtida elevada exatidão para as notificações com o grau Definitivo (sensibilidade 69.4% e VPP de 71.4%) e com o grau Provável (sensibilidade 91.1% e VPP 87.3%), e mais baixa para as notificações classificadas com o grau de Possível (sensibilidade de 25% e VPP de 28.9%) e Condicional. A rede revelou tendência para sobrestimar a causalidade (96.9% dos erros nos casos classificados pelo avaliador com o grau Possível foram avaliados pela rede com o grau Provável) ou para atribuir o grau imediatamente abaixo (90.8% dos erros nos casos classificados pelo avaliador com o grau Definitivo foram classificados pela rede com o grau Provável; 69.7% dos erros nos casos com o grau Provável foram classificados pela rede com o grau Possível). A mediana e respetivo intervalo interquartil (Q1:Q3) do tempo de

avaliação de causalidade foi de 4 dias (2:8) utilizando a rede e de 8 dias (5:14) através da introspeção global.

O **Capítulo 7** (concretamente, o subcapítulo 7.3.1) descreve o trabalho que continua a ser feito na criação da área pessoal do notificador no *website* da Unidade de Farmacovigilância do Norte. Atualmente, esta área já apresenta ao utilizador as suas próprias notificações de RAM submetidas *online*. Pretende-se ainda desenvolver um modelo de comunicação entre a unidade de farmacovigilância e os seus notificadores, fornecendo informação técnica sobre a reação adversa notificada e o medicamento suspeito. Após ter este modelo operacional, pretendemos (como trabalho futuro) avaliá-lo através de uma série de indicadores (por exemplo: aumento das notificações de RAM, aumento das visitas ao *site*, entre outros). Este trabalho não foi ainda concluído.

Muito trabalho pode ser desenvolvido para melhorar as atividades de farmacovigilância através dos sistemas de informação. Soluções promissoras podem passar pela integração das bases de dados de farmacovigilância nos registos clínicos eletrónicos usados habitualmente pelos profissionais de saúde, evitando que estes tenham trabalho adicional para submeter uma notificação de RAM. A inclusão de *hyperlinks* diretos nos registos clínicos eletrónicos e/ou nos ambientes de trabalho dos computadores dos profissionais de saúde para o formulário de notificação *online* de RAM é uma forma simples e custo-efetiva de alterar o comportamento dos profissionais de saúde relativamente à notificação de RAM e pode ser facilmente implementado nas instituições de saúde. Os sistemas de informação podem ainda ajudar na melhoria das atividades de rotina em farmacovigilância, melhorando a comunicação entre as Unidades de farmacovigilância e os seus notificadores. É também possível acelerar o processo de imputação de causalidade e subsequente *feedback*, utilizando métodos Bayesianos.

Thesis abstract

Decisions in the area of drug safety are made through regular reviews, based on available information from pharmacovigilance systems, which are mostly based on Adverse Drug Reactions (ADR) reports, voluntarily made by healthcare professionals and consumers. The ADR reporting system has the great value of early detection of drug safety problems, but also has a major limitation due to under-reporting. It is estimated that only about 10% of ADR that occur are actually reported to regulatory authorities in developed countries. To counter this problem, pharmacovigilance systems have been instituted to ensure that detected ADR are effectively reported to the regulatory authorities. The use of information systems is currently central in most of our lives, namely in healthcare institutions, and therefore represents an opportunity.

The aim of this thesis is to investigate strategies to promote ADR reporting using information systems to facilitate the process. It comprises the following six study aims: 1) to assess the state of the art regarding the utilisation of information systems in spontaneous ADR reporting; 2) to compare different approaches promoting ADR reporting and to determine their cost/effectiveness; 3) to promote spontaneous ADR reporting among healthcare professionals working in hospitals using hyperlinks to ADR online reporting forms; 4) to implement and evaluate the consumption of a webservice by the usual electronic health record used by a gastroenterologist multicentre study group; 5) to improve the ADR report causality assessment using a decision support tool and 6) to create a personal area in a pharmacovigilance website for each person that submits an ADR, aiming to turn the ADR reporting act into a motivating and informative activity.

A systematic review was performed regarding the use of information systems in pharmacovigilance, in bibliographic databases of the scientific fields of healthcare and information technology, as described in **Chapter 2**. From a total of 3865 articles, 33 articles were included in the analysis, describing 29 different projects. We also performed a meta-analysis on 7 of the 29 projects, to calculate the aggregated measure of increased ADR reporting, with an overall measure of 2.1 (meaning that the interventions doubled the number of ADR reports).

Several approaches taken by the Northern Pharmacovigilance Centre to promote ADR reporting are analysed and described in **Chapter 3**, regarding the number and relevance of ADR reports obtained and the costs involved. The costs of ADR reporting were calculated by

adding the initial costs and the running costs of each intervention. These costs were divided by the number of ADR reports obtained with each intervention, to assess its cost/effectiveness. All the approaches increased the number of ADR reports. The biggest increase was noted with protocols in hospital departments (321 ADR reports obtained, costing 1.96€ each), followed by an educational approach (265 ADR reports, 20.31€/report) and a hyperlink approach (136 ADR reports, 15.59€/report). According to serious ADR, the protocol approach was the most efficient, costing 2.29€/report, followed by the hyperlink approach at 30.28€/report (with no running costs). Concerning ADR unexpectedness, the best result was found with the protocol approach (5.12€/report), followed by the educational approach (38.79€/report).

Chapter 4 describes an ecological study performed in northern Portuguese hospitals from 2006 to 2011. We included hyperlinks to the online ADR report form either on Electronic Patient Records or on computer desktops. The median of spontaneous ADR reports (total and online) per month and the respective ranges were analysed before and after the intervention in all hospitals in this study. Sixteen hospital centres were involved in the study (27 hospitals). Eleven centres (18 hospitals) included the hyperlinks. Considering the hospitals with hyperlink access to the Electronic Patient Records, the median ADR reports per month increased significantly, from two (range 0-12) to five reports (range 1-17). The median of ADR reports per month using the online form also increased significantly, from one (range 0-5) before the intervention to two (range 1-17) after it. Moreover, serious ADR increased by 3-fold, and non-previously described ADR increased by 4.5-fold. None of these significant increases were observed in the hospitals where the hyperlink was not installed. We also found a significant increase in daily UFN website visits, from 10 before the intervention to 27 after it ($p < 0.001$).

Chapter 5 focuses on the creation of a webservice and its implementation in an electronic health record already in use by a group of gastroenterologists. A study was performed between 2013 and 2015 to analyse the trends of ADR reporting and also the type of ADR reported. From April 2013 to February 2015, 167 ADR reports were sent to the Northern Pharmacovigilance Centre through the webservice, meaning 10% of the total of ADR reports received in the same period. Of these 167 ADR, 118 cases were serious (one of them life-threatening). According to the northern region of Portugal, the studied physicians reported 9 ADR during the 23 months prior to webservice implementation and 121 ADR during the 23 months after webservice implementation, i.e. an increase of 81%.

To improve the process of causality assessment, a Bayesian network was developed, as described in **Chapter 6**. Network development was based on completely filled ADR reports, evaluated by the Portuguese Northern Pharmacovigilance Centre expert over 12 years, and

compared with global introspection on an independent validation cohort for sensitivity, positive predictive value (PPV) and time to causality assessment (TTA). Causality was classified as Definitive, Probable, Possible or Conditional, according to the World Health Organisation causality assessment. The derivation cohort included 593 ADR reports (10.1% Definitive, 58.4% Probable, 25.6% Possible and 5.9% Conditional) with a validation cohort including 463 reports (7.5%, 79.5%, 9.5% and 2.8%, respectively). High accuracy was reached for reports with Definitive causality (69.4% sensitivity, 71.4% PPV) and Probable causality (91.1%, 87.3%), but this was lower for reports with Possible (25%, 28.9%) and Conditional (15.4%, 50%) classification. The network tends to overrate causality (96.9% of errors in Possible cases classified as Probable) or give the level immediately below (90.8% of errors in Definitive cases classified as Probable; 69.7% of errors in Probable cases classified as Possible). The median (Q1:Q3) TTA was 4 (2:8) days using the network and 8 (5:14) days using global introspection.

The creation of a personal area within the UFN website was created and is described in **Chapter 7** (specifically, subchapter 7.3.1). We intend to design a model of communication between the pharmacovigilance centre and its users, providing technical information about the reported adverse reaction and the suspected drug. We expect to have the model in operation on the UFN website and evaluate its use through a set of indicators (e.g. increase in ADR reports, increase of website visits, etc.). This work is ongoing.

Much work can be done using information systems to improve pharmacovigilance. The authors see this as a promising solution the integration of pharmacovigilance databases with the habitually used electronic health records, avoiding an extra workload to submit an ADR report. The inclusion of hyperlinks to on-line ADR reporting forms on computer desktops and in Electronic Health Records is an easy and cost-effective way to change healthcare professional behaviours regarding spontaneous ADR reporting and can be easily implemented in healthcare institutions. Information systems can also improve pharmacovigilance routine activities, improving the communication between pharmacovigilance centres and its reporters. It is possible to accelerate the process of causality assessment and subsequent feedback using Bayesian methods.

Achievements and background

Working in pharmacovigilance for the last 12 years, it was fairly easy to choose this PhD theme, as I have always aimed to change the paradigm of spontaneous adverse drug reaction (ADR) reporting, from the idea of a passive and boring process to something appealing and simple to do. Considering the increasing use of information systems (IS) among healthcare institutions, it became clear that we could use IS to change the way people see the pharmacovigilance system. In this process, the contribution of my supervisor, Prof. Ricardo Correia, was crucial as he who always aroused my curiosity regarding the use of IS to promote spontaneous ADR reporting.

The development of this PhD thesis allowed me to face some challenges related to the differences between the structure of healthcare professionals' knowledge and the specific needs of electronic records. In this sense, I have participated in some discussion groups, both national and internationally (namely the FHIR/OpenEHR[1] and HL7[2] working groups), aiming to create a standard way in which information should be kept in the ADR registry.

In June 2014, I participated in the HL7 pharmacy group meeting, where the International Organisation for Standardisation (ISO) draft of the international standard for 'Requirements for electronic prescriptions' was discussed. This document remained under discussion for several months.

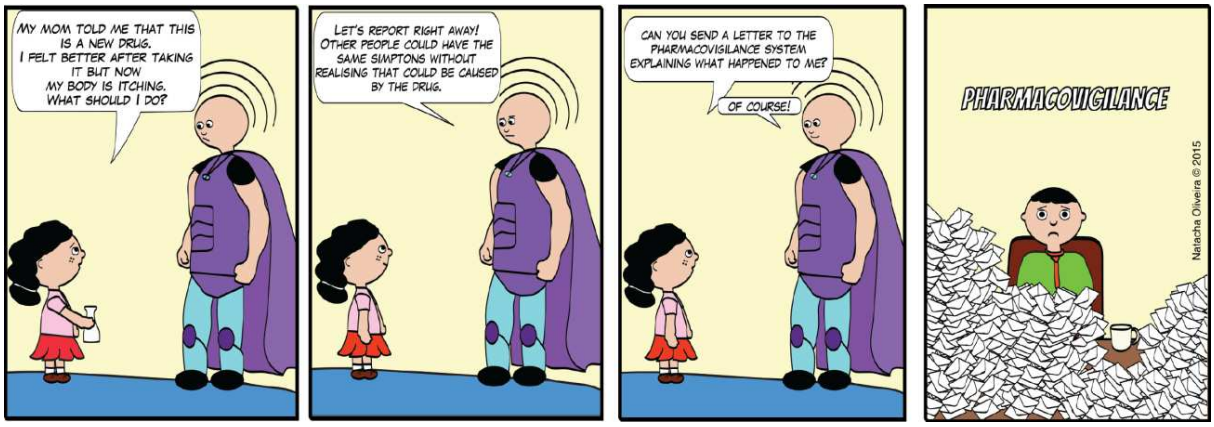
Contributions were also made to the last OpenEHR discussion, which took place in July 2014. It was focused on ADR definition, its characteristics and what should be kept during the registration of a ADR. At the moment, discussion is ongoing regarding the clinical content of the archetypal adverse reaction (FHIR/OpenEHR). Variables such as substance, status, seriousness, reaction type and certainty are under debate.

Nationally, important input was provided by this PhD team to the review of national legislation for the registration of allergies and adverse reactions (the Portuguese Catalogue for Allergies and Adverse Reactions - CPARA, in Portuguese). For this purpose, we created an archetypal Open EHR for the registry of ADR and allergies.

Another study developed during the PhD period, but not included in this thesis, was the creation of a list of 'alert drugs' to help hospital pharmacies detect ADR. For this purpose, a list of drugs was developed, adapted from Otero *et al* [3] and Classen *et al* [4], that should alert pharmacists to potentials ADR when the drugs are prescribed by physicians. The drugs included were chosen because they are used as specific treatments for ADR or as antidotes.

This list is now available on the Northern Pharmacovigilance Centre website[5] and, at the time of its disclosure, it was widely disseminated. It includes 16 drugs and their corresponding identifier codes to allow for easier integration on the IS used by pharmacies.

With all these small studies, together with the work developed to conclude this PhD thesis, it is my aim to increase the ADR reporting rate and to start changing the paradigm of pharmacovigilance in Portugal.



Chapter 1. General introduction

1.1 Spontaneous adverse drug reaction reporting

Most pharmacovigilance systems are based on spontaneous reporting of ADR[6]. Although there are some criticisms about this method and its known limitations, I strongly believe that spontaneous ADR reporting remains as an irreplaceable method of tracking a drug's safety profile.

Spontaneous ADR reporting has several limitations, as it suffers from incomplete data and, in many cases, inadequate data quality. Also, it depends on the motivation of healthcare professionals and consumers to report, which is not always easy to promote. The consequence of this is underreporting, which is a huge problem in all developed countries. It is estimated that only about 10% of the ADR that occurr are effectively reported to the regulatory authorities[7]. Another problem related to spontaneous ADR reporting is the difficulty of identification. If it is difficult to identify that an adverse event was caused by a drug, it will be even harder to report it.

However, this method as many advantages that should be highlighted. First of all, it involves all the drugs available to the whole population, during all the entire drug life cycle, unlike the situation with clinical trials. Rare and chronic ADR are mainly detected after drug commercialisation and, most of the time, through spontaneous ADR reporting.[8]

In recent years, data mining processes have been developed and tested in pharmacovigilance activities, through the detection of associations between drugs and adverse events. Although this could be a very efficient method to detect adverse events, we believe that important information, spontaneously reported as an ADR, would never be equal the information recovered from big databases. In fact, when one decides to report an ADR, the event/reaction is usually carefully described. Besides, ADR reporting systems emphasise among healthcare professionals and consumers the concept and the importance of drug safety surveillance. Moreover, this method allows for describing how the adverse event affected the well-being of the patient[9].

For all these reasons, I believe that data mining processes and computerised searches for ADR stored in databases will never replace spontaneous ADR reporting, but will rather complement it.

1.2 Thesis general aims

Globally, this thesis main aims are: to analyze strategies performed to increase spontaneous ADR reporting, to create tools to facilitate ADR reporting using IT and to create tools to improve pharmacovigilance activities. A secondary aim is to create the personal area on UFN website.

1.3 Thesis structure

This PhD Thesis is organised into eight chapters, some of them in the form of published or submitted scientific papers.

The two first chapters include the Introduction and the State of the Art, setting our studies within the framework of international research. Both of these chapters were published in scientific publications, the first published as an encyclopaedia chapter and the second as a scientific paper.

The four subsequent chapters (3-6) describe studies performed as part of our research programme; two of them were published in scientific journals and one as an oral communication at a scientific international meeting.

Therefore, the document refers to some ongoing and future work, beyond the limits of the PhD, but within the same scope. Finally, the last chapter consists of the Discussion.

Chapter 2 – State of the art

2.1 Abstract

Many studies have been performed worldwide to improve pharmacovigilance activities, some of them using information systems (IS). This chapter intends to frame our research within the state of the art (subchapter 2.2), covering the introduction and background of the thesis. We have also performed a systematic review with a meta-analysis on the use of IS to promote ADR reporting (subchapter 2.3).

The first work presented on this section was published, in an extended version, as an encyclopaedia chapter in the *Encyclopaedia of E-Health and Telemedicine*; a reprint can be found in the Annex. The systematic review was published at *BMC Medical Informatics & Decision Making* and a reprint can also be found in the Annex.

2.2 Pharmacovigilance Informatics

Inês Ribeiro-Vaz, Fabrício Alves, Ana Silva, Domingos Alves, Ricardo Correia

Encyclopedia of E-health and Telemedicine 2015

2.2 Pharmacovigilance Informatics

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Pharmacovigilance Informatics

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INTRODUCTION TO PHARMACOVIGILANCE INFORMATICS

All medicines have adverse effects, most of them unknown until the drug commercialization. As so, it is crucial to keep strategies to monitor the drug safety. Pharmacovigilance is the activity of drug surveillance, after its launch in the market, with the main goal of public health protection, ensuring that the drug benefit outweighs its risks. Worldwide, pharmacovigilance systems are mostly based on spontaneous Adverse Drug Reactions (ADR) reports made by healthcare professionals and consumers. Spontaneous ADR reporting has been described as an essential method to detect drug safety signals; however, underreporting is a major issue undermining the effectiveness of spontaneous reports. Several studies suggest that less than 10% of detected ADR are effectively reported to medicines regulatory authorities [e.g. Food and Drug Administration (FDA), European Medicines Agency (EMA), etc] (Hazell & Shakir, 2006; McGettigan, Golden, Conroy, Arthur, & Feely, 1997).

Tools used in pharmacovigilance are continually evolving and, worldwide, Information Systems (IS) to promote ADR reporting or to detect ADR occurred in healthcare institutions have been tested and used, such as software that allow voluntary and automated detection of ADR, tools that analyse clinical databases or Web sites that actively inform healthcare professionals (Molokhia, Tanna, & Bell, 2009).

In addition to the signal detection, ICT can also be used to encourage and facilitate reporting of suspected ADR, such as the creation of on-line reporting forms, development of tools to collect safety data from electronic health records (EHR), among others.

In this chapter, it will be described some tools to automatically detect ADR, or encourage ADR spontaneous report.

BACKGROUND ON PHARMACOVIGILANCE

Adverse Drug Reactions (ADR) defined as a response to a medicinal product which is noxious and unintended (WHO) are a well-recognized public health problem worldwide, and a major cause of death

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Introduction

All medicines have adverse effects, most of them unknown until the drug commercialization. As so, it is crucial to keep strategies to monitor the drug safety. Pharmacovigilance is the activity of drug surveillance, after its launch in the market, with the main goal of public health protection, ensuring that the drug benefit outweighs its risks. Worldwide, pharmacovigilance systems are mostly based on spontaneous Adverse Drug Reactions (ADR) reports made by healthcare professionals and consumers. Spontaneous ADR reporting has been described as an essential method to detect drug safety signals; however, underreporting is a major issue undermining the effectiveness of spontaneous reports. Several studies suggest that less than 10% of detected ADR are effectively reported to medicines regulatory authorities [e.g. Food and Drug Administration (FDA), European Medicines Agency (EMA), etc][7, 10].

Tools used in pharmacovigilance are continually evolving and, worldwide, Information Systems (IS) to promote ADR reporting or to detect ADR occurred in healthcare institutions have been tested and used, such as software that allow voluntary and automated detection of ADR, tools that analyse clinical databases or Web sites that actively inform healthcare professionals[11].

In addition to signal detection, IS can also be used to encourage and facilitate reporting of suspected ADR, such as the creation of on-line reporting forms, development of tools to collect safety data from electronic health records (EHR), among others.

In this chapter, it will be described some tools to automatically detect ADR, or encourage ADR spontaneous report.

Background

Adverse Drug Reactions (ADR) (defined as a response to a medicinal product which is noxious and unintended [6]) are a well-recognized public health problem worldwide, and a major cause of death and hospitalization in developed countries[12]. It is estimated that about 6,5% of the hospitalizations are related to ADR[13]. Besides, in the USA, about 100.000 people die each year due to ADR[12], and in Europe this annual mortality rate increases to 197.000[14]. ADR can be expressed in many ways and with different degrees of seriousness. An anaphylactic shock caused by penicillin is an example of a serious ADR (a serious ADR is any untoward medical occurrence that at any dose: results in death, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity or is life-threatening[6]). Another type of ADR, not always recognized as such, is the drug ineffectiveness, for example, a vaccination failure. This can be (or not) related with a product

quality issue and should be reported when detected in order to allow the regulatory authorities to take appropriate decisions.

Rare and long term ADR are difficult to detect during the drug development stage. Only when the drug begins to be used by a large population after marketing authorization it is possible to detect new ADR not previously identified during clinical trials. In reality, it is known that the safety of a new drug cannot be established until it has been on the market for several years[8]. Exceptionally, in a pandemic scenario, drug launch is urgent and, in this particular case, can be justifiable that drug safety profile is not well established. In this scenarios, it is even more important that all the detected ADR are reported (serious or not, expected or not). It is, therefore, essential to keep drugs under close surveillance, after its commercialization, through a pharmacovigilance system, to continuously evaluate their safety profile. In most of the European countries, pharmacovigilance system is based on spontaneous ADR reports, which is passive method, made by healthcare professionals and, since July 2012, also by consumers [15]. These reports can be made using paper, telephone, e-mail or through an on-line form and consist of a description of an Adverse Event (AE) apparently caused by a medicine.

To reverse the problem of underreporting of ADR, which is felt in most developed countries, several strategies have been tested[10, 16, 17]. Particularly, some studies were developed focused on educational interventions to raise awareness on the importance of ADR reporting[18-20] and showed to be very effective increasing the quantity and relevance of spontaneous ADR reports (among health professionals). However, these studies involved a large financial and personal outlay and the authors concluded that the effect was lost after a few months[10, 21].

In a recent American study, the authors developed a signal-detection strategy that combines the Adverse Event Reporting System (AERS) of the regulatory Authority (FDA) and EHR, by requiring signaling in both sources, with promising results[22]. Another study used the unstructured clinical notes included in EHR to detect ADR through a computerized system. The authors concluded that data mining can be used for hypothesis generation and for rapid analysis of suspected AE risk[23].

With a similar aim, a recent study used a physician's network, created through a mailing list, to send regular emails to doctors, with humorous component attached with informative component, recalling the importance of reporting their suspected ADR[24]. The results showed that this type of intervention has impact on the number of ADR reports made by these professionals (the study did not assess the relevance of reported ADR). In France, it is being

done a work that tries to facilitate the act to ADR reporting, habitually considered a tedious process by health professionals. The authors are using the information contained in EHR to make the semi-automatic filling of ADR notification forms. The objectives of this ongoing study is to increase the rate of ADR report, as well as improving the quality of information submitted to regulatory authorities[25].

Information Systems in Pharmacovigilance

Although some authors consider that ADR spontaneous reports suffers from latency and inconsistency, it is still considered as the most valuable method to early detect drugs safety problems. In fact, most of the decisions concerning to drug safety are triggered by daily ADR spontaneous reports. As so, Regulatory Authorities consider as crucial importance to achieve the greatest number of ADR reports possible and with high data quality.

The promotion of ADR report among healthcare professionals is a huge task, as it is necessary to regularly recall the importance of ADR reporting and, simultaneously, develop tools to facilitate this duty. Pharmacovigilance centres worldwide develop several strategies to continuously promote the importance of ADR reporting, as workshops, post-graduate courses, and also to make it easier, as development of online reporting forms, inclusion of electronic reporting systems into the hospital Information Systems (HIS), direct hyperlinks to online reporting forms, among others.

Along with the promotion of spontaneous ADR reporting, some systems are being tested to detect signals of adverse reactions in large databases, as hospitals databases, epidemiologic databases, or even among social networks.

Although the adoption of different strategies, it is consensual the need to obtain the highest quantity and quality of information about the safety of marketed drugs, for the protection of public health.

Another important issue in this field is the need to discuss/harmonize what should be recorded during an ADR report.

When analyzed the databases from the FDA, EMA and the Portuguese Northern Pharmacovigilance Centre (UFN, in portuguese), all of them with the same purpose of recording ADR reports, it was possible to realize that the variables are different between the 3 databases, as seen in the Table 1.

Table 1. Comparison of the variables included in three pharmacovigilance databases (Food and Drug Administration: FDA; European Medicines Agency: EMA and Portuguese Northern Pharmacovigilance Centre: UFN), grouped in main entities/sections (patients, problems, products and reporters)

Section	Variable	FDA	EMA	UFN
Patient	Patient identifier	✓	✓	✓
	Age at the time of event	✓	✓	✓
	Date of birth	✓	✓	✓
	Sex	✓	✓	✓
	Weight	✓	✓	✓
Problem	What kind of AE, product problem or error did you encounter?	- Adverse event - Product use error - Product problem - Problem with Different Manufacturer of the Same Medicine	---	---
	Outcomes Attributed to AE	- Death - Life-threatening - Congenital anomaly/birth defect - Disability or permanent damage - Hospitalization - Required intervention to prevent permanent impairment/damage - Other serious	- Fatal - Not recovered - Recovered with sequelae - Recovering - Recovered - Unknown	- Fatal - Not recovered - Recovered with sequelae - Recovering - Recovered - Unknown
	ADR Seriousness	---	- Yes - No	- Death - Life-threatening - Congenital anomaly - Results in persistent or significant incapacity - Hospitalization - Other serious
	Date of event	✓	✓	✓
	Describe events, problem, or product use error	✓	✓	✓
	Relevant test/laboratory data, including dates	✓	---	---
Product	Product name	✓	✓	✓
	Label strength	✓	✓	✓
	Manufacturer	✓	✓	✓
	Date of use	✓	✓	✓
	Reason for use	✓	✓	✓
	Problem went away after use stopped or dose reduced?	- Yes - No - Does not apply	---	✓
	Problem returned after person started taking or using the product again?	- Yes - No - Does not apply	---	✓
	Do you still have the product in case we need to evaluate it?	- Yes - No - Returned to Manufacturer	---	---
Reporter	Reporter name	✓	---	✓
	Address	✓	✓	✓

✓or list of options: Variable exists; ---: Variable does not exist.

For example, the concept of outcome for the FDA form as a similar meaning to the concept of seriousness for the two European databases analyzed. On the other hand, for these two databases, outcome means the evolution of the patient regarding the adverse scenario.

Active debate is maintained about this subject, aiming to create a standard to the information that should be kept during the ADR registry.

Promotion of Adverse Drug Reaction Reporting

Integration of pharmacovigilance system databases with other healthcare IS seems to be an obvious way to improve the knowledge about drugs safety. In fact, healthcare providers insert a lot of information in their EHR about ADR, which is not shared with pharmacovigilance systems. Every approach that promotes drug safety surveillance without increasing the workload of healthcare professionals, one of the main reasons for not reporting ADR, should be considered.

The creation and implementation of webservices to collect this information is one of the possible solutions for this problem. This solution is being tested in a Portuguese multi-center research project, in the field of gastrointestinal diseases[26], with promising preliminary results (See chapter 5). In this case, the physicians insert the usual clinic information during the appointment with the patient, and then, they only have to authorize the transmission of anonymized information about drug-related problems to the pharmacovigilance system. This tool allows ADR reporting without the need to fill the ADR reporting form and with no additional administrative work for the physician other than the normal registry of clinic patient data.

This solution is also available to be included in commercial prescription software. For the implementation of these webservices, it was necessary to map the form entries used by the doctors with the online ADR reporting form developed by the pharmacovigilance system, so that the information is correctly collected. This mapping would be easier if a standard as the one described in the previous section was already in use.

An ADR electronic reporting system included into a IS was developed in a Spanish hospital[27], allowing healthcare professionals (pharmacists, physician and nurses) to report suspected ADR through their usual IS. The biggest advantage of this system is that some data (already included in the IS) appears as default values into the form, which expedites the system and reduces transcription errors[28]. All the reports made by this system are reviewed by a pharmacist, which is responsible to confirm the included data and to report the case to

pharmacovigilance system. This might be a disadvantage, as some cases may be lost and not actually sent to regulatory authorities.

Another strategy that can be easily adopted is the inclusion of hyperlinks in the EHR to the online ADR reporting form. This solution was tested between 2006 and 2010, in an ecological study performed in 16 Portuguese hospitals centres[16]. The hyperlinks were included in either EHR or on computer desktops. Considering the hospitals with hyperlink included in the EHR, the median ADR reports per month significantly increased, from two (range 0–12) to five reports (range 1–17). The median of ADR reports per month using the online form also increased significantly, from one (range 0–5) before the intervention to four (range 1–17) after it. Moreover, serious ADR increased 3-fold, and non-previously described ADR increased 4.5-fold. None of these significant increases were observed in the hospitals where the hyperlink was not installed. It was also found a significant increase in daily pharmacovigilance centre website visits, from ten before the intervention to 27 after it ($p<0.001$). The increase in ADR reporting shows that the inclusion of hyperlinks to online ADR reporting forms is an easy way to change health professional behavior with regard to spontaneous ADR reports. Furthermore, this solution seems to be cost effective, when compared with other strategies to increase ADR report, as it has no running costs (after the hyperlink implementation, there are no additional costs to the pharmacovigilance system). (See chapter 4)

Clinical Decision Support and Alerting Systems

Informatics can be used in pharmacovigilance activities to support and alert healthcare professionals during their daily work. With the IS extensively used in health care institutions, all the improvements that can enhance patient safety should be taken into account. Clinical Decision Support Systems (CDSS), providing intelligently filtered knowledge in real-time, should be used in this area to improve public health and health care[29]. Besides, systems that triggered alerts of possible ADR can also be integrated in the IS with the same goal.

Many systems are used and tested worldwide to alert health providers about suspected ADR, which can help in the detection of drug safety problems. The exploitation of computer programs used in hospitals as a support in the detection of possible ADR[3, 4] is one of these systems. With this purpose, work has been developed in order to create lists of drugs used as ADR signals to support the detection of ADR in hospitals. The included drugs were chosen as they are mostly used as antidotes or therapeutic interventions for possible ADR. Furthermore, there are also lists of diagnosis that triggers an alert for possible ADR in the computer systems. These diagnoses indicate diseases that are mainly caused by drugs and, therefore, are signals of possible ADR. Besides the drugs and diagnosis, also laboratory values can help in ADR detection. In fact, some ADR are characterized by laboratory abnormalities, so the monitoring of these values can be an improvement in the promotion of drug safety among hospitalized patients. The main goal is to incorporate the described lists in the software used in the hospital pharmacies in order to be triggered an ADR alert each time an alerting drug is prescribed, or each time an alerting diagnosis is made or even each time a laboratory result reaches a suspected toxicity value[30, 31].

It has been advocated that EHR should be provided with CDSS in order to maximize its benefits to patient safety[29]. These CDSS are being used to inform physicians during the prescription about identified drug-drug interactions[32], patient allergies[33] or to support the prescribing decision[34, 35]. CDSS integrated in the computerized physician order entry (CPOE) can effectively prevent potential harmful medication errors and ADR [36, 37].

In particular, a Dutch CDSS is being in use at the hospital pharmacy to support hospital pharmacist to select patients at risk of ADR, and its effectiveness was evaluated[38]. For this purpose, the system retrieves data from IS, and uses clinical rules. During the study period, the CDSS generated 2650 safety alerts, 270 (10%) of them were considered as relevant. In these cases, the pharmacist contacted the physician or nurse and in 204 (76%) cases this led to an

advice to prevent a possible ADR. Most alerts were generated with clinical rules linking pharmacy and laboratory data (1685 alerts).

Pharmacovigilance should use informatics to promote and complement spontaneous ADR reporting. Worldwide, some strategies has been performed to reach this goal, as described in the next sub-chapter (sub-chapter 2.3).

2.3 How to Promote Adverse Drug Reaction Reports Using Information Systems – a Systematic Review and Meta-Analysis

Inês Ribeiro-Vaz, Ana-Marta Silva, Cristina Costa Santos, Ricardo Cruz-Correia

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2.3 How to Promote Adverse Drug Reaction Reports Using Information Systems – a Systematic Review and Meta-Analysis

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RESEARCH ARTICLE Open Access

How to promote adverse drug reaction reports using information systems – a systematic review and meta-analysis

Inês Ribeiro-Vaz[1,2*], Ana-Marta Silva[1,2], Cristina Costa Santos[2,3] and Ricardo Cruz-Correia[2,3]

Abstract

Background: Adverse drug reactions (ADRs) are a well-recognized public health problem and a major cause of death and hospitalization in developed countries. The safety of a new drug cannot be established until it has been on the market for several years. Keeping drug reactions under surveillance through pharmacovigilance systems is indispensable. However, underreporting is a major issue that undermines the effectiveness of spontaneous reports. Our work presents a systematic review on the use of information systems for the promotion of ADR reporting. The aim of this work is to describe the state of the art information systems used to promote adverse drug reaction reporting.

Methods: A systematic review was performed with quantitative analysis of studies describing or evaluating the use of information systems to promote adverse drug reaction reporting. Studies with data related to the number of ADRs reported before and after each intervention and the follow-up period were included in the quantitative analysis.

Results: From a total of 3865 articles, 33 articles were included in the analysis; these articles described 29 different projects. Most of the projects were on a regional scale (62 %) and were performed in a hospital context (52 %). A total of 76 % performed passive promotion of ADR reporting and used web-based software (55 %). A total of 72 % targeted healthcare professionals and 24 % were oriented to patient ADR reporting. We performed a meta-analysis of 7 of the 29 projects to calculate the aggregated measure of the ADR reporting increase, which had an overall measure of 2.1 (indicating that the interventions doubled the number of ADRs reported).

Conclusions: We found that most of the projects performed passive promotion of ADR reporting (i.e., facilitating the process). They were developed in hospitals and were tailored to healthcare professionals. These interventions doubled the number of ADR reports. We believe that it would be useful to develop systems to assist healthcare professionals with completing ADR reporting within electronic health records because this approach seems to be an efficient method to increase the ADR reporting rate. When this approach is not possible, it is essential to have a tool that is easily accessible on the web to report ADRs. This tool can be promoted by sending emails or through the inclusion of direct hyperlinks on healthcare professionals' desktops.

Keywords: Adverse drug reactions report, Information systems, Pharmacovigilance

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Abstract

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Background

Adverse drug reactions (ADRs) are a well-recognized public health problem worldwide and a major cause of death and hospitalization in developed countries[12]. Rare and long-term ADRs are difficult to detect during the drug development stage. Detecting new ADRs not previously identified during clinical trials is only possible when the drug begins to be used by a large population after marketing authorization (MA). The safety of a new drug cannot be established until it has been on the market for several years [8]. As such, it is indispensable to keep drug reactions under close surveillance after commercialization through a pharmacovigilance system to continuously evaluate the drug's safety profile. In most countries, the pharmacovigilance system is based on spontaneous ADR reports made by healthcare professionals and consumers [15]. These reports can be made using paper, telephone, e-mail or through an on-line form and consist of a description of an adverse event apparently caused by a medicine. Spontaneous ADR reporting has been described as an efficient method to detect drug safety signs [39]; however, underreporting is a major issue that undermines the effectiveness of spontaneous reports. Several studies have suggested that less than 10% of detected ADRs are effectively reported to medicine regulatory authorities [10, 40].

Worldwide, systems using informatics to promote ADR reporting or to detect the occurrence of ADRs in healthcare institutions have been tested and used, such as computer programs that allow voluntary and automated detection of ADR [4, 41] informatics tools created to analyse clinical databases [42] or websites that actively inform healthcare professionals [43].

In addition to signal detection, information and communication technologies can also be used to encourage and facilitate reporting of suspected ADR.

In the present work, a systematic review is presented on the use of information systems in pharmacovigilance. Our main goal is to describe the state of the art information systems for the passive or active promotion of adverse drug reaction reporting.

Methods

Eligible studies

Studies describing or evaluating the use of information systems to promote adverse drug reaction reports were selected.

Review team

The review team is composed of two pharmacists who are experts in pharmacovigilance (Inês Ribeiro Vaz (IV) and Ana Marta Silva (AS)) and the computer scientist Ricardo Cruz Correia (RC), who is an expert in medical informatics.

Search methods

Studies were searched in April 2014 in the bibliographic databases. We developed a search query that included the concepts adverse drug reaction, adverse drug reaction reporting system, pharmacovigilance and information system. Only articles written in English, Portuguese or French were included. We did not establish any criteria for the publication date.

Four distinct bibliographic databases were searched: Medline (via PubMed); ISI (ISI Web of Knowledge); IEEE (IEEE Xplore) and Scopus. The query search string used in Medline® was *((ADR OR "adverse drug reaction" OR "adverse drug reactions" OR "adverse drug event" OR "adverse drug events" OR "adverse dug effect" OR "adverse drug effects") OR "pharmacovigilance").* A similar query was used in the other databases and was adapted to the search engine.

Selection of studies for the review

The first selection was based on the study title and abstract (when available). Two reviewers on the review team (IV and AS) were involved in study selection and read all titles/abstracts. The study was considered eligible when at least one of the reviewers decided that the title/abstract mentioned the key concept of using information systems for ADR reporting. In cases of disagreement, a consensus meeting was held with the third reviewer (RC) to decide whether the article should be selected.

The second phase of study selection was based on the full text. The team leader (IV) reviewed each full-text article. In this stage, articles were excluded based on the following criteria: (1) the articles were only focused on medication errors; (2) the articles focused on ADR detection; (3) the articles were studies without any information system implemented; (4) the articles were studies concerning data quality; (5) the articles were studies focused on website

usability; (6) the articles were only the authors' reflections on the theme; (7) the articles were studies only related to incidents that occurred in health institutions; (8) the articles were studies concerning signal detection and (9) the articles were studies concerning electronic transmission between the authority and other institutions (pharmaceutical companies or regional pharmacovigilance centres).

The articles remaining after this review were included in the final statistical analysis.

These articles were grouped into research projects to avoid the distortion created by multiple papers describing the same project (Figure 1). All statistical analyses were based on the projects and not on the articles.

Definition of variables

The variables examined in these reviews were related to the projects, papers and information systems described in each project.

We used the following data for project identification: (1) project number; (2) Information system name (if any); (3) country; (4) publication date; (5) type of study and (6) reference(s).

According to the description of the projects, the following variables were analysed:

1. Area covered by the project (i.e., region, country, or hospital)
2. Type of action promoted by the project (passive promotion of ADR reporting or active promotion of ADR reporting)
3. Type of software (i.e., web-based or mobile)
4. Type of institution (i.e., regulatory authority or universities)
5. Target (healthcare professionals or patients)
6. Type of medicine (all, vaccines, chemotherapy, or others)
7. Type of ADR (all/serious ADRs based on the World Health Organization seriousness criteria[44])

Statistical analysis

The inclusion criteria for the quantitative analysis were the availability of data related to the number of ADRs reported before and after each intervention and a follow-up period.
Studies that only disclosed the increased ADR rate and studies that reported zero ADRs before the project implementation were excluded because it was not possible to perform the analysis in these cases.

For each study with available data, the rate of ADRs reporting increase (quotient between ADR reports after and ADR reports before) and the respective 95% confidence intervals were calculated. A rate of ADR reporting increase equal to 2 indicated that the ADR reports doubled after the intervention. Conversely, a rate of ADR reporting increase equal to 1 indicated that the number of ADR reports after the intervention was equal to the number of ADR reports before the intervention. The aggregated rate of the ADR reporting increase was calculated with the inverse variance method using a random effects model and a forest plot was presented. The confidence intervals, aggregated rate of ADRs and forest plot were performed using a Microsoft Excel spreadsheet. The description of the Microsoft Excel spreadsheet and the respective statistical methods used were described by Neyeloff[45].

Results

Our search method found 2519 articles in PubMed, 68 in IEEE, 2603 in ISI and 192 in Scopus. After eliminating duplicate articles, 3835 articles were selected.

Two reviewers (IV and AS) read all 3835 titles/abstracts. In cases of disagreement, which occurred with 151 articles, a consensus meeting was held with the third reviewer (RC) to decide whether the article should be selected.

A total of 643 studies were excluded because they were not related to pharmacovigilance, 85 were excluded because they were not related to information systems and 2993 were excluded for other reasons (mostly because their focus was on data mining in large databases instead of ADR reporting).

A total of 114 of the 3835 articles were selected in this first selection based on the title and abstract.

The team leader (IV) reviewed each of the 114 full-text articles. After this review, 33 articles remained for the final statistical analysis. At this stage, most of the articles were excluded because: (1) they were only related to medication errors; (2) they were focused on ADR detection; (3) they were studies without any information system implemented; (4) they were studies concerning data quality; (5) they were studies focused on website usability; (6) they were only authors' reflections on the theme; (7) they were studies only related to incidents that occurred at health institutions; (8) they were studies concerning signal detection or (9) they were studies concerning electronic transmission between the authority and other institutions (pharmaceutical companies or regional pharmacovigilance centres).

These 33 articles were grouped into 29 distinct research projects to avoid the distortion created by multiple papers describing the same project (Figure 1.). All statistical analyses was based on projects and not on articles.

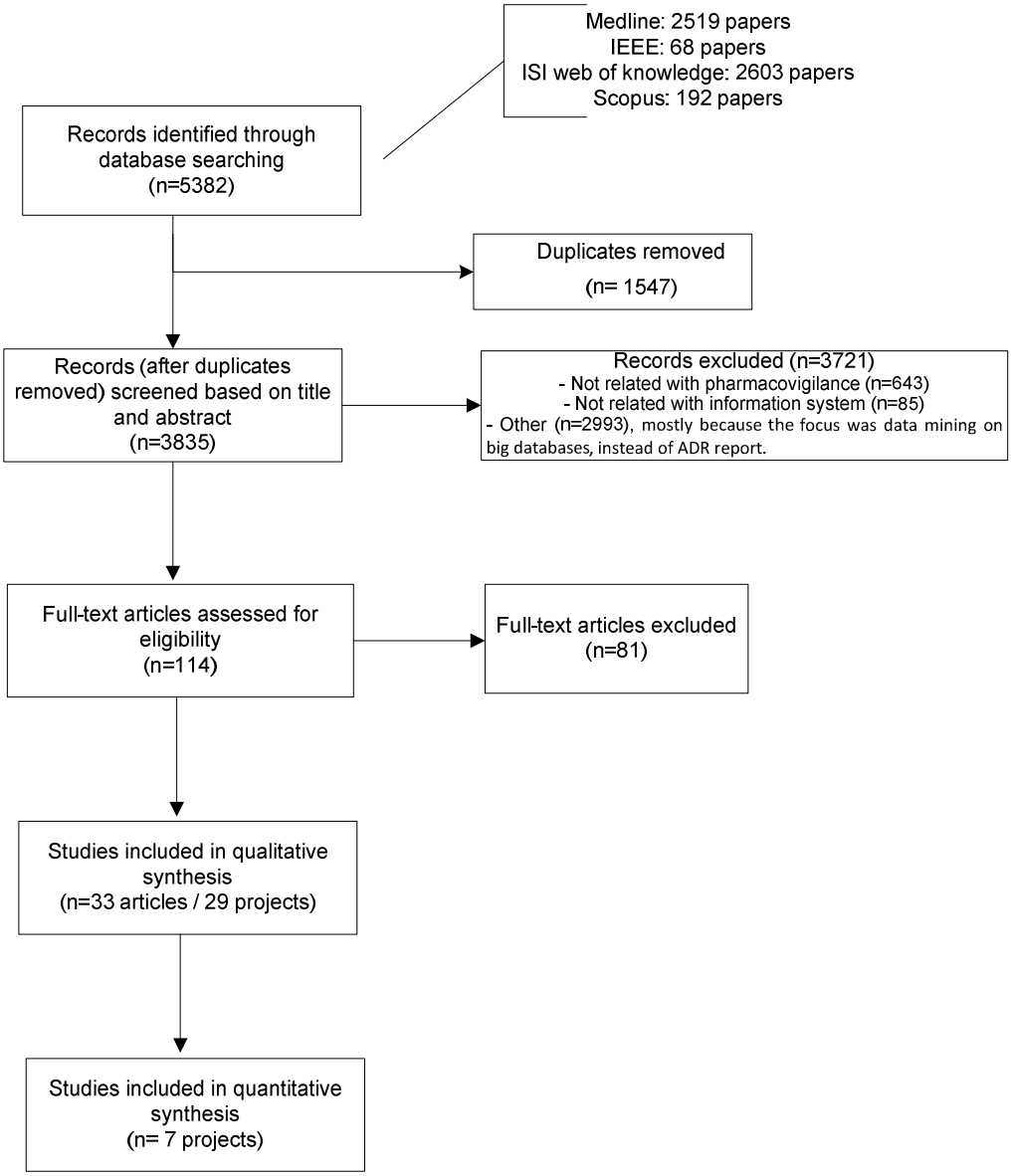

Figure 1. Flowchart of study selection

Table *2* lists all 29 projects, their country, the number of publications, the publication year and the journal. The country with the most published projects was the USA (11), followed by the United Kingdom (3).

Trends

There was an increasing trend in publication, especially after 2009, as seen in Figure 2.

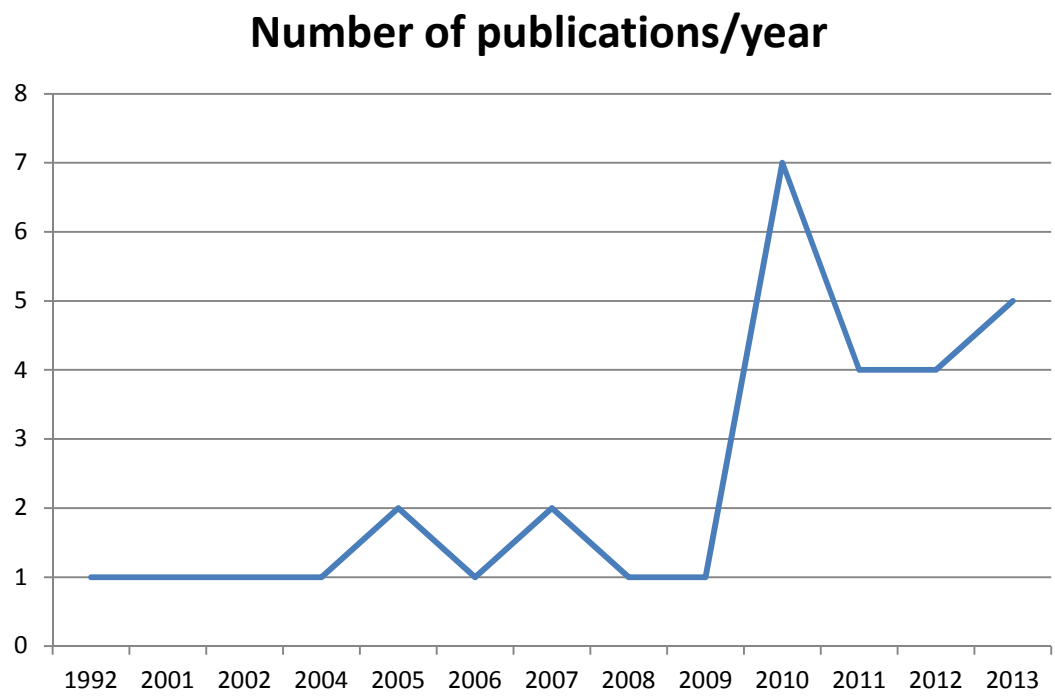

Figure 2. Number of publications by year

Table 2. Project identification

Project number	System name (if any)	Country	Number of publications	Publication date(s)	References	Journals
4		USA	1	1992	[4]	Hospital pharmacy
28		France	1	2001	[46]	Fundamental & Clinical Pharmacology
11		Japan	1	2002	[47]	Yakugaku Zasshi-Journal of the Pharmaceutical Society of Japan
17		USA	1	2004	[48]	American Journal of Health-System Pharmacy
2		USA	3	2005, 2007	[49-51]	Journal of Clinical Oncology, Journal of American Medical Information Association
22		USA	2	2005, 2006	[52, 53]	Biosecurity and Bioterrorism-Biodefense Strategy Practice and Science, Health Expectations
10		USA	1	2007	[54]	Journal of the American Medical Informatics Association
9	MEADERS	USA	2	2007, 2010	[55, 56]	Annals of Family Medicine, AMIA Annual Symposium proceedings
21		Spain	1	2008	[27]	Annals of Pharmacotherapy
7		Sweden	1	2009	[57]	European Journal of Clinical Pharmacology
5		Canada	1	2010	[58]	International Journal of Medical Informatics
13		Canada	1	2010	[59]	Vaccine
18		USA	1	2010	[60]	Pharmacoepidemiology and Drug Safety
19		United Kingdom	1	2010	[61]	Archives of Disease in Childhood
23	ALIAS	USA	1	2010	[62]	Contemporary Clinical Trials
27		Taiwan	1	2010	[63]	Value in Health
8		United Kingdom	1	2011	[64]	Journal of Psychiatric and Mental Health Nursing
12		Serbia	1	2011	[65]	Drug Safety
14		France	1	2011	[66]	Therapie
15		USA	1	2011	[67]	Paediatrics
6		United Kingdom	1	2012	[68]	Drug Safety
16		Korea	1	2012	[69]	Yonsei Medical Journal.
20		Portugal	1	2012	[16]	Drug Safety
25		USA	1	2012	[70]	2012 Ninth International Conference on Information Technology: New Generations
1		Cambodge	1	2013	[71]	Journal of Medical Internet Research
3		Netherlands	1	2013	[72]	Studies in health technology and informatics
24	SALUS	France	1	2013	[73]	Studies in health technology and informatics
26		Spain	1	2013	[74]	International Journal of Clinical Pharmacy
29		Denmark	1	2013	[75]	European Journal of Hospital Pharmacy-Science and Practice

Qualitative analysis

The qualitative variables analysed in each project are listed in Table 3 and described below. Globally, we found that there was an increase in the publication of projects over the study period, with 4 projects published before 2001, 4 projects between 2005 and 2007, 8 projects between 2008 and 2010 and 13 projects between 2011 and 2013.

Geographic area covered by the projects

Most of the projects were regional (62%), followed by national projects (34%). We found only 1 international project based on Facebook®. This international project was developed in the last time period (2011-2013).

Areas covered by the projects

Most of the projects (52%) were developed in hospitals, followed by community projects (21%). A total of 14% covered primary care institutions and 10% (3 projects) were developed for use in any type of healthcare institution. One project was dedicated to a multicentre clinical trial. We also found that all of the projects oriented to the community were developed in the last three years (2011-2013).

Types of actions promoted by the projects

The majority of the projects passively promoted ADR reporting (76%); the remainder actively promoted reporting (24%).

Types of software

More than half of the projects (55%) used web-based technology and 41% used electronic health records. Only one project used mobile phone technology. There was an increasing trend in software using web-based technology over all of the time intervals considered. The mobile technology appeared during the last time period.

Types of institutions promoting the studies

Most of the projects were promoted by hospitals and universities (31% e*x aequo*). There were 4 projects developed by national institutions (not regulatory) and 5 projects implemented by regulatory authorities.

Targets

A total of 72% of the projects were geared to healthcare professionals, 24% to patients and one project was geared to both targets. Most of the projects targeting patient ADR reporting were developed in the last years considered (2011-2013).

Types of medicine

Most of the projects (72%) covered all medicines, but 17% were specific to vaccines. There were also projects specific to reporting ADRs due to chemotherapy, human albumin and radiopaque agents (1 project for each of these medicines).

Types of ADR

Only a small percentage of the projects were specific for serious adverse drug reactions. The majority (93%) covered all ADR.

Table 3. Qualitative analysis of the projects

Variable	Time period				Total (%)	Project numbers
	<2004 4 projects	2005-2007 4 projects	2008-2010 8 projects	2011-2013 13 projects		
Geographic area covered by the project						
Regional	4	3	5	6	18 (62)	2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 20, 21, 22, 26, 27, 28, 29
National	0	1	3	6	10 (34)	1, 3, 6, 9, 15, 18, 19, 23, 24, 25
International	0	0	0	1	1 (3)	12
Area covered by the project						
Hospital	4	2	5	4	15 (52)	2, 4, 5, 8, 11, 13, 17, 18, 20, 21, 22, 26, 27, 28, 29
Community	0	0	0	6	6 (21)	1, 3, 12, 14, 15, 16
Primary care	0	2	1	1	4 (14)	6, 7, 9, 10
Other healthcare institutions *(different from hospitals or primary care)*	0	0	1	2	3 (10)	19, 24, 25
Clinical trials	0	0	1	0	1 (3)	23
Type of action promoted by the project						
Passive promotion of ADR reporting	3	3	6	10	22 (76)	4, 5, 6, 8, 9, 10, 11, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 29
Active promotion of ADR reporting	1	1	2	3	7 (24)	1, 2, 3, 7, 12, 13, 28
Type of software						
Web-based	1	3	6	6	16 (55)	2, 3, 5, 7, 9, 12, 13, 14, 15, 16, 19, 20, 22, 23, 27, 28
System inside the Electronic Health Record	3	1	2	6	12 (41)	4, 6, 8, 10, 11, 17, 21, 24, 25, 26, 18, 29
Mobile	0	0	0	1	1 (3)	1
Type of institution promoting the study						
Hospital	2	1	3	3	9 (31)	2, 4, 8, 17, 18, 21, 26, 27, 29
University	1	1	3	4	9 (31)	5, 10, 11, 12, 13, 19, 20, 24, 25
National institution	0	2	0	2	4 (14)	1, 9, 15, 22
Regulatory authority	1	0	1	3	5 (17)	6, 7, 14, 16, 28
Other*	0	0	1	1	2 (7)	3, 23
Target						
Healthcare professionals	4	2	7	8	21 (72)	4, 6, 7, 8, 9, 10, 11, 13, 14, 16, 17, 18, 19, 21, 23, 24, 25, 26, 27, 28, 29.
Patients	0	2	1	4	7 (24)	1, 2, 3, 5, 12, 20, 22
Healthcare professionals and patients	0	0	0	1	1 (3)	15
Type of medicine						
All	4	1	5	11	21 (72)	3, 4, 5, 6, 7, 8, 9, 11, 12, 14, 16, 17, 18, 19, 20, 21, 24, 25, 26, 28, 29
Vaccines	0	2	1	2	5 (17)	1, 10, 13, 15, 22
Chemotherapy	0	1	0	0	1 (3)	2
Human albumin	0	0	1	0	1 (3)	23
Radiopaque agents	0	0	1	0	1 (3)	27
Type of ADR						
All	4	4	8	11	27 (93)	2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29
Serious	0	0	0	2	2 (7)	1, 3

*Other institutions are: Clinical trial team (project 23) and website producer (project 3)

Quantitative analysis

From the 29 projects analysed, seven projects met the criteria for inclusion in the quantitative analysis (meta-analysis). The criteria used were the availability of data related to the number of ADR reported before and after each intervention and a follow-up period.

From the seven projects included in the quantitative analysis, six had the same follow-up period (12 months) and only one (project 14) differed on this item (18 months of follow-up). The results are described in Table 4.

Table 4. Effect of Intervention on increased ADR reporting

Study	ADR reports before	ADR reports after	Rate	CI lower	CI upper
Project 14	287	415	1,44	-0,18	3,07
Project 7	89	111	1,25	-0,51	3,00
Project 29	30	162	5,4	4,56	6,24
Project 6	3279	4716	1,44	-0,20	3,072
Project 17	118	294	2,49	1,25	3,73
Project 27	20	62	3,1	1,99	4,21
Project 20	82	212	2,58	1,37	3,80

We performed a meta-analysis with these seven projects to calculate the aggregated measure of the ADR reporting increase. The overall measure was 2.1 (95% IC 1.7-2.6), which indicated that the interventions performed in the analysed projects doubled the number of ADR reports (Figure 3).

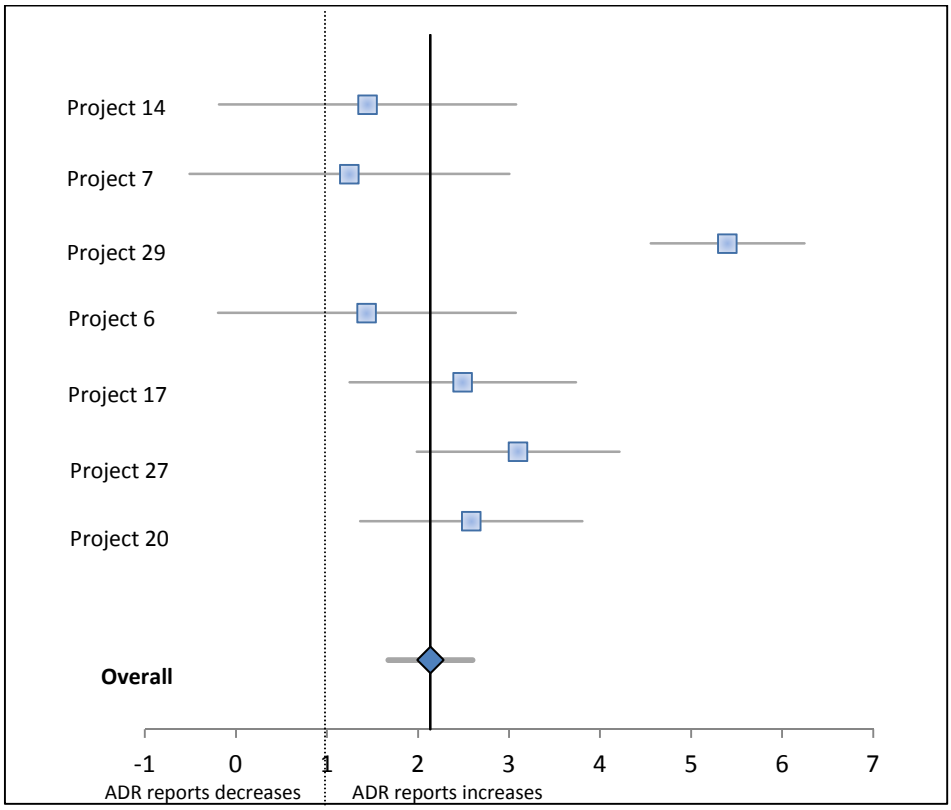

Figure 3. Rate (ADR reports after/ADR reports before) of ADR report increase (95% IC)

Projects 14, 7 and 6, which had similar ADR reporting increases, used different approaches. The authors of project 14 assessed an online ADR reporting form, in project 7 the authors send repeated e-mails with ADR information to healthcare professionals and project 6 evaluated the inclusion of a reporting system inside the clinical information system.

Four of the information systems that contributed to the improvement of ADR reporting used web-based technology. Two used an online reporting form (Project 14 [66] and Project 27 [63]) to facilitate ADR reporting. A Swedish group opted to evaluate the effect of repeated emails to health care professionals that contained attached ADR information (Project 7 [57]). A Portuguese study tested the inclusion of hyperlinks to the online ADR reporting form on hospitals' electronic patient records (Project 20 [16]) to facilitate access to the ADR form.

Three projects explored the use of electronic health records to directly report the ADRs (projects 29, 6 and 17). Among these, project 29 [75], which had the best result in terms of the ADR reporting increase, was a system that completed the ADR report whenever a physician required assistance.

Discussion

Although a limited number of projects was included in our work (n=29), our data suggest that the number of projects that aimed to promote ADR reporting using information technologies increased over time.

Study selection was performed as a manual review; this approach caused a huge workload because we obtained more than 3000 articles. An optimized query would reduce the workload but lose sensitivity.

As expected, most of the projects that aimed to promote adverse drug reactions reporting were developed in hospitals and tailored to healthcare professionals. In fact, most of the serious ADRs were detected in hospitals and reported by healthcare professionals[72]. For example, in Europe direct reporting (ADRs reported by patients) has only been allowed for every country since 2012[76]. This finding may also explain why most of the projects that targeted direct ADR reporting were developed in the last three years of the study period (2011-2013)[65, 67, 71, 72].

Most of the authors chose to develop systems for the passive promotion of ADR reporting because busy healthcare professionals only submit their suspected ADR if it does not increase their workload[55, 77]. Active promotion of ADR reporting is difficult and not always ethically acceptable because no material reward can be given to the reporters. Thus, projects that aimed to actively promote ADR reporting involved teaching sessions[50] or e-mails containing ADR information[46, 57, 59, 72].

Our results suggested that there was an increasing trend in the use of web-based software to promote ADR reporting, which could be explained by the dissemination of internet use. Nevertheless, mobile technology was also appearing.

Most of the retrieved projects covered all medicines and ADR, whereas only a few were specific. However, we found 5 projects dedicated to vaccine adverse reactions[52, 54, 59, 67, 71] and in the last three years two projects were developed to specifically report serious ADR[71, 72].

The institutions that primarily promoted this work were universities and hospitals because universities have the know-how to perform these actions and hospitals have specific needs to be solved. However, regulatory authorities have been increasing their involvement in the development of this type of project.

A limitation of this study is that a grey literature search was not performed. However, we think that this lack does not cause a large bias because regulatory authorities are less likely to

produce this type of project. When regulatory authorities are involved in projects of this scope, they usually associate with universities and hospitals that have a greater incentive to publish.
Based on our quantitative analysis, we can conclude that all of the projects analysed increased the ADR reporting numbers (most by approximately two-fold). We found two projects that increased ADR reporting by more than two-fold [63, 75], perhaps because their basal values were much lower compared with the other five projects. A similar effect was noted previously in two other studies when the same population of health care professionals was exposed to the same educational interventions two different times [18, 20]. After the first intervention, the authors achieved a much higher effect and ADR reporting increased compared to the second intervention due to the differences in the initial values.

In our quantitative analysis, we found a limitation concerning the aggregation of the information because we found only 7 studies that provided data concerning its impact on the increase in ADR reporting. These data were not available for the other studies even after we contacted the authors. However, we did not identify any variable that could distinguish these 7 projects from the other 22 projects. We must reiterate the importance of providing quantitative data when publishing studies focused on interventions that aim to promote ADR reporting.

Worldwide underreporting of ADR is a major concern, and many institutions are aware that it is feasible to use information systems to improve ADR reporting. The most commonly used platform is web-based and exhibits an increasing trend, but interventions inside electronic health records also have the potential to improve pharmacovigilance activities and particularly ADR reporting. Direct ADR reporting is being increasingly taken into account when the aim is to improve information on drug safety.

Based on our results, we believe that it would be useful to adopt a system to assist healthcare professionals with completing ADR reporting within electronic health records because this approach seems to be an efficient method to increase the ADR reporting rate. When this approach is not possible, it is essential to have a tool that is easily accessible on the web to report ADR. This tool can be promoted by sending emails or through the inclusion of direct hyperlinks on healthcare professionals' desktops.

Conclusions

Our systematic review allowed us to note some facts about interventions that aim to improve ADR reporting using information systems. According to our aggregation analysis, these interventions doubled the number of ADR reports. We also found that most projects passively promoted ADR reporting (facilitating the reporting process) and the countries involved in this type of project were Northern America countries (USA and Canada), European countries and in a smaller number Far East countries.

Authors' contributions

Inês Vaz and Ricardo Correia were responsible for the development of the query.

Inês Vaz also performed data collection and was the team leader for article screening and the writing of the manuscript.

Ana Silva performed the article screening.

Ricardo Correia was involved on the article selection when there was disagreement between the other two reviewers (Inês Vaz and Ana Silva).

Cristina Santos performed the quantitative analysis.

All four authors were involved in the writing of the manuscript, discussion and the revision of the whole article.

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Competing interests: The authors declare that they have no competing interests.

Chapter 3 - Promoting ADR reports: Comparison of different approaches

Inês Ribeiro-Vaz, Cristina Costa Santos, Ricardo Cruz-Correia

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3 Promoting ADR reports: Comparison of different approaches

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Promoting adverse drug reaction reporting: comparison of different approaches

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ABSTRACT

OBJECTIVE: To describe different approaches to promote adverse drug reaction reporting among health care professionals, determining their cost-effectiveness.

METHODS: We analyzed and compared several approaches taken by the Northern Pharmacovigilance Centre (Portugal) to promote adverse drug reaction reporting. Approaches were compared regarding the number and relevance of adverse drug reaction reports obtained and costs involved. Costs by report were estimated by adding the initial costs and the running costs of each intervention. These costs were divided by the number of reports obtained with each intervention, to assess its cost-effectiveness.

RESULTS: All the approaches seem to have increased the number of adverse drug reaction reports. We noted the biggest increase with protocols (321 reports, costing 1.96 € each), followed by first educational approach (265 reports, 20.31 €/report) and by the hyperlink approach (136 reports, 15.59 €/report). Regarding the severity of adverse drug reactions, protocols were the most efficient approach, costing 2.29 €/report, followed by hyperlinks (30.28 €/report, having no running costs). Concerning unexpected adverse drug reactions, the best result was obtained with protocols (5.12 €/report), followed by first educational approach (38.79 €/report).

CONCLUSIONS: We recommend implementing protocols in other pharmacovigilance centers. They seem to be the most efficient intervention, allowing receiving adverse drug reactions reports at lower costs. The increase applied not only to the total number of reports, but also to the severity, unexpectedness and high degree of causality attributed to the adverse drug reactions. Still, hyperlinks have the advantage of not involving running costs, showing the second best performance in cost per adverse drug reactions report.

DESCRIPTORS: Drug-Related Side Effects and Adverse Reactions. Forms and Records Control. Drug Monitoring. Adverse Drug Reaction Reporting Systems. Pharmacovigilance.

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3.1 Abstract

Objective: To describe different approaches to promote adverse drug reaction reporting among health care professionals, determining their cost/effectiveness.

Methods: We analyzed and compared several approaches taken by the Northern Pharmacovigilance Centre (Portugal) to promote adverse drug reaction reporting. Approaches were compared regarding the number and relevance of adverse drug reaction reports obtained and costs involved. Costs by report were estimated by adding the initial costs and the running costs of each intervention. These costs were divided by the number of reports obtained with each intervention, to assess its cost-effectiveness.

Results: All the approaches seem to have increased the number of adverse drug reaction reports. We noted the biggest increase with protocols (321 reports, costing 1.96 € each), followed by first educational approach (265 reports, 20.31 €/report) and by the hyperlink approach (136 reports, 15.59 €/report). Regarding the severity of adverse drug reactions, protocols were the most efficient approach, costing 2.29 €/report, followed by hyperlinks (30.28 €/report, having no running costs). Concerning unexpected adverse drug reactions, the best result was obtained with protocols (5.12 €/report), followed by first educational approach (38.79 €/report).

Conclusions: We recommend implementing protocols in other pharmacovigilance centers. They seem to be the most efficient intervention, allowing receiving adverse drug reactions reports at lower costs. The increase applied not only to the total number of reports, but also to the severity, unexpectedness and high degree of causality attributed to the adverse drug reactions. Still, hyperlinks have the advantage of not involving running costs, showing the second best performance in cost per adverse drug reactions report.

3.2 Introduction

Adverse drug reactions (ADR) are inherent to medicines use [78], and most of them can only be detected after the commercialization of the drug [8]. In fact, during clinical trials, rare reactions are hardly detected, as well as the ones associated with chronic utilization of the drug. It is also difficult to predict the drug effect among special populations (pregnant, children, elderly), as they usually are not part of the clinical research.

Because of these limitations, post-marketing surveillance is essential, which is why most countries have pharmacovigilance centres for monitoring of detected ADR. The fundamental tool used by these centres is the spontaneous report of ADR, made by healthcare professionals and consumers. This method consists in describing an adverse episode suspected to be caused by one or more drugs, and provides valuable information to the regulatory health authorities, which is important for the decisions about marketed medicines. The biggest problem of this method is the underreporting, ie, ADR are detected but not reported to national regulatory health authorities. Most developed countries suffers from this problem [10, 40], and Portugal is not an exception [19]. Worldwide, many approaches have been completed to combat the major problem of ADR underreporting, such as regular visits to health professionals [79], questionnaire studies [80], educative interventions (including workshops, meetings and presentations) [19, 81, 82], among others.

This study aims to describe several approaches that intended to improve ADR reporting and determine the cost-effectiveness of each one of them.

3.3 Methods

From its creation (in 2000) to 2003, Northern Pharmacovigilance Centre, a Portuguese regional pharmacovigilance centre, had an extremely low rate of ADR reports, about 43 ADR reports per year/1 million of inhabitants. We realize this value is very low, when compared with the World Health Organization (WHO) recommendation for an Optimal National Centre which is, at least, 200 reports per year/1 million of inhabitants[1].

To reach its objectives, in 2004, the Centre established a collaboration protocol (*protocol approach*) with the Immunoallergology Department of a Central Hospital (located on the same street as the Centre), in order to collect every suspected case of ADR emerged in appointments related to drug allergies. This collaboration includes regular visits of the pharmacovigilance staff to the Immunoallergology department, to collect the detected cases in ADR report forms, under the physician supervision. Then, the form is signed by the physician and it follows the normal course of all the ADR spontaneous reports. This approach was replicated two more times, in 2007 and 2009, in two other immunoalergology departments, one from a specialized hospital (pediatric hospital, located at 6 km from the Centre), and another from a central hospital (located 11 km from the Centre). These three protocols remain active.

A study conducted in 2004 provided educational interventions (educational approach) for physicians and pharmacists [19, 20]. Those interventions were based on a previous case-control study that identified the reasons for underreporting [83, 84]. The educational approach includes workshops about pharmacovigilance at health care professionals' working places.

Since the effect of educational interventions decreased over time, the authors of the previously described work promote reinforcement interventions (educational and telephone approach). We started a new study in 2007, also among physicians and pharmacists. This study consisted not only in outreach interventions (workshops), but also in telephone interviews [17, 18]. The phone interviews followed a script about ADR and the importance of reporting. Details are described in a previous publication [18].

Meanwhile, we propose a new approach: the inclusion of a hyperlink (*hyperlink approach*) to an online ADR reporting form on hospitals' electronic patient records (EPRs). The main aim of this study, performed from 2006 to 2010 was to evaluate the impact of these hyperlinks on the number of spontaneous ADR reports[16]. The inclusion of hyperlinks began in December 2007 and continued over the following five months.

[1] Farmacovigilância em Portugal. Lisboa: INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.; 2004.

The temporal distribution of all these approaches is shown in Figure *4*

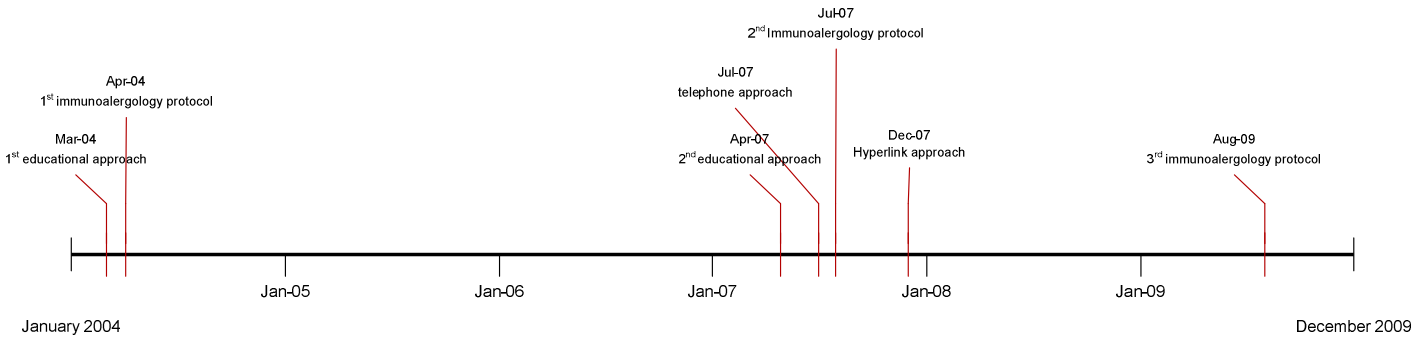

Figure 4. Timeline of the studied approaches

In the present work, we analyzed the number of ADR reports obtained with each one of the described approaches. We know exactly which ADR reports were originated at the three departments participating in the protocol intervention and analyzed them separately. Four physicians were involved.

The first educational intervention (in 2004) involved three hospitals, 26 healthcare centres and 73 pharmacies. About 900 healthcare professionals attended these interventions [19]. About 340 healthcare professionals (physicians and pharmacists) attended the second intervention (second workshop + telephone, both in 2007). Five healthcare centres, two hospitals and 40 pharmacies received the telephone intervention, and 16 healthcare centres, 2 hospitals and 23 pharmacies were intervened with the 2nd educational intervention.

For the hyperlinks, we estimated 15,000 health care professionals potentially affected by the intervention, as this is the total number of professionals working at the 12 participating hospital centers (corresponding to 22 hospitals). It was the first exposure to any intervention for eight of these hospital centers.

The variables analyzed were: type of approach, ADR relevance, initial costs of the interventions, running costs of the interventions, and costs per ADR report. Each of these variables is described as follows.

Type of approach: hyperlink approach, protocol approach, educational and telephone approach.

Number of ADR reports obtained with each intervention: the difference between ADR reports received two years after the intervention and ADR reports received two years before the intervention.

ADR relevance: we adopted the following criteria: (1) ADR seriousness; (2) ADR expectedness; and (3) causality attributed to the ADR report. A serious ADR is any untoward medical occurrence that results in death, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent, or significant disability or incapacity, or is life-threatening[2]. An unexpected ADR is the one which the nature or severity is not consistent with domestic labeling or market authorization, or expected from characteristics of the drug[2]. According to the causality attributed we considered that an ADR was more relevant if it was evaluated with one of the 2 higher degrees of causality: Definitive/certain or probable (the evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction)[2].

Interventions initial costs: We consider as initial costs the expenses needed for the establishment of the approach, as educational material and staff working hours. These costs are described in Table 5.

Table 5. Estimated values of each approach

Approach	Initial costs		Annual running costs	
	Value	**Description**	**Value**	**Description**
protocol approach	150€	pharmacovigilance and clinical services staff working hours	240€	fuel, material and pharmacovigilance and clinical staff working hours
hyperlink approach	2120€	pharmacovigilance and software development staff working hours	---	---
educational approach	200€	educational material and pharmacovigilance staff working hours	2500€	fuel, material and pharmacovigilance staff working hours
telephone approach	400€	telephone calls during the pilot-study and pharmacovigilance staff working hours	800€	telephone calls, material and pharmacovigilance staff working hours

Interventions running costs: Annual running costs are the expenses needed for the continuation of the projects, as fuel, material and staff working hours. These costs are described in table 1. In our study, we did not consider the normal (daily) costs of ADR reports processing, as we only meant to compare the costs involved to obtain ADR reports.

[2]World Health Organization. The Uppsala Monitoring Centre Uppsala WHO Collaborating Centre for International Drug Monitoring [09 Aug 2013]; Available from: http://www.who-umc.org/DynPage.aspx?id=22682.

Costs per ADR report: Costs for ADR report were calculated adding initial costs and running costs. Initial cost per ADR report were obtained by dividing initial costs by the difference between the ADR reports received two years after the intervention and ADR reports received two years before the intervention (which we consider to have been the number of reports earned with each intervention). Running costs were obtained by dividing the running costs of the two-year intervention by the number of notifications earned with each intervention. To assess the cost/effectiveness of each intervention, we considered these added costs (initial + running costs), as this total means the total cost of each ADR obtained in two years following each intervention.

The pharmacovigilance center website uses a web server and has audit trails that read each site visit since 2006. These audit trails are processed using the Webalizer program (www.webalizer.org) to estimate site hits, user logins and visits. ADR reports obtained by these approaches are included in a database. We collect them by selecting the report date and origin.

We presented the total number of reports received in each quarter during the period studied. For each health institution, ADR reports made before and after the intervention, if any, were measured.

To examine whether each intervention increased the ADR report trend, an interrupted time series analysis using autoregressive integrated moving average (ARIMA) was performed using quarter data of ADR reports, as well as each intervention (first and second educational approach, telephone approach, and hyperlink approach) as dichotomous variables (before and after intervention).

We performed an additional analysis with the hyperlinks approach, to consider the institutions exposed to any type of intervention for the first time. With this sub-analysis we intended to isolate the ADR reports obtained with each intervention.

This study was approved by the local Ethics Committee of the Faculdade de Medicina of the Universidade do Porto (Process PCEDCSS-FMUP 08/2014, approved in May 7, 2014).

3.4 Results

We found an increasing trend in the number of ADR reports received by the Northern Pharmacovigilance Centre (UFN) during the studied period: 2000-2012. The number of annual ADR reports increased from the year in which the first interventions were made (2004) to the end of the study period (Figure 5).

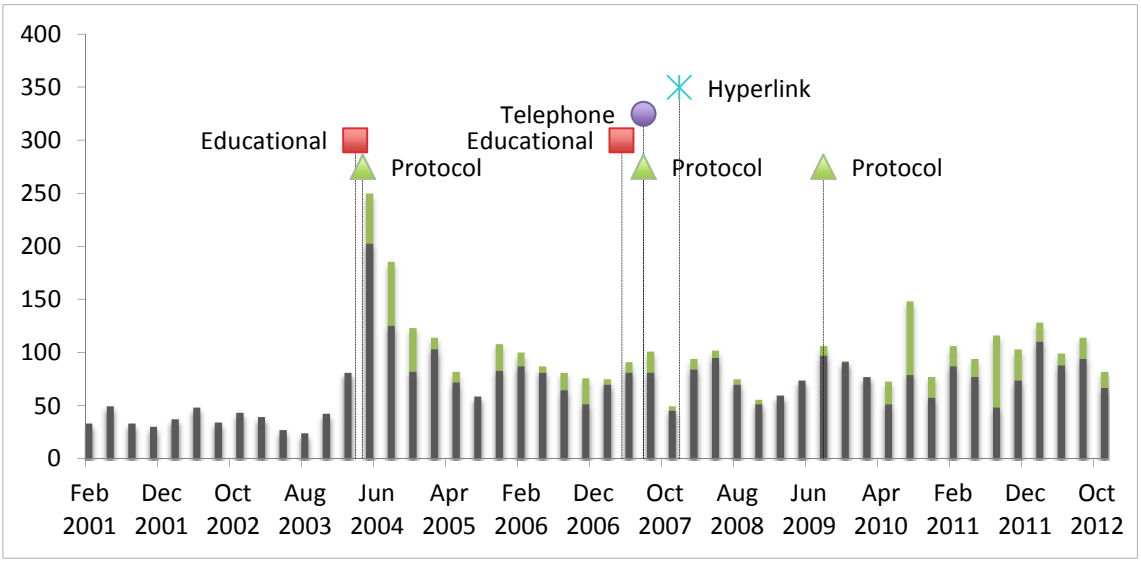

Figure 5. Total number of ADR reports received in the Northern Pharmacovigilance Centre during the studied period, per trimester (in green, those obtained with protocols)

Excluding the ADR reports obtained with the protocols approaches, the only intervention that significantly increased the ADR report trend was the first educational approach, in the first quarter of 2004 ($p<0.001$).

We did not found a significantly increase in the ADR report trend in the second educational approach in second quarter of 2007 ($p=0.203$). The telephone approach also failed to significantly increase ADR reporting in third quarter of 2007 ($p=0.243$). With the hyperlink approach we observed a slight increase in the ADR reporting, although without statistical significance ($p=0.193$).

All the approaches increased the number of ADR reports, when we compare the two years before with the two years after the interventions. We noted the biggest increase with the protocol approach (321 ADR reports obtained), followed by the first educational approach, with 265 ADR reports obtained, and by the hyperlink approach, with 136 ADR reports. For the hyperlink approach, we isolated the institutions exposed to an intervention for the first time; these cases obtained 141 ADR reports.

According to the initial costs involved, our results suggest that the protocol approach is the most cost-effective, costing 0.47€ per ADR report, followed by the first educational approach costing 0.78€ per ADR report. Analyzing running costs, the hyperlinks approach is the most favorable, having none. On the other hand, we can conclude that the second educational approach is the intervention that entails more costs, with 123.81€ per report (Table 6.)

Table 6. Number and costs of ADRreports obtained with each intervention

Approach	**Intervention**	**ADR**				**Costs (€) per report**		
		Before		After				
		2 years	1 year	1 year	2 years	Initial costs	Running costs (2 years)	Total
Protocols		0	0	204	117	0.47	1.49	1.96
Hyperlinks		153	120	277	132	15.59	0.00	15.59
*Hyperlinks NPE**		*68*	*47*	*146*	*110*	*15.03*	*0.00*	*15.03*
Educational	1st workshop	36	24	257	68	0.78	19.53	20.31
	Pharmacies	2	8	110	25	1.60	40.00	41.60
	Healthcare centres	25	7	102	17	2.29	57.47	59.77
	Hospitals	9	9	45	26	3.77	94.34	98.11
Phone Interview		47	26	87	34	8.33	33.33	41.67
	Pharmacies	23	10	37	14	22.22	88.88	111.11
	Healthcare centres	3	1	8	2	66.67	266.67	333.33
	Hospitals	21	15	42	18	16.67	66.67	83.33
Educational	2nd workshop	54	40	106	30	4.76	119.05	123.81
	Pharmacies	39	25	69	18	8.70	217.39	226.09
	Healthcare centres	10	13	26	6	22.22	555.55	577.78
	Hospitals	5	2	11	6	20.00	500.00	520.00

** NPE: Not Previously Exposed. Considering only the institutions without any previous intervention*

Regarding the relevance of ADR reports, we analyzed the seriousness, expectedness and degree of causality attributed to the ADR report. Regarding serious ADR, the protocol approach was the most cost-effective, costing 2.29€ per report. The hyperlink approach obtained the second lowest value (30.28€ per report), having no running costs cost. We found similar results for the relevance criterion of causality assessment. Concerning ADR expectedness, the best result belonged to the protocol approach (5.12 € per report), followed by the first educational approach (38.79€ per report). (Table 7)

Table 7. Number and costs of serious, ADR classified with a high degree of causality and unexpected ADR reports obtained with each intervention

Approach	**Intervention**	**ADR**				**Costs (€) per report**		
		Before		After				
		2 years	1 year	1 year	2 years	Initial costs	Running costs (2 years)	Total
Serious								
Protocols		0	0	180	94	0.54	1.75	2.29
Hyperlinks		113	96	193	86	30.28	0.00	30.28
Educational	1st workshop	12	15	111	42	1.59	32.68	34.27
Phone Interview		29	19	55	21	14.29	57.14	71.43
Educational	2nd workshop	37	23	44	8	---	---	---
High degree of causality								
Protocols		0	0	165	66	0.65	2.08	2.73
Hyperlinks		114	86	232	109	15.03	0.00	15.03
Educational	1st workshop	14	17	169	47	1.08	27.03	28.11
Phone Interview		40	17	65	26	11.76	47.06	58.82
Educational	2nd workshop	37	27	74	22	6.25	156.25	162.5
Unexpected								
Protocols		0	0	70	53	1.22	3.90	5.12
Hyperlinks		63	40	69	37	706.67	0.00	706.67
Educational	1st workshop	10	7	111	40	1.49	37.30	38.79
Phone Interview		17	11	22	7	400.00	1600.00	2000.00
Educational	2nd workshop	24	17	28	6	---	---	---

3.5 Discussion

Although there is some overlap of interventions, making it difficult sometimes to differentiate the gains from each one of them, our results show that, in general, all interventions increased the number of ADR reports when comparing two years before with two years after.

Protocols in hospital immunoallergology departments seem to be the most efficient intervention. In fact, this intervention is the one that allows obtaining ADR reports with lower costs involved, with an increase not only in the total number of ADR reports, but also in the severity, unexpectedness, and high degree of causality attributed to the ADR.

Nevertheless, these protocols have the disadvantage of increasing the reports of ADR in patients of a specific population (patients with allergies), which can bias the global pharmacovigilance data. We started to establish these protocols at the request of one of the immunoallergology department, but we are trying to establish similar protocols in other departments (as oncology departments, hospital pharmacies, among others), to solve the bias issue.

On the other hand, hyperlinks approach has the great advantage of not involving running costs, and seems to have the second best performance in costs per ADR report. Even when we consider only the hospitals exposed to an intervention for the first time (to avoid the overlap effect), this behavior remains.

We also conclude that the first educational intervention was much more efficient than the second one. In fact, the second intervention seemed to be counterproductive, as shown by the results of serious and unexpected ADR reports (these numbers decreased after the intervention). We already had this conviction since this intervention was performed. In fact, in most health care institutions where the second intervention took place, we found professionals less receptive than in the first intervention, as they already knew the subject and did not seem to believe they needed another workshop about it.

Unfortunately, we are not able to compare our results with other authors' results, as we failed to find any study addressing the issue of ADR report costs. Many studies proposed strategies to improve ADR reports [57, 66, 75] and some authors have already studied the costs of an ADR[85, 86]. However, no one had studied the costs involved in obtaining ADR reports before, which is the novelty of our work.

Although there might be some overlap and eventual contamination among the interventions, we believe that this did not introduce an important bias in our conclusions. First, we knew

exactly which reports were originated at the departments participating in the protocols. Moreover, we included in our results the ADR reports obtained after the hyperlink inclusion in the hospitals that had an intervention for the first time. Thus, we could infer that the gain in ADR reports after hyperlink inclusion was caused by this intervention. Furthermore, there is no problem of overlapping for the first educational approach (workshops in 2004) because this was the first intervention made. The only interventions for which we cannot resolve the overlapping limitation is the second educational intervention and the phone intervention. However, these two interventions were planned as complementary to the first one.

We believe that our work can help pharmacovigilance centers worldwide choose the best set of interventions to promote adverse drug reactions report. This choice must be based on the particular characteristics of each center, such as available staff and budget, geographic location, proximity to hospitals, among others.

Based on our results, we recommend the implementation of protocols with hospital immunoallergology departments, as they seem to be the most cost-effective intervention, followed by hyperlinks to ADR reporting forms, and the promotion of educational interventions to health care professionals for the first time.

Chapter 4 - Promoting spontaneous ADR reporting in Hospitals using a hyperlink to the on-line reporting form.

Inês Ribeiro-Vaz, Cristina Santos, Altamiro da Costa-Pereira, Ricardo Cruz-Correia

Drug Saf. 2012

4. Promoting spontaneous Adverse Drug Reaction reporting in Hospitals using a hyperlink to the on-line reporting form: An ecological study in Portugal

SHORT COMMUNICATION

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0114-5916/12/0005-0387/$49.95/0

Promoting Spontaneous Adverse Drug Reaction Reporting in Hospitals Using a Hyperlink to the Online Reporting Form

An Ecological Study in Portugal

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Abstract

Background: Spontaneous adverse drug reaction (ADR) reporting has been described as an efficient method to detect drug safety signals. However, under-reporting is a major issue undermining the effectiveness of spontaneous reports. Among hospitalized patients, ADRs are a particularly serious problem because these patients are often treated with more than one drug, and these drugs are often new and aggressive.

Objective: To promote spontaneous ADR reporting by healthcare professionals working in hospitals in the northern regions of Portugal, we propose the inclusion of a hyperlink to an online ADR reporting form on hospitals' electronic patient records (EPRs). The main aim of this study was to evaluate the impact of these hyperlinks on the number of spontaneous ADR reports to the Northern Pharmacovigilance Centre (UFN – Unidade de Farmacovigilâ ncia do Norte). We also assess the number of daily UFN website visits before and after the inclusion of the hyperlinks.

Methods: An ecological study was performed in northern Portuguese hospitals from 2006 to 2010. The hyperlinks were included in either EPRs or on computer desktops. The median of spontaneous ADR reports (total and online) per month and the respective ranges were presented before and after the intervention in all hospitals in this study. The comparisons were performed using the Mann-Whitney U-test.

Results: Sixteen hospital centres were involved in the study (27 hospitals). Eleven centres (18 hospitals) included the hyperlinks. Considering the hospitals with hyperlink access to the EPRs, the median ADR reports per month significantly increased, from two (range 0 –12) to five reports (range 1 –17). The median of ADR reports per month using the online form also increased

4.1 Abstract

Background: Spontaneous Adverse Drug Reactions (ADR) reporting has been described as an efficient method to detect drug safety signs. However, underreporting is a major issue undermining the effectiveness of spontaneous reports. Among hospitalized patients, adverse drug reactions are a particularly serious problem, because these patients are often treated with more than one drug, and with new and aggressive drugs.

Objective: In order to promote spontaneous ADR reporting by healthcare professionals working in northern region Portuguese hospitals, we propose the inclusion of a hyperlink to an on-line ADR reporting form on the Electronic Patient Records (EPR) of hospitals. The main aim of this work is to evaluate the impact of these hyperlinks in the number of spontaneous ADR reports to Northern Pharmacovigilance Centre (UFN – Unidade de Farmacovigilância do Norte). We also assess the number of UFN web site daily visits before and after the hyperlinks inclusion.

Methods: An ecologic study was performed in the Northern Portuguese Hospitals from 2006 to 2010. The hyperlinks were included either in EPR or computers desktops. The median of spontaneous ADR reports (total and on-line) per month and respective range were presented before and after the intervention in all hospitals. The comparisons were performed using the Mann-Whitney U test.

Results: There were 16 hospital centres involved in the study. Eleven centres (18 hospitals) included the hyperlinks. Considering the hospitals with hyperlink, the median ADR reports per month significantly increased, from 2 (range 0-12) to 5 reports (range 1-17). The median of ADR reports using the on-line form per month also increased significantly, from 1 (range 0-5) before the intervention to 4 (range 1-17) after it. Moreover, serious ADR increased 3 fold, and non-previously described ADR increased 4.5 fold. None of these significant increments were observed in the other hospitals without the hyperlink. We also found a significant increase of UFN web site daily visits from 10 before the intervention to 27 after it ($p<0.001$).

Conclusions: The increase in ADR reporting shows that the inclusion of hyperlinks to on-line ADR reporting forms is an easy and cost-effective way to change health professional behaviours on ADR spontaneous report.

4.2 Introduction

Background

Adverse Drug Reactions (ADR) are a well-recognized public health problem worldwide, and a major cause of death and hospitalization in developed countries [12]. In fact, rare and long term ADR are difficult to detect during the drug development stage. Only when the drug begins to be used by a large population after Marketing Authorization (MA), it is possible to detect new ADR not previously identified during clinical trials. In reality, it is known that the safety of a new drug cannot be established until it has been on the market for several years [8]. As such, it is indispensable to keep drug reactions under close surveillance, after its commercialization, through a pharmacovigilance system.

In Portugal, this system is based on spontaneous ADR reports made by healthcare professionals and, since 2012, also by consumers[15]. These reports can be made using paper, telephone, e-mail or through an on-line form[87] and consist of a description of an adverse event supposedly caused by a medicine. Spontaneous ADR reporting has been described as an efficient method to detect drug safety signs [39]. However, underreporting is a major issue undermining the effectiveness of spontaneous reports. Several studies suggest that less than 10% of detected ADR are effectively reported to medicines regulatory authorities [10, 40]. Besides, spontaneous ADR report rate in Northern Portugal was 90 reports/million inhabitants in 2009, which is highly unsatisfactory according the World Health Organization recommendations (200 reports/million inhabitants [88]).

Worldwide, systems using informatics to promote ADR reporting or to detect ADR occurred in healthcare institutions have been tested and used, such as computer programs that allow voluntary and automated detection of ADR[4, 89], informatics tools created to analyse clinical databases[90], or Web sites that actively inform healthcare professionals[43].

Among hospitalized patients, adverse drug reactions are a particularly serious problem. In fact, these patients are often treated with more than one drug, and with new and aggressive drugs. In spite of this, there are no specific systems for monitoring or reporting ADR in Portuguese hospitals. According to the characteristics of Portuguese Healthcare Professionals, we believe that making the reporting system easier would increase considerably the number of ADR reports.

Intending to promote spontaneous ADR reporting by healthcare professionals working in hospitals, we propose the inclusion of a hyperlink to an on-line ADR reporting form [part of the Northern Pharmacovigilance Centre (UFN) web site] on the Electronic Patient Records (EPR) or on the desktop of hospital computers. With this system, we expected to reach not only the physicians, but also the pharmacists and nurses working at the hospitals. In Portuguese hospitals, pharmacists has an important role in ADR detection and reporting, because physicians discuss with them the adverse events that occurred during medical treatment, asking for alternative drugs available at the pharmacy. Besides, some pharmacists are part of the clinical visit and detect ADR.

Aim

Our main aim is to evaluate the impact of the hyperlinks implemented in Portuguese hospitals in the number of ADR reported by these hospitals using the hyperlink or not, and in the visits to the UFN web site.

4.3 Methods

Intervention

Hyperlinks to the ADR on-line reporting UFN form were proposed to the 18 Northern Portuguese Hospitals Centres. The hyperlinks can be included either in healthcare professional specific software (typically EPR or Pharmacy specific applications used by doctors, nurses and pharmacists), or at the computer desktop (see Figure 6 for examples of both situations). It should be noticed that most of the Portuguese EPR are web-based and so the hyperlink opens the UFN form in a new browser window.

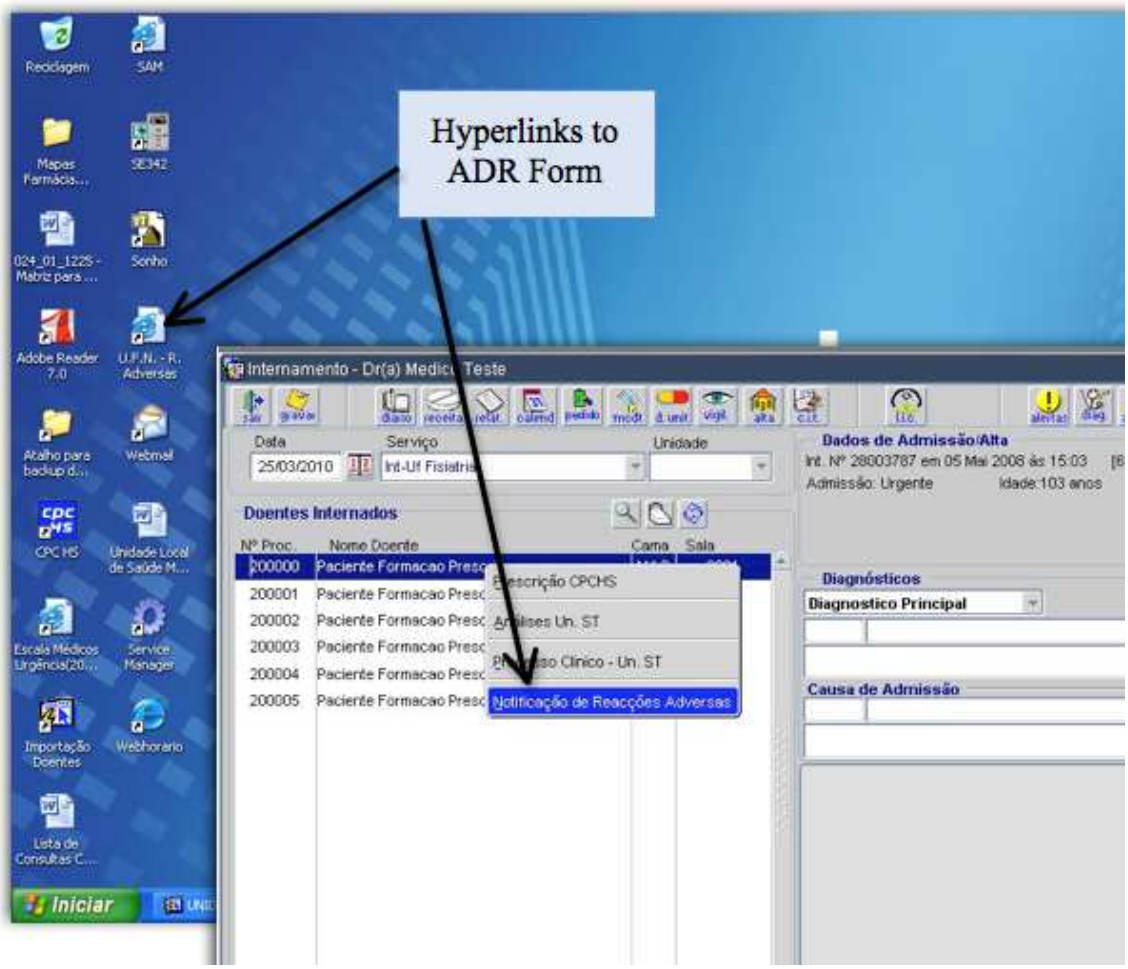

Figure 6. Two examples of hyperlinks in a computer desktop (back image), and on an Electronic Patient Record (front image)

The on-line reporting UFN form requires the health professional to login with their personal account. The patient data is collected in an anonymous way (only the initials of the patient name are required aiming to help the health professional identify each case) and the data is secured in an Oracle database with proper access restrictions.

In the beginning of October 2007 a letter was sent to the chief physicians of the 18 Northern Portuguese Hospital Centres suggesting the inclusion of the hyperlink. If there was no answer in two weeks, clinical administration boards were reminded by telephone. Thirteen centres forwarded this issue to the respective informatics departments and only one to the pharmaceutical department. Five of them have not answered until the end of 2010. After the approval by the hospital board and the forward to the respective departments, UFN made a third contact in order to explain technical doubts and to send the specific hyperlink of each Hospital.

Study design and data collection

An ecologic study was carried out in the Northern Portuguese Hospitals from 2006 to 2010. The number of spontaneous ADR reports and on-line spontaneous ADR reports originated in hospitals were analysed before and after an intervention without a control group. Five hospital centres implemented the hyperlink on December 2007 and the other 6 implemented it during the next 5 months. We considered 23 months before and the 31 months after each hospital implementation.

The UFN web site uses an Apache web-server having the web logs related to the site visits recorded since January 2006. These logs were initially processed using Webalizer software (www.webalizer.org) to calculate site hits, users and visits.

Telephonic interviews with the informatics departments of each hospital were performed to collect where each institution putted the hyperlink to the UFN website, and screen-shots illustrating the interventions were taken.

Variables

The main variables collected for analysis were:

- Date – date and time of the ADR report;
- Hospital – institutions were the ADR was detected;
- Health professional – type of the health professional that reported (doctor, nurse, pharmacist and others);
- Seriousness – seriousness of ADR grouped in “Serious” or “Non-serious” according to the WHO criteria;
- Previous knowledge – was the ADR previously described on the Summary of Product Characteristics or not.

Bias

From the initial 18 centres (31 hospitals), we excluded 4 hospitals that established other cooperation protocols with UFN in order to avoid possible confounder’s bias (see Figure 7). For the other 16 hospitals, we believe that there were no external interventions that could potentially explain the observed results.

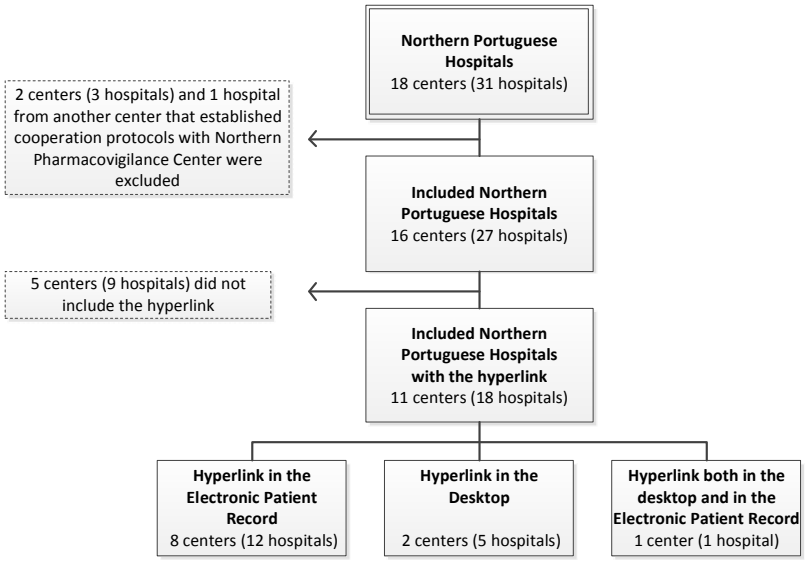

Figure 7. Diagram describing the hospitals and hospital centres of the Portuguese northern region included and excluded from the study.

Statistical methods

The number of spontaneous ADR reports and on-line spontaneous ADR reports per month were compared between the two periods (before and after the intervention). The number of ADR reports per quarter before and after the installation of the hyperlinks was presented graphically (see Figure 8). The number of ADR reports per quarter in the excluded hospitals and in the hospitals that did not participate (did not installed the hyperlinks) was also presented graphically.

Median values of number of daily UFN web site visits were reported because of the skewed distribution of data. The number of daily UFN web site visits was compared before and after the intervention using the Mann-Whitney U test.

A significance level of 0.05 was used.

4.4 Results

Participants

From the 16 centres involved in the study, 11 centres (18 hospitals) included the hyperlinks. Eight centres included the hyperlink only in the EPR, two centres included the hyperlink in the computer desktop and one included in both desktop and EPR (see Figure 7). From the 18 involved hospitals one is a University hospital and three are specialized hospitals.

Main results

Considering the 16 centres that implemented the project, the median of ADR reports per month, significantly increased after the project implementation. In fact, before the intervention the median of total ADR reports per month was 2, range from 0 to 12, and 31 months after the intervention was 5, range from 1 to 17 (p=0.043). Four months after the project implementation the median number of reports per month was 4.

Considering only the reports using the on-line form, before the project implementation the median of total on-line ADR reports per month was 1, range from 0 to 5, and after the intervention was 4, range from 1 to17 (p=0.009).

Figure 8 shows the number of ADR reports per quarter before and after the intervention and Figure 9 presents the number of ADR reports per quarter in the excluded hospitals and in the hospitals that did not installed the hyperlinks.

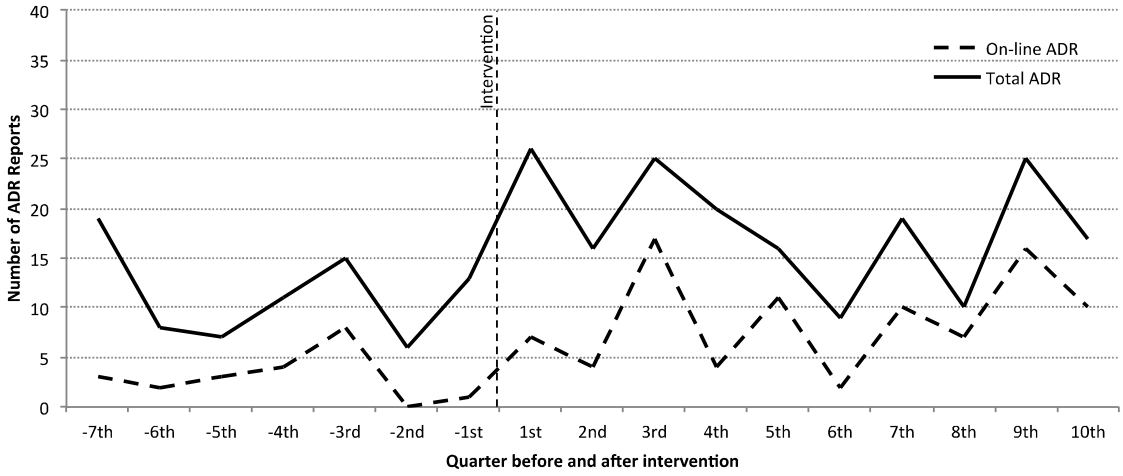

Figure 8. Evolution of ADR reports (total and just on-line) in hospitals with the intervention. The quarters were adjusted for the time of intervention. 5 hospitals centres implemented the hyperlink on Dec. 2007, 2 on Jan. 2008, 1 on Feb., 1 on Mar., 1 on Apr. And 1 on May

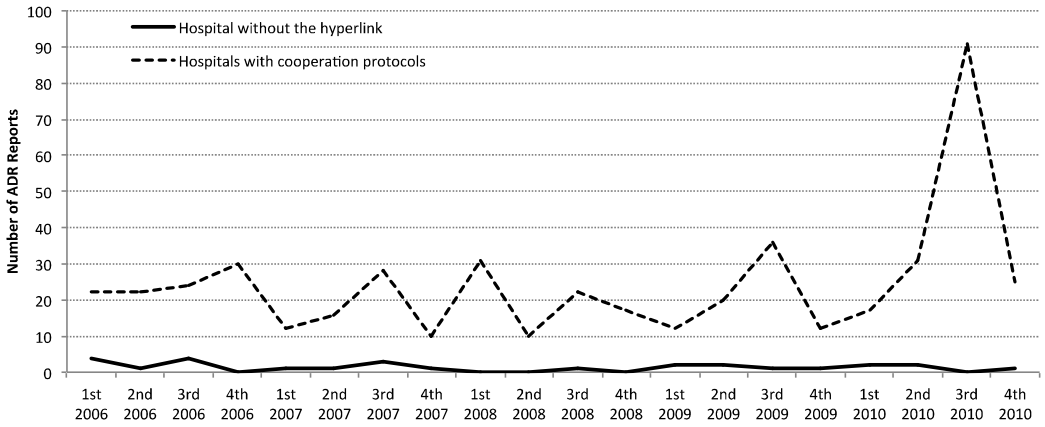

Figure 9. Evolution of ADR reports in the excluded hospitals (with cooperation protocols) and in the hospitals that did not install the hyperlinks

The 11 included centres, reported 17 in 23 months serious ADR using the on-line form before the intervention, and 69 in 31 months (increase of 3 fold) after the intervention. Before the intervention these centres reported 7 non-previously described ADR using the on-line form and reported 42 after (increase of 4.5 fold).

The hospital with the larger increase of ADR reports submitted on-line was the one that included the hyperlink in both EPR and desktop, with a mean of 3 on-line reports per year before the intervention and 18 after. The three hospitals that included the hyperlink in the desktop (one of them simultaneously with EPR) were in the top five of hospitals with higher increasing of ADR reports submitted on-line.

There were no ADR reports sent both by paper and on-line by the same professional.

Other analysis

There was a significantly increase of UFN web site daily visits after the intervention ($p<0.001$). Before there was a median of 10 UFN web site daily visits and after increased to 27.

4.5 Discussion

Our results show that the inclusion of hyperlinks to an on-line ADR reporting form on the EPR does change health professional behaviours on ADR report. In reality, there was an increase in ADR reporting in the hospitals involved in this project both in the total amount of ADR reports (more than 2 fold), in the amount of ADR reports submitted on-line (4 fold), in serious ADR reported on-line (3 fold) and non-previously described (more then 4 fold). Additionally, daily visits to the UFN website increased about 3 fold after the intervention.

A similar intervention based on changing the EPR of a hospital to facilitate ADR reporting is presented in Ortega et al.[27]. The measured impact was higher as they moved from zero to 1.6 ADR per month in just one hospital when compared with our ADR reporting growth. We argue that this difference may be due to the fact that they were able to fine-tune the EPR to increase ADR reporting as they had more control over the application, whilst in our case we were limited to placing hyperlinks in existing heterogeneous EPR. Therefore, our approach seems more easily widespread as hospitals are known to have many different information systems[91] and a national pharmacovigilance institution is probably not able to impose the changes described in Ortega el al.[27] to most commercial EPR.

In the study by Figueiras et al.[92], which was performed in the same region as our own, an educational intervention to improve physician reporting is described, namely by performing outreach visits to groups of health professionals. Their results present a very expressive increase (90 fold) in ADR reporting in the intervention group, and 30 fold in serious ADR. When compared with our results, it is clear that the educational intervention has proven to be much more effective, but also to need more resources (human and financial). Also, the effectiveness of these interventions appears to decrease through time. In the study Pedrós et al.[93], an educational (periodic meetings) and economic incentives intervention was initiated in 2003. Their results present an increase of 5.6 folds in all ADR, and 2 fold in serious ADR. Their impact is similar to our study but again using more financial resources.

When compared with other types of interventions, being those just educational[92] or combined with economic incentives[93], our intervention seems to have less impact although more long-lasting and less expensive.

As an additional outcome, we can see that the hospital with higher increasing of ADR reports submitted on-line was the one that included the hyperlink in the EPR and desktop, simultaneously. According to our results, the computer desktop seems more efficient than the EPR to place the hyperlink. It is the authors' opinion that these improvements could also be effective in other countries, because we think they are more related to generic usage of graphical user interfaces than to local practices.

It should also be noticed that making the ADR forms easily accessible might also potentiate other future ADR reporting promotion initiatives that can now take advantage of the visibility to the users of the hyperlink. Therefore, we argue that our solution is cost-effective, appropriate for widespread use in many healthcare institutions and for consistent increase over time.

Limitations

In some hospitals, we found out that although the hyperlink was included, the professionals did not know about it. In the near future we aim to increase the knowledge of the hyperlink by informing more actively health professionals using flyers to send to the hospitals, posters to be placed, and an e-mail showing specifically how to find the hyperlink. Another problem detected was the impossibility to use the hyperlink in some hospitals because the users did not have permission to access to Internet.

Future work

To solve the problem of not being able to access the Internet, we are now developing Web-services [94] to be used by other systems available at hospitals intranets. With this tool, it will not be necessary to access the UFN web site, and health care professionals can simply use the existing information systems as proposed in Ortega et al. [27]. With this future work, we expect to eliminate all the technical obstacles to ADR report, further increasing the reporting rate. Meanwhile, we also aim to implement this project in Northern Portugal primary care healthcare centres and providing the hyperlink to general practitioners and nurses.

Conclusions

The inclusion of hyperlinks in computer desktops and EPR to on-line ADR reporting forms is an easy and cost-effective way to change health professional behaviours on ADR spontaneous report. Actually, daily visits to the UFN website significantly increased after the hyperlinks inclusion, but, even more important, the amount and relevance of ADR reports significantly increased after the hyperlink inclusion in the hospitals involved in this project.

Acknowledgements

The authors would like to thank all the people involved in including the hyperlinks in the EPR and desktop, namely the hospital IT departments and Pedro Farinha for the log analysis, and also to the reviewers for their valuable comments.

Author contributions

Inês Ribeiro-Vaz was responsible for most of the intervention and data collection. Cristina Santos performed the statistical analysis. Altamiro Costa-Pereira and Ricardo Cruz-Correia supervised the writing of the paper. Ricardo Cruz-Correia also conceptualized the interventions.

Chapter 5 – Using webservices to link electronic clinical records to pharmacovigilance databases

Inês Ribeiro-Vaz, Ricardo João Cruz-Correia

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5. Using webservices to link electronic clinical records to pharmacovigilance databases

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Using Web Services to Link Electronic Clinical Records to Pharmacovigilance Databases

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Abstract

Purpose: Adverse Drug Reaction (ADR) reporting is an efficient method to assess the safety of drugs. However, underreporting is a major issue undermining the effectiveness this method. Among patients with Inflammatory Bowel Disease (IBD), ADR are a serious problem, because these patients are often treated with new and potent drugs. Electronic registries usually include information on ADR, recorded by physicians. To promote ADR reporting by gastroenterologists working in a multicentre IBD study group, we proposed the utilisation of a web service in their usual Electronic Health Records (EHR) to collect ADR. The aim of this work was to describe the impact of this intervention on the number of ADR reported to the regulatory authority through a regional pharmacovigilance centre.

Methods: A study was performed between 2013 and 2015. A web service was created and implemented in an EHR in use. We analysed the trends and type of ADR reported through this service.

Results: From April 2013 to February 2015, 167 ADR reports were sent to the Northern Pharmacovigilance Centre through the web service, comprising 10% of the total ADR reports received in the same period. Of these, 118 cases were serious (one was life-threatening). In the northern region of Portugal, GEDII physicians reported 9 ADR during the 23 months previous to web service implementation and 121 ADR during the 23 months after web service implementation, i.e. an increase of 81%.

Conclusions: This solution allowed for reporting 167 ADR during the first 23 months of implementation, simply by clicking a button included in the usual EHR used by gastroenterologists. These results suggest that information systems (IS) should facilitate the reporting of ADR.

Keywords: Adverse Drug Reactions; Inflammatory Bowel Disease; Pharmacovigilance; Electronic Health Records

Introduction

All medicines have adverse effects, some of them unknown until the drug is commercialised. Thus, it is crucial to implement strategies to monitor drug safety. Pharmacovigilance is the activity of drug surveillance, after its launch onto the market, with the main goal of public health protection, ensuring that the drug benefit outweighs its risks. Worldwide, pharmacovigilance systems are mostly based on spontaneous ADR reports made by healthcare professionals and consumers. Spontaneous ADR reporting has been described as an essential method to detect drug safety signals; however, underreporting is a major issue undermining the effectiveness of spontaneous reports. Several studies suggest that fewer than 10% of detected ADR are effectively reported to medicine regulatory authorities (e.g. Food and Drug Administration - FDA, European Medicines Agency - EMA, etc.) [1,2].

It is known that, one of the main reasons why healthcare professionals do not report ADR is due to an increase in their workload [3,4]. So, in order to reduce ADR reporting efforts, Information Systems (IS) to promote ADR reporting or to detect ADR in healthcare institutions have been tested and used, such as software for voluntary and automated detection of ADR, tools that analyse clinical databases or web-sites that actively inform healthcare professionals [5]. Information and communication technologies can also be used to facilitate and promote ADR reporting, such as the creation of on-line reporting forms and the development of tools to collect safety data from Electronic Health Records (EHR), among others [6,7].

In Portugal, there is a multi centre research project, in the field of gastric diseases (Study Group of Inflammatory Bowel Disease – GEDII) [8] whose members use the same electronic health record to collect patient information. As these patients are often treated with new and potent drugs (e.g. immunomodulating agents), the EHR has a field related to medication and ADR. Since the group members already fill in this field, it was considered an advantage to create a tool to send the data to the pharmacovigilance system.

Aim

The aim of this work was to implement and describe the implementation of a web service in an EHR to collect ADR reports and analyse the number of ADR reports sent to the Portuguese regulatory authority (INFARMED), through a regional pharmacovigilance centre.

5.1 Abstract

Purpose: Adverse drug reaction (ADR) reporting is an efficient method to assess the safety of drugs. However, underreporting is a major issue undermining the effectiveness of this method. Among patients with inflammatory bowel disease (IBD), ADR are a serious problem, because these patients are often treated with new and potent drugs. Electronic registries usually include information on ADR, recorded by physicians. To promote ADR reporting by gastroenterologists working in a multicentre IBD study group, we proposed the utilisation of a webservice in their usual electronic health records (EHR) to collect ADR. The aim of this work was to describe the impact of this intervention on the number of ADR reported to the regulatory authority through a regional pharmacovigilance centre.

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It is known that one of the main reasons why healthcare professionals do not report ADR is due to an increase in their workload [48, 54]. So, in order to reduce ADR reporting efforts, information systems (IS) to promote ADR reporting or to detect ADR in healthcare institutions have been tested and used, such as software for voluntary and automated detection of ADR, tools that analyse clinical databases or web-sites that actively inform healthcare professionals[11]. Information and communication technologies can also be used to facilitate and promote ADR reporting, such as the creation of on-line reporting forms and the development of tools to collect safety data from electronic health records (EHR), among others[16, 27].

In Portugal, there is a multi centre research project, in the field of gastric diseases (Study Group of Inflammatory Bowel Disease – GEDII)[26] whose members use the same electronic health record to collect patient information. As these patients are often treated with new and potent drugs (e.g. immunomodulating agents), the EHR has a field related to medication and ADR. Since the group members already fill in this field, it was considered an advantage to create a tool to send the data to the pharmacovigilance system.

Aim

The aim of this work was to implement and describe the implementation of a webservice in an EHR to collect ADR reports and analyse the number of ADR reports sent to the Portuguese regulatory authority (INFARMED), through a regional pharmacovigilance centre.

5.3 Methods

Intervention

The multi-centre research project, the Study Group of Inflammatory Bowel Disease – GEDII[26], has its own electronic health record (EHR) to collect patient information, with a field related to medications and ADR.

The GEDII members asked for a collaboration with the Northern Pharmacovigilance Centre (UFN in Portuguese) and the Health Information and Decision Sciences Department (CIDES) of the Faculty of Medicine to develop a tool to allow for easy reporting of ADR included in the EHR to the pharmacovigilance system. The two entities had, at the time, released a new information service (a webservice) to collect suspected adverse reactions directly from prescription and medical records. This system was easily adapted to the EHR used by the GEDII group.

The Northern Pharmacovigilance Centre, as part of the Portuguese Pharmacovigilance System, receives ADR reports from healthcare professionals (and, since 2012, from consumers as well) through an on-line form, a paper form, e-mail and by telephone. Since 2013, UFN has also received ADR reports through the webservice.

The webservice anonymises patient data (converting the full name of the patient into initials), according to the data protection standards of the Portuguese Pharmacovigilance System. Figure 10 shows the information flow from the electronic health record to the pharmacovigilance system.

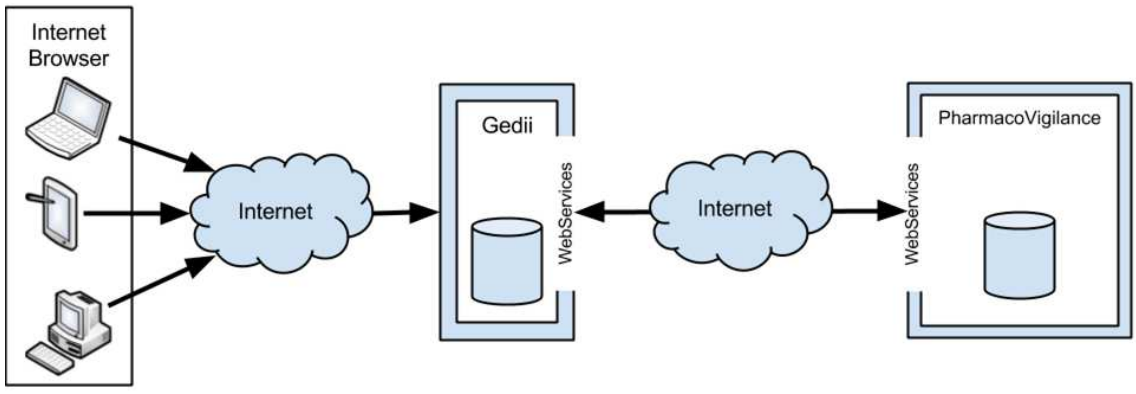

Figure 10 Information flow

To use this service, there is a button asking the doctor if he/she will allow the information to be sent to the pharmacovigilance database (see Figure 11). If the physician does not allow for this information to be sent to the system, it will only be stored in the health record.

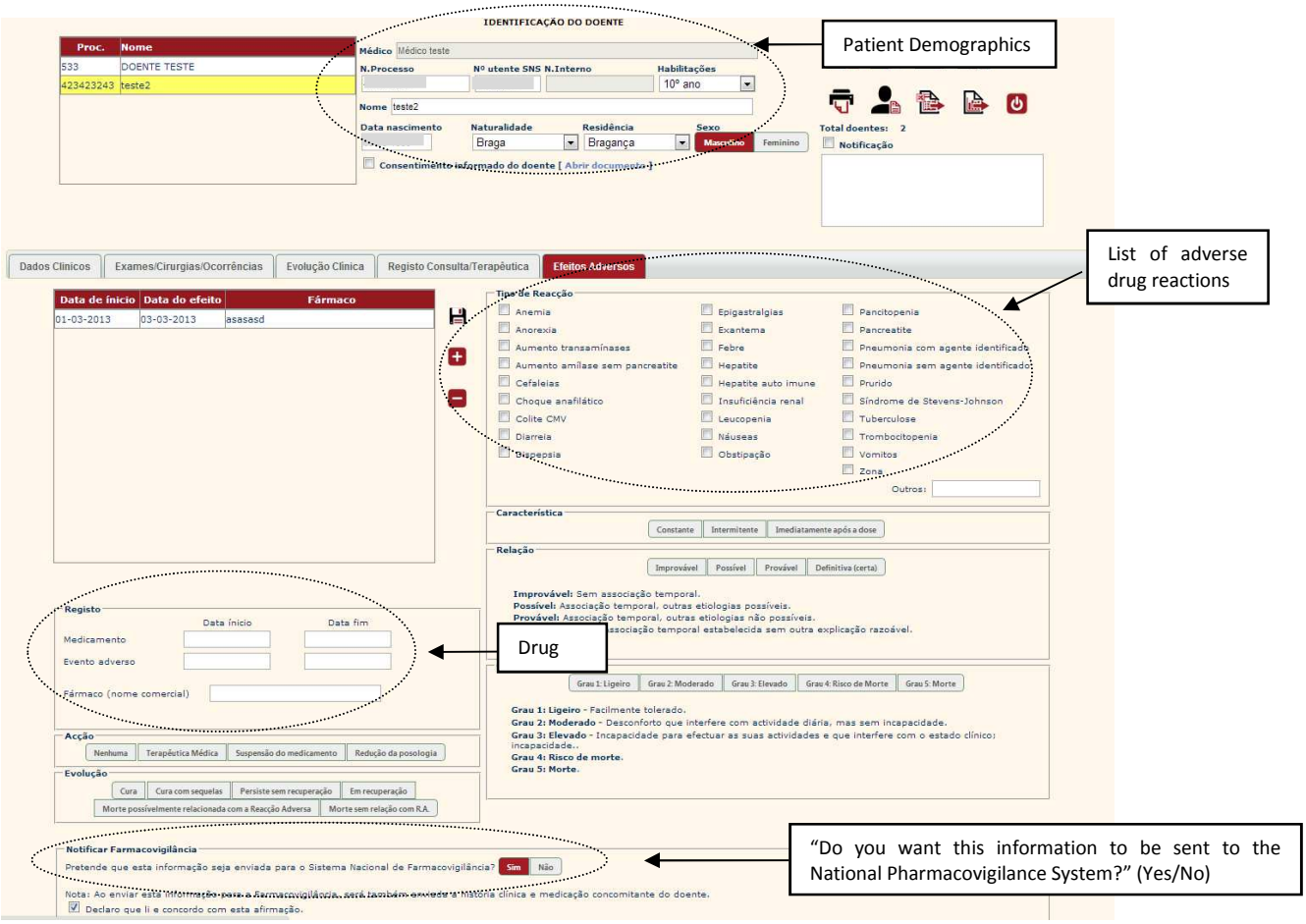

Figure 11 Screen shot of the ADR section on the GEDII electronic health record.

Study design and data collection

The webservice was implemented in the GEDII electronic health record (used only by gastroenterologists) in April 2013. There are 15 hospitals using this information system, covering a total of 4031 patients. The database has 39 registered users, which means that, potentially, 39 physicians could report ADR through this information system[26].

In order to use this webservice, it is necessary to access a specific URL, provided by the Northern Pharmacovigilance Centre and CIDES. The service was incorporated in the GEDII software to collect the ADR already stored by the physicians in the system. Each physician, in the context of the patient, sends the ADR to the Regional Pharmacovigilance Centre.

After the ADR report is received by the Regional Pharmacovigilance Centre, their technical staff process the report according to the pharmacovigilance guidelines[14], sending it to the Portuguese Regulatory Authority (INFARMED).

If the doctor does not want to send the information to the pharmacovigilance system, it will only be stored in the medical history.

To analyse the trends and type of ADR reported through this service, we performed a descriptive analysis on the number and seriousness of ADR reported. The seriousness was assessed using the World Health Organisation seriousness criterion[6]. According to this criterion, a serious ADR is any untoward medical occurrence that at any dose: results in death, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity or is life-threatening.

5.4 Results

From April 2013 to February 2015, physicians from GEDII reported 167 ADR through the described webservice.

Of the 167 reported ADR, 118 (71%) were serious ADR, considering the World Health Organisation seriousness criterion[6]. One of the cases was life-threatening and none were fatal.

To calculate the increase in ADR reporting in this period, we used data from the northern region, which is the delimited area of the Northern Pharmacovigilance Centre, as we did not have access to national ADR reporting data. Thus, considering the physicians from the GEDII group that work at the northern region of Portugal, 9 ADR were reported during the 23 months prior to webservice implementation and 121 ADR were reported during the 23 months after webservice implementation, i.e. an increase of 81%.

Drugs involved in the reported ADR

Most of the cases had one only suspected drug, but in six cases there were two suspected drugs involved.

Of the reported ADR, 106 cases (63%) were presumably due to azathioprine, 23 cases (14%) to infliximab, 14 cases (8%) to adalimumab and 9 (5%) cases to methotrexate (Figure 12).

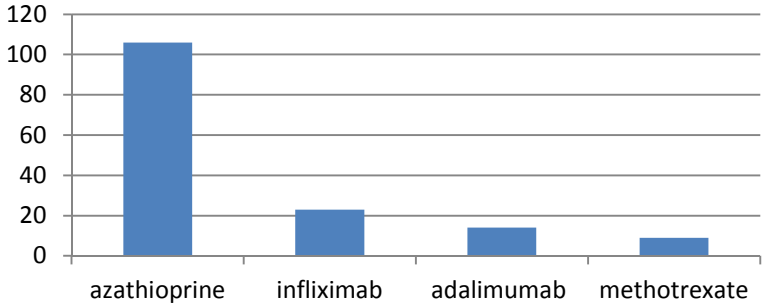

Figure 12 Drugs involved in the reported ADR

All of these drugs are classified as antineoplastic and immunomodulating agents, according to the WHO Anatomical Therapeutic Chemical (ATC) classification system[95]. Azathioprine, infliximab and adalimumab are immunosuppressants and methotrexate is an antimetabolite.

5.5 Discussion

Worldwide, many systems use electronic health records to facilitate adverse event reporting, with the same goal as our work, which is to not overload healthcare professionals with additional administrative work to report ADR [27, 55, 64]. These systems can be included in the EHR and be easily completed [64] or can actively help in form filling with the automatic input of certain information already included in the EHR[27]. During the ALIAS (Albumin in Acute Stroke Trial) experience, authors decided to integrate an electronic safety reporting module into the existing web-based system to deal with safety reporting obligations of a multicentre clinical trial[62]. This system pre-populates the reporting form with the existing information, which needs to be completed and validated by clinical staff. The ASTER pilot study also brought an important contribution to the development of these systems, as it triggered ADR within the EHR, collected patient data, populated the ADR reporting form and made the report available to the physician for review [60]. This work is different from ours, because it asks the clinician to provide additional information on the adverse event and then submits the report. All these systems incur extra work on the part of physicians, which is difficult to eliminate. The novelty of our work is the detail of allowing the physician to report ADR without any additional administrative work beyond the usual clinical registry. In addition, the EHR remained the same, without the need to change the physicians' routine. This system adapts to the routines of the healthcare professionals and not *vice versa*, which can explain the increasing of ADR reporting among the studied group.

It is also important to note that most of the reported ADR were serious. In fact, the studied group deals with innovative and powerful drugs that often cause serious adverse events. This finding reinforces the importance of our work, as Pharmacovigilance Systems seek mainly information about serious (and unexpected) ADR[88].

Our study has some limitations, such that it only included gastroenterologists. However, this webservice is available to be used in several software. Even so, it is currently in use only in two software systems: the one described in this study and an electronic prescription software system. Another issue is that our study does not have a control group, which limits the conclusions drawn. For this reason, the only comparison that the authors were able to perform was for the number of ADR reports made by the same group of gastroenterologists before the webservice implementation.

Conclusions

The simple solution described in our work allowed for reporting 167 ADR during the first 23 months of implementation, simply by clicking a button included in the usual electronic health record used by gastroenterologists. Our results suggest that doctors would report more ADR if they do not have to take on any further workload to do it. We propose that IS used to support multicentre studies should be used to report detected ADR.

Author contributions

The first author was responsible for data collection and writing the paper. The second author conceptualised the intervention and supervised writing of the paper.

Conflict of interest

The authors declare that they have no conflicts of interest.

Chapter 6 - Decision support tool

Bayesian network model to support the causality assessment of adverse drug reactions reports: a regional pharmacovigilance centre experience

Inês Ribeiro-Vaz, Pedro Pereira Rodrigues, Ana Silva, Jorge Polónia

WHO Winter Meeting. 2015.

6.1 Abstract

Utrecht | WHO Winter Meeting 2015

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Bayesian network model to support causality assessment of adverse drug reaction reports: a regional pharmacovigilance centre experience

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[1] Centre for Health Technology and Services Research (CINTESIS), University of Porto, Portugal.
[2] Northern Pharmacovigilance Centre, Faculty of Medicine, University of Porto, Portugal.
[3] Health Information and Decision Sciences Department, Faculty of Medicine, University of Porto, Portugal.

Background

In pharmacovigilance, reported cases are considered suspected adverse drug reactions (ADR). Health authorities have thus adopted structured causality assessment methods, allowing the evaluation of the likelihood that a medicine was the causal agent of an adverse reaction. The aim of this work is to develop a new causality assessment support system to be used in pharmacovigilance centres.

Methods

A Bayesian network was developed based on completely-filled ADR reports, evaluated by the Portuguese Northern Pharmacovigilance Centre expert over 12 years, and compared with global introspection on an independent validation cohort for sensitivity, positive predictive value (PPV) and time to causality assessment (TTA). Causality was classified as Definite, Probable, Possible or Conditional, according to the WHO causality assessment.

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Preliminary results

Derivation cohort included 593 ADR reports (10.1% Definite, 58.4% Probable, 25.6% Possible, 5.9% Conditional) with validation cohort including 463 reports (7.5%, 79.5%, 9.5%, 2.8%). High accuracy was reached for reports with Definite causality (69.4% sensitivity, 71.4% PPV) and Probable causality (91.1%, 87.3%), being lower for reports with Possible (25%, 28.9%) and Conditional (15.4%, 50%) degrees. The network tends to overrate causality (96.9% of errors on Possible cases classified as Probable) or give the immediately below level (90.8% of errors on Definite cases classified as Probable; 69.7% of errors on Probable cases classified as Possible). The median (Q1:Q3) TTA was 4 (2:8) days using the network and 8 (5:14) days using global introspection.

Conclusions

The network allowed a faster time to assessment, which has a procedural deadline of 25 days, improving daily activities in the centre. Moreover, the model was accurate on most cases, with a slight causality overrate on Possible cases, which is nevertheless a good quality in the context of use. The exception was the Conditional degree, which complexity is probably too high to be accurately modeled with formal methods.

WHO Collaborating Centre for Pharmaceutical Policy and Regulation

Universiteit Utrecht

6.2 Introduction

In the same line as other our studies, we aimed to improve the feed-back given to the reporter according to the causality assessment made in each report (causal relationship judgment). Pharmacovigilance systems are mostly based on suspected ADR reported by health professionals and users. Thus, regulatory health authorities have adopted methods of causal attribution, which allow for the assessment of the probability that a drug was the causative agent of the ADR. Worldwide, many methods are used for causality assessment of ADR, such as expert judgements (also called global introspection), algorithms and Bayesian approaches[96]. The Portuguese pharmacovigilance system has adopted the method of global introspection [88], during which one or several experts express their judgment on the possible causal relationship between the suspected drug and the ADR. This judgement is based on expert knowledge and background, considering all available data about the ADR. This method has some limitations related to its reproducibility[96] and compliance with legal deadlines, as it depends on the availability of experts.

Aim

Our objective was to design and implement a decision support system based on a Bayesian network that will expedite the response to the reporter. This work also improved the process of ADR report causality assessment according to: (1) time spent on the process and (2) reproducibility.

6.3 Methods

The Bayesian network was developed based on completely-filled ADR reports, evaluated by a Portuguese Northern Pharmacovigilance Centre expert over 12 years, and compared with global introspection on an independent validation cohort for sensitivity, positive predictive value (PPV) and time to causality assessment (TTA). Causality was classified as Definitive (Certain), Probable, Possible or Conditional, according to the WHO causality assessment.

6.4 Preliminary results

The derivation cohort included 593 ADR reports (10.1% Definitive, 58.4% Probable, 25.6% Possible, 5.9% Conditional) with a validation cohort including 463 reports (7.5%, 79.5%, 9.5%, 2.8%). High accuracy was reached for reports with Definitive causality (69.4% sensitivity, 71.4% PPV) and Probable causality (91.1%, 87.3%), but the accuracy was lower for reports with Possible (25%, 28.9%) and Conditional (15.4%, 50%) degrees of causality. The network tends to overrate causality (96.9% of errors in Possible cases classified as Probable) or give the level immediately below (90.8% of errors in Definitive cases classified as Probable; 69.7% of errors in Probable cases classified as Possible). The median (Q1:Q3) TTA was 4 (2:8) days using the network and 8 (5:14) days using global introspection.

This network has been in use at the Northern Pharmacovigilance Centre since April 2014. The appearance of the system is shown in Figure 13.

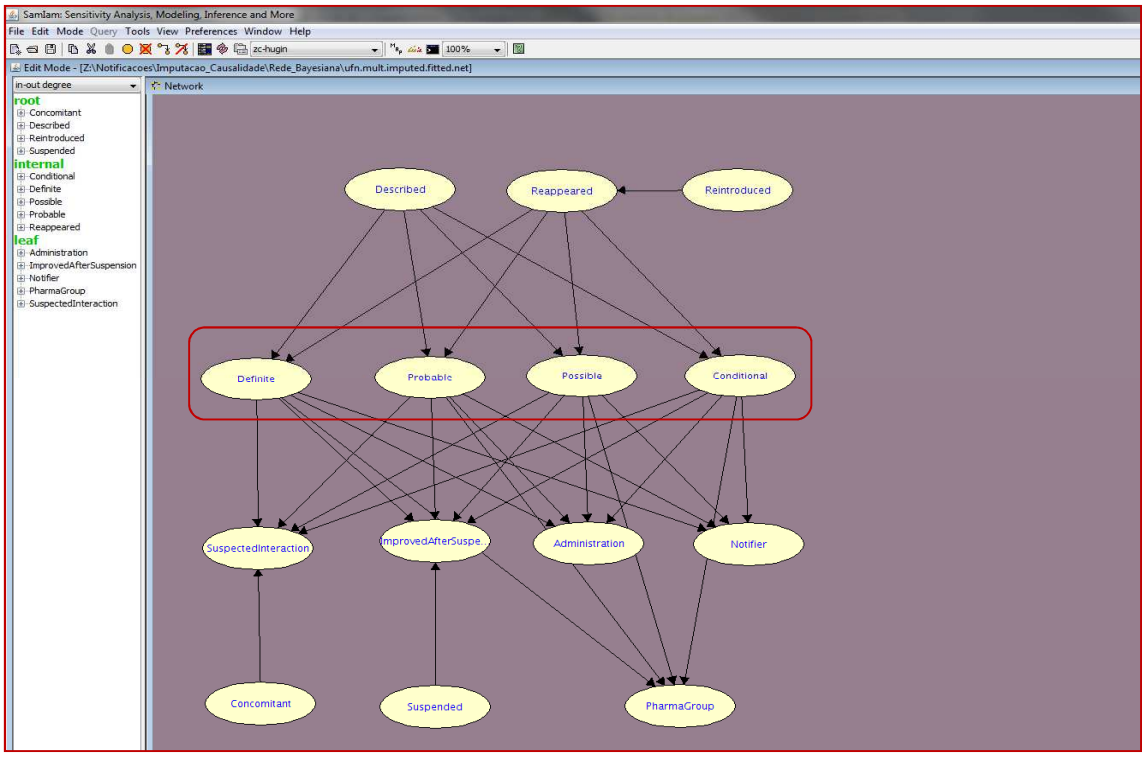

Figure 13. Screen shot of the Bayesian network

The preliminary results of this work were presented, as an oral communication, at the World Health Organisation Winter Meeting, at Utrecht University, in January 2015.

Currently, the model is being improved to fit a recent directive from the Portuguese pharmacovigilance system concerning the assessment of cases of drug ineffectiveness.

Chapter 7 - Ongoing and future work

7.1 Abstract

Some of the studies that were part of the thesis plan were not finished within the thesis development period, and are still in development. Furthermore, some other studies, not initially planned, were started by the research team. In fact, our investigation addresses a broad topic and many ideas were conceptualized during the daily work in pharmacovigilance and research activities.

One of the unplanned works is being performed within a local health unit, in order to develop an information system to facilitate information exchange about ADR within the healthcare unit. This work started in June 2014 and is currently being tested by healthcare professionals at the institution (subchapter 7.2).

In the course of our quotidian activity, we found that websites and social networks are excellent media to disseminate information about pharmacovigilance and drug safety issues. This belief was further supported during the performance of the systematic review. In line with this, we started to design a personal area on our website (sub-subchapter 7.3.1), and we also developed an online ADR reporting form for consumers (sub-subchapter 7.3.2) and start to develop a mobile application for ADR reporting (Chapter 7.4).

The expected results of this works are detailed in the following subchapters.

7.2 Managing several players at several institutions dealing with the same adverse event. A pilot-study called SIRAI.

Introduction

In June 2014, this PhD team proposed the development of a pilot study within the local health unit of Matosinhos, Portugal (ULSM in Portuguese) to test some strategies regarding the use of IS on the information exchange about ADR.

The first goal of this study was to design an information system (a single database) that will gather all the information about ADR that is disseminated around the institution, allowing for better use by healthcare professionals. Subsequently, the included ADR will be automatically submitted to the regulatory authority (National Authority of Medicines and Health Products; INFARMED, IP) through a regional pharmacovigilance centre (the Northern Pharmacovigilance Centre), with the permission of each healthcare professional.

When the database is in full use, an intervention study will be performed, with the following main outcomes: (1) the number of databases integrated into the single database, (2) the number of ADR included in the single database and (3) the number of ADR reports submitted to the regulatory authority by health professionals from the hospital.

To measure the submitted ADR reports, the Northern Pharmacovigilance Centre database will be used, which is registered in the Portuguese commission for data protection, and follows the confidentiality and data protection guidelines imposed by the Portuguese pharmacovigilance system.

This study was approved by the local ethics committee and the hospital's board of directors.

Methods

In June 2014, a working group was created to design the information system. This expert group was composed of:

- two physicians: one an expert in primary care and the other an expert in hospital care who is also responsible for the risk management department at the institution
- two pharmacists: one an expert in hospital pharmacy and the other an expert in pharmacovigilance
- two nurses
- two informaticians: one responsible for the hospital informatics department and the other one from the Faculty of Medicine.

From June 2014 to June 2015, this working group met in person 10 times. During these meetings, a discussion took place regarding the type of database that is most appropriate for the institution's healthcare professionals, and its contents were approved.

The screens were designed and improved between meetings, according to the group's opinions. The content was also developed with the contribution of each participant. Namely, lists of adverse reactions, severity criteria and routes of administration were developed and approved, to facilitate form completion.

To meet the needs of health professionals at the institution, we also developed a form to report incidents with medical devices. This form based on the INFARMED paper form.

In February 2015, the first version of the prototype was shown, and a name was assigned to the information system: SIRAI[3]. The system is currently being tested.

[3] The acronym means ***S****istema de* ***I****nformação de* ***R****eações* ***A****dversas e* ***I****ncidentes* (Information System for Adverse Reactions and Incidents).

Workflow

The project aims to promote ADR reports identified in the ULSM to the regulatory authority, through the following tasks:

Task #1: Design and implementation of an information system for the management of information on drug safety.

Task #2: Integration in a single database of all the ADR detected at the institution (ULSM).

Task #2.1: Identification of databases that could include information about ADR detected at ULSM.

Task #3: Submission of the ADR collected in the database referred in #2 to the regulatory authority through the Northern Pharmacovigilance Centre.

Task #4: Feedback on ADR reports will be send to the reporters.

Expected results

As the main outcome, we have developed a functional information system on drug safety that is being used at the institution.

The intervention impact will be measured on the number of ADR submitted to the regulatory authority. In the last four years, healthcare professionals from ULSM reported about 22-43 ADR each ear, without a regular trend. As we strongly believe that, during daily activities, many more ADR are detected by these healthcare professionals, so we expect that the number of ADR submitted will increase by about 50% each year.

In addition to the number of ADR reports, an increase in relevance is also expected. Established relevance criteria include ADR seriousness, ADR expectedness and the causality degree attributed to the ADR.

7.3 Social networks and portals for patients and healthcare professionals

Internet users are increasing and many of them use the web for issues related to health. According to Cybercitizen Health® Europe[97], in 2012, 72% of European online adult consumers (ages over 18) were social health users (which means individuals that "have conducted any of the following activities online for health within the past 12 months: used a community, group or social networking website, or conducted any social-related activity online such as reading or posting on health blogs, message boards or health ratings websites"). Additionally, 44% of European online consumers use social networking for issues related to health, 33% read or posted patient testimonials and 34% used health ratings or reviews.

To take advantage of this reality, it is important to adopt strategies to use the internet in the promotion of pharmacovigilance and ADR reporting, using for this purpose social networks and portals for patients and healthcare professionals.

Social networks are excellent media and can be used to disseminate information about pharmacovigilance and drug safety issues. In 2011, Knezevic *et al.* studied the use of social networks, such as Facebook®, to increase spontaneous ADR reporting. This study tested if the creation of a group in Facebook® increased ADR detection and reporting by its members[65]. For this purpose, an open group (available to the general public) was created where regular information about ADR was posted. During the experience period (seven months), 21 ADR were reported, by 2% of the total group members (n=1034). Among the 1034 members, 370 provided their educational profile (88% had a university degree and 12% a high school degree). For those with a university degree, 67% had a degree in medicine, dentistry or pharmacy. None of the 21 ADR reported were serious or unexpected. Based on their results, the authors stated that Facebook® can be useful for improving spontaneous ADR reporting.

In line with this, UFN created its own Facebook® page in October 2013, and currently stands at 876 "likes" (in april 2016). On this public page, we publish information about drug safety and also about our events (open classes and post-graduate courses, among others). We also publish images and messages promoting spontaneous ADR reporting and emphasising the importance of this subject. In the future, we expect that this will be a source of debate about ADR reports, with the creation of an online forum and maybe part of a study similar to the one performed by Knezevic *et al.*[65].

7.3.1 Creation of the personal area on the UFN website

Websites of pharmacovigilance centres and regulatory authorities are important for providing information about drug safety and to promote ADR reporting, both by patients and healthcare professionals. Some of these websites also provide online ADR reporting forms. In these cases, it is essential that the provided form is simple, intuitive, quick to fill in and with few mandatory fields. Otherwise, the experience of reporting may seem too complicated for the users and discourage them [43].

Thus, we aimed to create a model of communication between our pharmacovigilance centre and its reporters (health professionals) through our website. With this model, we wanted to turn ADR reporting into an informative and motivating activity.

To develop this project, the first step was to redesign the former Northern Pharmacovigilance Centre website, in order to make it more appealing and user-friendly (Figure 14 and Figure 15):

Figure 14. UFN website 2005-2016

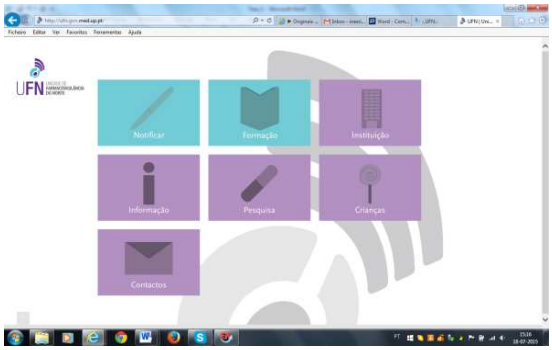

Figure 15. UFN website 2016

The new website was launched on 18 January 2016. On the new website, we created a reporter area dedicated to healthcare professionals. This area compiles all the ADR reports submitted online by each healthcare professionals, and are only available after authentication, to ensure the confidentiality.

Our aim was to provide our users also with feedback after submitting their ADR report. Each healthcare professional will have access to a report that compiles the research results generated by the ADR report. The search will be conducted using selected information sources, each time a healthcare professional reports an ADR through the ADR online form. The results of the searches will be presented in the form of ADR frequency, ADR absolute value, ADR expectedness and percentage of ADR by age and gender.

We selected the following information sources to perform the searches:

- The European database of suspected ADR[4], which provides information on absolute number and percentage of ADR by sex, age and other criteria.
- The WHO Global Database of Individual Case Safety Reports (Vigilyze®)[5], which provides information on the number of cases reported, describing each case individually.
- Medscape®[6], which provides information on the frequency (%) of ADR.
- The Medicines & Healthcare Product Regulatory Agency[7] (MHRA), which provides information on the number of cases reported.

We are still working, together with software development staff, to conclude the creation of the personal area on our website.

[4] www.adrreports.eu
[5] www.vigilyze.who-umc.org
[6] http://reference.medscape.com/medscapetoday
[7] https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency

7.3.2 ADR online reporting form for consumers

In Portugal, consumers have been allowed to directly report their own suspected ADR since July 2012 [76]. To facilitate the ADR reporting process among consumers, we have started to develop an ADR report online form for consumers in Portugal, taking advantage of our website redesign.

To develop the consumer's online form, we used the printable form as a standard. The form was carefully developed and adjusted for patient reporting. A heuristic evaluation of the form was performed to obtain the final version, which is already finished (see Figure 16, designed by Natacha Oliveira) and available on the Northern Pharmacovigilance Centre website[5].

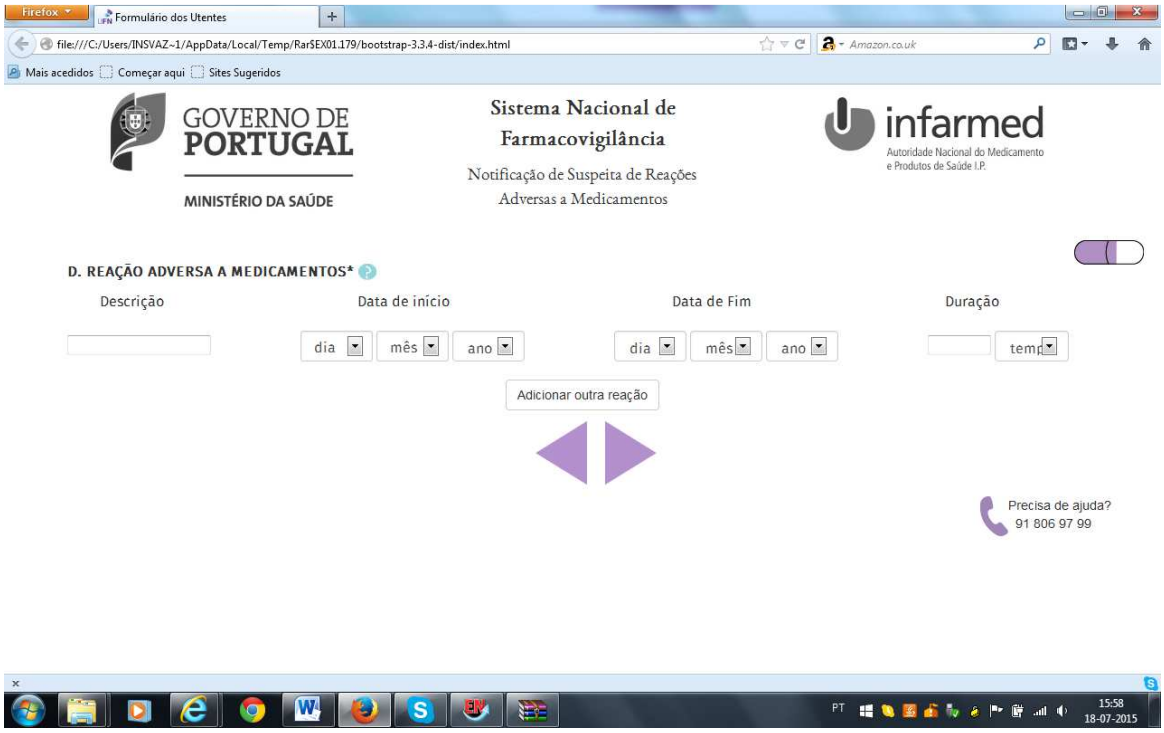

Figure 16. Screen shot of the online patients reporting form (ADR screen).

7.4 App for ADR reporting

During this study, the idea arose of developing a smartphone application for ADR reporting. For this purpose, the user interface has been designed (as seen in Figure 17 and Figure 18, both designed by Natacha Oliveira), consistent with the new image of the UFN website. This project is in the implementation phase.

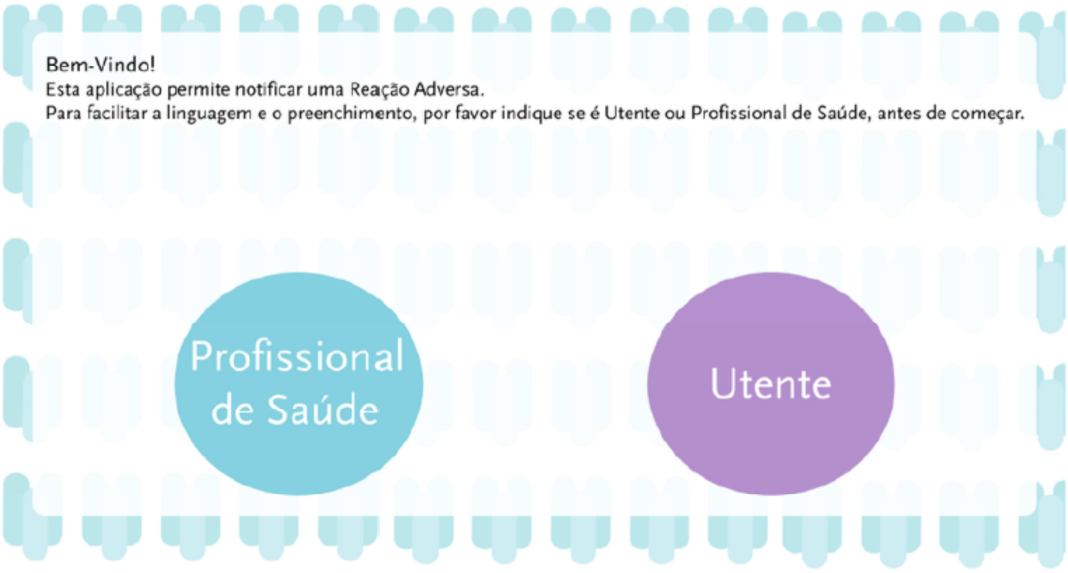

Figure 17. User interface of the ADR reporting app (first screen).

Figure 18. User interface of the ADR reporting app (suspected drug screen).

Chapter 8 – General discussion

These studies have allowed us to realise that much work can be done using informatics to improve pharmacovigilance.

Worldwide underreporting of ADR is a major concern, and many institutions are aware that it is feasible to use IS to improve ADR reporting. Currently, the most commonly used technological platform is web-based and shows an increasing trend, but interventions within electronic health records also have the potential to improve pharmacovigilance activities, particularly ADR reporting. ADR directly reported by consumers (direct ADR reporting) is being increasingly taken into account when the aim is to improve information on drug safety[98].

Most international studies that aimed to promote ADR reporting were developed in hospitals and tailored to healthcare professionals. In fact, most serious ADR are detected in hospitals and reported by healthcare professionals[72]. Additionally, in Europe, direct reporting (ADR reported by patients) has only been allowed in all countries since 2012[76]. This may also explain why most of the projects that target direct ADR reporting have only been recently developed[65, 67, 71, 72].

As with most of international groups, we developed systems for the passive promotion of ADR reporting because most busy healthcare professionals only submit their suspected ADR if it does not increase their workload[55, 77]. Active promotion of ADR reporting is difficult and not always ethically acceptable because no material reward can be given to the reporters. Thus, projects have aimed to actively promote ADR reporting involving teaching sessions[50] or e-mails containing ADR information[46, 57, 59, 72].

Based on our research, we believe that it would be useful to adopt systems to assist healthcare professionals with completing ADR reporting within electronic health records because this approach seems to be an efficient method to increase the ADR reporting rate[75]. When this approach is not possible, it is essential to have tools that are easily accessible to healthcare professionals (e.g. on the web) to report ADR. These tools can be promoted by sending emails or through the inclusion of direct hyperlinks on healthcare professionals' desktops, which is a simple and cost-effective way to change the behaviour of healthcare professionals regarding spontaneous ADR reporting, as seen in Chapters 3 and 4, and can be easily implemented and disseminated in healthcare institutions[16].

We also see as a promising solution the integration of pharmacovigilance databases within the habitually used electronic health records, avoiding extra workload to submit an ADR, as described in Chapter 5. ADR collected this way would then be sent to the relevant authority through regional pharmacovigilance centres, which would provide feedback related to the reported ADR. This strategy increased the ADR report rate in the studied group and could be easily replicated among other healthcare groups.

Furthermore, we propose that pharmacovigilance websites can be explored to create personal areas for each person that submits an ADR report, aiming to turn ADR reporting into a motivating and informative activity. It should provide technical information about the reported adverse reaction and the suspected drug, thereby improving feedback.

Besides the promotion of ADR reporting, Information Systems can also improve pharmacovigilance routine activities by upgrading the communication between pharmacovigilance centres and reporters. We have concluded that it is possible to accelerate the process of causality assessment and subsequent feedback using Bayesian models (Chapter 6). We believe these models could be linked to the electronic reporting form, turning causality assessments into a semi-automatic process, and it is our aim to perform such an intervention, as future work, on our website.

Pharmacovigilance should adapt to technological developments, benefiting reporters (both healthcare professionals and consumers) by facilitating the ADR reporting act and turning it into a valuable and appealing activity. Additionally, Information Systems can benefit pharmacovigilance staff, simplifying some of the required procedures, making them faster and, where possible, semi-automatic.

Overall conclusion

Despite the fact that the personal area on our website is still being built jointly with the software development staff (as described in sub-chapter 7.3.1), we can consider that the main objectives of the thesis have been achieved. Having analysed several strategies to increase ADR reporting (chapters 2 and 3), we have not only created a decision support system to improve pharmacovigilance activities (chapter 6) but also developed new tools to facilitate ADR reporting (three tools have been designed and two of which fully implemented, as seen in chapters 4, 5 and sub-chapter 7.2).

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Annex

Annex

This annex contains reprints of all the published papers included in this thesis, as follows:

1. Inês Ribeiro-Vaz, Fabrício Alves Barbosa Silva, Ana-Marta Matos Silva, Domingos Alves, Cruz-Correia R. Pharmacovigilance informatics. In: Maria Manuela Cruz-Cunha, Isabel Maria Miranda, Ricardo Martinho, Rijo R, editors. Encyclopedia of E-health and telemedicine: IGI Global; 2016. p. 299-315.
2. Ribeiro-Vaz I, Silva AM, Costa Santos C, Cruz-Correia R. How to promote adverse drug reaction reports using information systems - a systematic review and meta-analysis. BMC Medical Informatics and Decision Making. 2016;16(1):27.
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5. Ribeiro-Vaz I, Correia RJC (2016) Using Web Services to Link Electronic Clinical Records to Pharmacovigilance Databases. Int J Pharmacovigil 1(1): 4.

This annex also contains the approval document of the local Ethics Committee of the Faculty of Medicine of the University of Porto (Process PCEDCSS-FMUP 08/2014, approved in May 7, 2014).

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Pharmacovigilance Informatics

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INTRODUCTION TO PHARMACOVIGILANCE INFORMATICS

All medicines have adverse effects, most of them unknown until the drug commercialization. As so, it is crucial to keep strategies to monitor the drug safety. Pharmacovigilance is the activity of drug surveillance, after its launch in the market, with the main goal of public health protection, ensuring that the drug benefit outweighs its risks. Worldwide, pharmacovigilance systems are mostly based on spontaneous Adverse Drug Reactions (ADR) reports made by healthcare professionals and consumers. Spontaneous ADR reporting has been described as an essential method to detect drug safety signals; however, underreporting is a major issue undermining the effectiveness of spontaneous reports. Several studies suggest that less than 10% of detected ADR are effectively reported to medicines regulatory authorities [e.g. Food and Drug Administration (FDA), European Medicines Agency (EMA), etc] (Hazell & Shakir, 2006; McGettigan, Golden, Conroy, Arthur, & Feely, 1997).

Tools used in pharmacovigilance are continually evolving and, worldwide, Information Systems (IS) to promote ADR reporting or to detect ADR occurred in healthcare institutions have been tested and used, such as software that allow voluntary and automated detection of ADR, tools that analyse clinical databases or Web sites that actively inform healthcare professionals (Molokhia, Tanna, & Bell, 2009).

In addition to the signal detection, ICT can also be used to encourage and facilitate reporting of suspected ADR, such as the creation of on-line reporting forms, development of tools to collect safety data from electronic health records (EHR), among others.

In this chapter, it will be described some tools to automatically detect ADR, or encourage ADR spontaneous report.

BACKGROUND ON PHARMACOVIGILANCE

Adverse Drug Reactions (ADR) defined as a response to a medicinal product which is noxious and unintended (WHO) are a well-recognized public health problem worldwide, and a major cause of death

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and hospitalization in developed countries(Lazarou, Pomeranz, & Corey, 1998). It is estimated that about 6,5% of the hospitalizations are related to ADR(Pirmohamed et al., 2004). Besides, in the USA, about 100.000 people die each year due to ADR(Lazarou et al., 1998), and in Europe this annual mortality rate increases to 197.000(European Medicines Agency, 2014). ADR can be expressed in many ways and with different degrees of seriousness. An anaphylactic shock caused by penicillin is an example of a serious ADR (a serious ADR is any untoward medical occurrence that at any dose: results in death, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity or is life-threatening(WHO). Another type of ADR, not always recognized as such, is the drug ineffectiveness, for example, a vaccination failure. This can be (or not) related with a product quality issue and should be reported when detected in order to allow the regulatory authorities to take appropriate decisions.

Rare and long term ADR are difficult to detect during the drug development stage. Only when the drug begins to be used by a large population after marketing authorization it is possible to detect new ADR not previously identified during clinical trials. In reality, it is known that the safety of a new drug cannot be established until it has been on the market for several years(Lasser et al., 2002). Exceptionally, in a pandemic scenario, drug launch is urgent and, in this particular case, can be justifiable that drug safety profile is not well established. In this scenarios, it is even more important that all the detected ADR are reported (serious or not, expected or not). It is, therefore, essential to keep drugs under close surveillance, after its commercialization, through a pharmacovigilance system, to continuously evaluate their safety profile. In most of the European countries, pharmacovigilance system is based on spontaneous ADR reports, which is passive method, made by healthcare professionals and, since July 2012, also by consumers (Ministério da Saúde, 2006). These reports can be made using paper, telephone, e-mail or through an on-line form and consist of a description of an Adverse Event (AE) apparently caused by a medicine.

To reverse the problem of underreporting of ADR, which is felt in most developed countries, several strategies have been tested(M. T. Herdeiro et al., 2012; McGettigan et al., 1997; Ribeiro-Vaz, Santos, da Costa-Pereira, & Cruz-Correia, 2012). Particularly, some studies were developed focused on educational interventions to raise awareness on the importance of ADR reporting(Figueiras A., Herdeiro T, Polonia J, & JJ, 2006; M. T. Herdeiro, Polonia, Gestal-Otero, & Figueiras, 2008; Ribeiro-Vaz, Herdeiro, Polonia, & Figueiras, 2011) and showed to be very effective increasing the quantity and relevance of spontaneous ADR reports (among health professionals). However, these studies involved a large financial and personal outlay and the authors concluded that the effect was lost after a few months(McGettigan et al., 1997; Nazario, Feliu, & Rivera, 1994).

In a recent American study, the authors developed a signal-detection strategy that combines the Adverse Event Reporting System (AERS) of the regulatory Authority (FDA) and EHR, by requiring signaling in both sources, with promising results(Harpaz et al., 2013). Another study used the unstructured clinical notes included in EHR to detect ADR through a computerized system. The authors concluded that data mining can be used for hypothesis generation and for rapid analysis of suspected AE risk(LePendu et al., 2013).

With a similar aim, a recent study used a physician's network, created through a mailing list, to send regular emails to doctors, with humorous component attached with informative component, recalling the importance of reporting their suspected ADR(Goldstein, Berlin, Saliba, Elias, & Berkovitch, 2013). The results showed that this type of intervention has impact on the number of ADR reports made by these professionals (the study did not assess the relevance of reported ADR). In France, it is being done a work that tries to facilitate the act to ADR report, habitually considered a tedious process by health

professionals. The authors are using the information contained in EHR to make the semi-automatic filling of ADR notification forms. The objectives of this ongoing study is to increase the rate of ADR report, as well as improving the quality of information submitted to regulatory authorities(Pares, Declerck, Hussain, Ng, & Jaulent, 2013).

INFORMATION SYSTEMS IN PHARMACOVIGILANCE

Issues, Controversies, and Problems

Although some authors consider that ADR spontaneous reports suffers from latency and inconsistency, it is still considered as the most valuable method to early detect drugs safety problems. In fact, most of the decisions concerning to drug safety are triggered by daily ADR spontaneous reports. As so, Regulatory Authorities consider as crucial importance to achieve the greatest number of ADR reports possible and with high data quality.

The promotion of ADR report among healthcare professionals is a huge task, as it is necessary to regularly recall the importance of ADR reporting and, simultaneously, develop tools to facilitate this duty. Pharmacovigilance centres worldwide develop several strategies to continuously promote the importance of ADR reporting, as workshops, post-graduate courses, and also to make it easier, as development of online reporting forms, inclusion of electronic reporting systems into the Hospital Information Systems (HIS), direct hyperlinks to online reporting forms, among others.

Along with the promotion of spontaneous ADR reporting, some systems are being tested to detect signals of adverse reactions in large databases, as hospitals databases, epidemiologic databases, or even among social networks.

Although the adoption of different strategies, it is consensual the need to obtain the highest quantity and quality of information about the safety of marketed drugs, for the protection of public health.

Another important issue in this field is the need to discuss/harmonize what should be recorded during an ADR report.

When analyzed the databases from the FDA, EMA and the Portuguese Northern Pharmacovigilance Centre (UFN), all of them with the same purpose of recording ADR reports, it was possible to realize that the variables are different between the 3 databases, as seen in the Table 1.

For example, the concept of outcome for the FDA form as a similar meaning to the concept of seriousness for the two European databases analyzed. On the other hand, for these two databases, outcome means the evolution of the patient regarding the adverse scenario.

Active debate is maintained about this subject. The authors participate in some discussion groups, both national and internationally [namely the FHIR/OpenEHR(OpenEHR, 2014) and HL7(Health Level Seven, 2014) working groups], aiming to create a standard to the information that should be kept during the ADR registry.

Authors also participate, in June 2014, in the HL7 pharmacy group meeting, where was discussed the International Organization for Standardization (ISO) draft of international standard for 'Requirements for electronic prescriptions'. This document is still under discussion until February 2015.

The last OpenEHR discussion took place in July 2014 and was focused in the ADR definition, its characteristics and what should be kept for the registration of a suspected ADR. At the moment, it is in discussion the clinical content of the Archetype Adverse Reaction (FHIR/OpenEHR). Variables as substance, status, seriousness, reaction type, certainty are under debate.

Table 1. Comparison of the variables included in 3 pharmacovigilance databases (Food and Drug Administration: FDA; European Medicines Agency: EMA and Portuguese Northern Pharmacovigilance Centre: UFN), grouped in main entities/sections (patients, problems, products and reporters)

Section	Variable	FDA	EMA	UFN
Patient	Patient identifier	✓	✓	✓
	Age at the time of event	✓	✓	✓
	Date of birth	✓	✓	✓
	Sex	✓	✓	✓
	Weight	✓	✓	✓
Problem	What kind of AE, product problem or error did you encounter?	• Adverse event • Product use error • Product problem • Problem with Different Manufacturer of the Same Medicine	---	---
	Outcomes Attributed to AE	• Death • Life-threatening • Congenital anomaly/birth defect • Disability or permanent damage • Hospitalization • Required intervention to prevent permanent impairment/damage • Other serious	• Fatal • Not recovered • Recovered with sequelae • Recovering • Recovered • Unknown	• Fatal • Not recovered • Recovered with sequelae • Recovering • Recovered • Unknown
	ADR Seriousness	---	• Yes • No	• Death • Life-threatening • Congenital anomaly • Results in persistent or significant incapacity • Hospitalization • Other serious
	Date of event	✓	✓	✓
	Describe events, problem, or product use error	✓	✓	✓
	Relevant test/laboratory data, including dates	✓	---	---
Product	Product name	✓	✓	✓
	Label strength	✓	✓	✓
	Manufacturer	✓	✓	✓
	Date of use	✓	✓	✓
	Reason for use	✓	✓	✓
	Problem went away after use stopped or dose reduced?	• Yes • No • Does not apply	---	✓
	Problem returned after person started taking or using the product again?	• Yes • No • Does not apply	---	✓
	Do you still have the product in case we need to evaluate it?	• Yes • No • Returned to Manufacturer on	---	---
Reporter	Reporter name	✓	---	✓
	Address	✓	✓	✓

✓or list of options: Variable exists; ---: Variable does not exist

PROPOSED SOLUTIONS AND RECOMMENDATIONS

D

Promotion of Adverse Drug Reaction Reporting

Integration with IS (Patient Records, Multi-Center Research Projects)

Integration of pharmacovigilance system databases with other healthcare IS seems to be an obvious way to improve the knowledge about drugs safety. In fact, healthcare providers insert a lot of information in their EHR about ADR, which is not shared with pharmacovigilance systems. Every approach that promotes drug safety surveillance without increasing the workload of healthcare professionals, one of the main reasons for not reporting ADR, should be considered.

The creation and implementation of webservices to collect this information is one of the possible solutions for this problem. This solution is being tested in a Portuguese multi-center research project, in the field of gastric diseases(Study Group of Inflammatory Bowel Disease, 2014), with promising preliminary results (5% of all of the ADR reports received in the 1st semester of 2014 were collected by webservice). In this case, the physicians insert the usual clinic information during the appointment with the patient, and then, they only have to authorize the transmission of anonymized information about drug-related problems to the pharmacovigilance system. This tool allows ADR reporting without the need to fill the ADR reporting form and with no additional administrative work for the physician other than the normal registry of clinic patient data.

This solution is also available to be included in commercial prescription software. For the implementation of these webservices, it was necessary to map the form entries used by the doctors with the online ADR reporting form developed by the pharmacovigilance system, so that the information is correctly collected. This mapping would be easier if a standard as the one described in the previous section was already in use.

An ADR electronic reporting system included into a HIS was developed in a Spanish hospital(Ortega et al., 2008), allowing healthcare professionals (pharmacists, physician and nurses) to report suspected ADR through their usual IS. The biggest advantage of this system is that some data (already included in the IS) appears as default values into the form, which expedites the system and reduces transcription errors(Cruz-Correia et al., 2009). All the reports made by this system are reviewed by a pharmacist, which is responsible to confirm the included data and to report the case to pharmacovigilance system. This might be a disadvantage, as some cases may be lost and not actually sent to regulatory authorities.

Another strategy that can be easily adopted is the inclusion of hyperlinks in the EHR to the online ADR reporting form. This solution was tested between 2006 and 2010, in an ecological study performed in 16 Portuguese hospitals centres(Ribeiro-Vaz et al., 2012). The hyperlinks were included in either EHR or on computer desktops. Considering the hospitals with hyperlink included in the EHR, the median ADR reports per month significantly increased, from two (range 0–12) to five reports (range 1–17). The median of ADR reports per month using the online form also increased significantly, from one (range 0–5) before the intervention to four (range 1–17) after it. Moreover, serious ADR increased 3-fold, and non-previously described ADR increased 4.5-fold. None of these significant increases were observed in the hospitals where the hyperlink was not installed. It was also found a significant increase in daily pharmacovigilance centre website visits, from ten before the intervention to 27 after it ($p<0.001$). The increase in ADR reporting shows that the inclusion of hyperlinks to online ADR reporting forms is an easy way to change health professional behavior with regard to spontaneous ADR reports. Furthermore, this solution seems to be cost effective, when compared with other strategies to increase ADR report,

as it has no running costs (after the hyperlink implementation, there are no additional costs to the pharmacovigilance system).

Clinical Decision Support and Alerting Systems

Informatics can be used in pharmacovigilance activities to support and alert healthcare professionals during their daily work. With the IS extensively used in health care institutions, all the improvements that can enhance patient safety should be taken into account. Clinical Decision Support Systems (CDSS), providing intelligently filtered knowledge in real-time, should be used in this area to improve public health and health care(Kilbridge & Classen, 2008). Besides, systems that triggered alerts of possible ADR can also be integrated in the IS with the same goal.

Many systems are used and tested worldwide to alert health providers about suspected ADR, which can help in the detection of drug safety problems. The exploitation of computer programs used in hospitals as a support in the detection of possible ADR(Classen, Pestotnik, Evans, & Burke, 1992; Otero & Domínguez-Gil, 2000) is one of these systems. With this purpose, work has been developed in order to create lists of drugs used as ADR signals to support the detection of ADR in hospitals. The included drugs were chosen as they are mostly used as antidotes or therapeutic interventions for possible ADR. Furthermore, there are also lists of diagnosis that triggers an alert for possible ADR in the computer systems. These diagnoses indicate diseases that are mainly caused by drugs and, therefore, are signals of possible ADR. Besides the drugs and diagnosis, also laboratory values can help in ADR detection. In fact, some ADR are characterized by laboratory abnormalities, so the monitoring of these values can be an improvement in the promotion of drug safety among hospitalized patients.

The main goal is to incorporate the described lists in the software used in the hospital pharmacies in order to be triggered an ADR alert each time an alerting drug is prescribed, or each time an alerting diagnosis is made or even each time a laboratory result reaches a suspected toxicity value(Kilbridge et al., 2009; Levy et al., 1999).

It has been advocated that EHR should be provided with CDSS in order to maximize its benefits to patient safety(Kilbridge & Classen, 2008). These CDSS are being used to inform physicians during the prescription about identified drug-drug interactions(Phansalkar et al., 2013), patient allergies(Abookire et al., 2000) or to support the prescribing decision(Osheroff et al., 2007; Saxena, Lung, & Becker, 2011). CDSS integrated in the computerized physician order entry (CPOE) can effectively prevent potential harmful medication errors and ADR (Rommers, Teepe-Twiss, & Guchelaar, 2007, 2011).

In particular, a Dutch CDSS is being in use at the hospital pharmacy to support hospital pharmacist to select patients at risk of ADR, and its effectiveness was evaluated(Rommers, Zwaveling, Guchelaar, & Teepe-Twiss, 2013). For this purpose, the system retrieves data from IS, and uses clinical rules. During the study period, the CDSS generated 2650 safety alerts, 270 (10%) of them were considered as relevant. In these cases, the pharmacist contacted the physician or nurse and in 204 (76%) cases this led to an advice to prevent a possible ADR. Most alerts were generated with clinical rules linking pharmacy and laboratory data (1685 alerts).

Detection of Adverse Drug Reactions

Data mining is *a general term for computerised extraction of potentially interesting patterns from large data sets, often based on statistical algorithms* (WHO). Is an active method that complements the pharmacovigilance system (Harpaz et al., 2012).

Computational methods commonly referred as "signal detection" or "tracking" algorithms allow drug safety evaluators to analyze a large amount of data to find signs of potential ADR risks. These methods have been shown to have great significance.

FDA routinely uses a signal tracking process to calculate statistics reporting associations for all the millions of combinations of drugs and events in their ADR communications system. Nevertheless, these signs alone are not sufficient to establish a causal relationship, being considered early warnings that require in-depth evaluation by experts to establish causality. This new evaluation typically consists of a complex process in which the evaluators analyze drug safety information, such as time relations, published case reports in the literature, biological and clinical plausibility, data from clinical trials and epidemiological studies in multiple related health databases(Harpaz et al., 2012).

The analysis of ADR through the data mining process has some limitations in terms of quality and distortion of data. Data distortions can compromise the integrity of any information related with detection of ADR. In terms of individual cases records, the limitations are related to factors that may impact the quality and integrity of the reported information, source of reports, class of drugs, time on the market, the database mined, temporal relationship between drug-ADR, information follow-up, etc. Although much work has been done to develop statistical algorithms to identify outliers that might be considered signals there is still much more to be done to address the impact of the limitations of data, since much human intervention is necessary to triage cases detected through data mining(Stephenson & Hauben, 2007).

Disproportionality Analysis

Methods of disproportionality analysis (DPA) in pharmacovigilance represent the main class of analytical methods for spontaneous report systems data analysis(Harpaz et al., 2012). These reports comprise one or more drugs, of one or more ADR, and possibly some basic demographic data.

These methods include the Multi-item Gamma Poisson Shrinker (MGPS), the Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR), and the Bayesian Confidence Propagation Neural Network (BCPNN). These methods identify relevant associations in databases, focusing on projections of lower data dimensionality, more specifically two-dimensional contingency tables (see Table 2).

The main objective of a DPA method is the classification of tables in the order of interest. Different DPA methods focus on various statistical measures of association as its measure of interest. The MGPS, for example, is a Bayesian version of Relative Reporting Ratio (RR)(Harpaz et al., 2012). The RR for the combination drug (i) - ADR (j) (RRij) is the observed number of occurrences of the combination drug (i) - ADR (j) (40 in the example above), divided by the expected number of occurrences. Specifically, in the above example, the ADR (j) occurs in 10% of reports (140/1400). Thus, if the drug (i) and ADR (j) are statistically independent, 10% of the reports containing drug (i) must include ADR (j), which corresponds to 14 reports in this case. However, 40 reports associate the drug (i) and ADR (j). Thus,

Table 2. Two-dimensional contingency table; ADR means "adverse drug reaction". The values refer to occurrences.

	ADR *(j)* = Yes	**ADR *(j)* = No**	**Total**
Drug *(i)* = Yes	*(a)* = 40	*(b)* = 100	n = a + b = 140
Drug *(i)* = No	*(c)* = 100	*(d)* = 1160	c + d = 1260
Total	m = a + c = 140	b + d = 1260	t = a + b + c + d = 1400

the relative risk for this example is 40/14 or approximately 2,857. Therefore, this combination occurred approximately 185% higher than expected.

Natural estimates of several probabilities (although not necessarily unbiased) emerge from Table 2. For example, one can compute the conditional probability of ADR (j) given drug (i) by a/(a+b) (i.e. 40/140, in the example above). That is, the fraction observed reports listing drug (i) that also mentions ADR (j). Table 3 presents the formulas for the different association measures most commonly used, together with his probability interpretation(Harpaz et al., 2012; Zorych, Madigan, Ryan, & Bate, 2013). Here $\overline{drug}$ denotes the reports that do not include the target drug. RR, PRR, ROR and IC is the "Information Component" used by the BCPNN (Bate et al., 1998; Evans, Waller, & Davis, 2001; Szarfman, Machado, & O'Neill, 2002).

For all these four measures, a particular drug that is more likely to cause an ADR specific than any other drug usually receives a higher score. If an ADR and a drug are stochastically independent, all measures will return a null value(Zorych et al., 2013).

Frequentist approaches using one of the measures shown in Table 3 to estimate associations are usually accompanied by independence hypothesis tests (Harpaz et al., 2012). The independence hypothesis tests are used as an additional precaution, taking into account the size of the sample used in the association calculation. On the other hand, Bayesian approaches try to account for the uncertainty in the disproportionality measure associated with small observed counts through the "shrinkage" of the measure toward the base case (no association) in proportion to the statistical variability of disproportionality. The result of this shrinkage is the reduction in the number of spurious associations that are supported by an insufficient set of data.

The MGPS computes a measure known as Empirical Bayesian Geometric Mean (EBGM), which is a measure of centrality of the posterior distribution of the actual value of RR in a population(Harpaz et al., 2012). MGPS defines an a priori distribution of RR, which encapsulates a previous belief that most RR are close to the average value of all RR. Only in the face of substantial evidence of data that

Table 3. Mathematical definitions of measures of association

Measure of Association	Mathematical Definition	Probabilistic Interpretation
RR- *Relative Reporting Ratio*	(t. a)/(m n)	$\frac{P(ADR \mid drug)}{P\left(ADR\right)}$
PRR- *Proportional Reporting Ratio*	(a. (t-n))/(c.n)	$\frac{P(ADR \mid drug)}{P(ADR \mid \overline{drug})}$
ROR- *Reporting Odds Ratio*	(a. d)/(c.b)	$\frac{\frac{P(ADR \mid drug)}{P(\overline{ADR} \mid drug)}}{\frac{P(ADR \mid \overline{drug})}{P(\overline{ADR} \mid drug)}}$
IC-Information Component	Log_2 (RR)	$log_2\left(\frac{P(ADR \mid drug)}{P\left(ADR\right)}\right)$

the MGPS outputs an RR that is substantially greater than one. For example, a RR=1000 that derives from an observed count of a=1 (see Table 3) can result in an estimate of RR-MGPS (corresponding to EBGM) of 1.5 (i.e. the value of the RR is shrunk to a value near 1), while a RR=1000 that derives from an observed count of a=100 may result in EBGM estimate of approximately 1000. For the specific Bayesian configuration used by MGPS, numbers of reports of value greater than 10 results in estimates of RR which normally receive virtually no reduction, although in practice this depends on the threshold values used(Hauben, 2004; Hauben & Reich, 2004; Hauben & Zhou, 2003). Typically, ad-hoc thresholds are applied to the association measures in order to highlight strong associations. The thresholds selected usually do not have theoretical or empirical justification(Harpaz et al., 2012). Rather, they are a preliminary means of filtering or sorting.

EBGM is the average measurement of the posterior distribution of the true RR. Other measures are possible. For example, Dumouchel has introduced the measure "EB05"(DuMouchel, 1999). This measure corresponds to 5th percentile of the posterior distribution-which means that there is a 95% probability that the "true" RR exceeds EB05. As the EB05 is always less than EBGM, the EB05 represents a more conservative choice than the EBGM.

The Bayesian approach is more adopted by health authorities. The FDA uses the MGPS, more specifically EB05(Harpaz et al., 2012). The WHO, uses the BCPNN, which estimates a Bayesian version of the Information Component(Harpaz et al., 2012).

It is worth mentioning that there is no consensus on which DPA approach is best, and no gold-standard has been established to evaluate the performances of the various approaches (Harpaz et al., 2012; Huang, Guo, Zalkikar, & Tiwari, 2014). Frequentist approaches are more computationally efficient that Bayesian measures, but may generate more false positives. The Bayesian approaches also incorporate information about disproportionality and sample size in a single dimension. Nevertheless, none of the approaches can effectively address reporting biases or confounding factors(Harpaz et al., 2012).

Big Data

Big data is a term used to describe datasets whose processing by conventional database management systems is problematic, due to any combination of their size (volume), update frequency (speed), or diversity (heterogeneity)(Hay, George, Moyes, & Brownstein, 2013).

The concept of Big Data is strongly related to the Data Deluge phenomenon(Hey & Trefethen, 2003). The data deluge refers to the situation where the exponential growth in the generation of new data makes the management and analysis of these data increasingly complex.

Exponential data growth not only requires new technologies for accessing and integrating these data, but also the development of new analytical methods that are computationally efficient and effective data processing can be very noisy(Reshef et al., 2011).

Indeed, the processing of a large volume of data can be used to identify unknown associations between drugs and AE. For example, White and colleagues investigated the use of search logs in pharmacovigilance(White, Tatonetti, Shah, Altman, & Horvitz, 2013). During this research, it was observed an association between hyperglycemia and the simultaneous utilization of paroxetine and pravastatine. This Association has been subsequently confirmed by other data. This analysis processed 82 million search logs, obtained from 6 million users during the 2010 year.

The combination of data from multiple sources can make more effective the detection of AE associated with drugs. One possible combination is the joint analysis of AERS and EHR. Harpaz and colleagues(Harpaz et al., 2013) used this combination of heterogeneous data to identify a new associa-

tion between rasburicase and acute pancreatitis, by processing of 4 million of AERS and 1.2 million of EHR. The combined system indicated an association between rasburiscase and a high level of pancreatic enzymes. This association was not established before the data collection related to this study, and it was confirmed afterwards.

It is worth noting that the use of Big Data in conjunction with a large processing power is also being used as a complementary system to traditional epidemiological surveillance networks. For example, you can use Google's search logs for tracking of influenza in a population(Ginsberg et al., 2008). Ginsberg and colleagues showed that the relative frequency of certain queries in Google is highly correlated with the percentage of doctor visits in which a patient presents with symptoms of influenza. Of the 50 million most frequent queries made through Google, 45 consultations with high level of correlation with data from medical visits related to influenza, provided by the CDC, were selected to compose the linear prediction model. Thus, it was possible to accurately estimate the level of weekly influenza activity in each region of the United States, with a lag of information one day. This approach makes possible the use of search logs to detect influenza epidemics in areas with a large population of web users. A similar system was developed for the monitoring of dengue(Chan, Sahai, Conrad, & Brownstein, 2011).

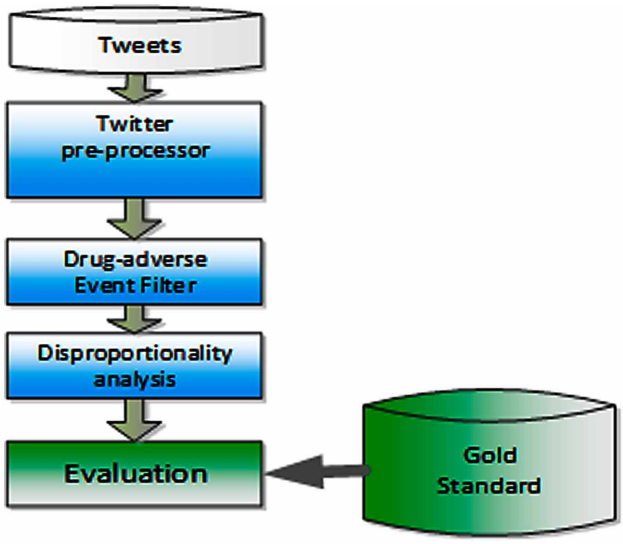
Searching on Social Networks

Other equivalent systems, this time using Twitter messages as a source of data to monitor flu symptoms, are described in the literature(Lampos & Cristianini, 2012; Signorini, Segre, & Polgreen, 2011). It is noteworthy, however, that these systems are subject to errors, as overestimations(Butler, 2013).

One research objective is to prove that Twitter can be used as a source to find new and already known ADR. This proposal has a prominent social relevance, as it will support already established pharmacovigilance systems. Some preliminary results in that direction were presented at Duval et al. 2014 and summarized below. The corresponding processing pipeline is presented in Figure 1.

Twitter(F, ER, OG, & FAB, 2014) is a social network and microblogging service made up of 140-character messages called tweets. In the pre-processing stage, data is processed in order to facili-

Figure 1. Twitter processing pipeline



tate the identification of a drug and the potential ADR associated to it. This stage has an initial step that consists of collecting tweets to process them afterwards. A filtering process that extracts drugs, diseases and symptoms information from tweets to be mapped to Concept Unique Identifiers defined by the UMLS(Bodenreider, 2004). The remaining tweets are processed in the disproportionality analysis stage, and the main results of this analysis are evaluated against a gold-standard of ADR (see Figure 1).

We calculated the amount of tweets related to some neglected diseases since its creation in 2006, but until 2008 there were few per month (less than 200), so we decided to process only tweets from 2008/Jan to 2014/Jun.

We searched for tuberculosis (n=196790), chagas disease (n=19999), leishmania (n=53338), dengue (n=3587284) and malaria (n=2161169) (see Figure 2) and their related drugs: mefloquine, lariam, chloroquine, doxycycline and primaquine.

We also queried AIDS/HIV and its drugs: efavirenz, abacavir, stavudine, delavirdine, didanosine, etravirine, emtricitabine, zidovudine, nevirapine, lamivudine, rilpivirine (see Table 4).

This system is still under construction, and this is one of multiple pipelines, each one with different data sources that will then be combined to obtain new ADR and historical changes in already knew ADR. We already found strong indication that tweets can be used as a source for pharmacovigilance.

List of Recommendations

The main recommendations are:

- Give access to pharmacovigilance forms from existing IS or on computer desktops links.
- Implement webservices to exchange ADR information and feedback between the pharmacovigilance IS and other IS (e.g. EHR, prescription software, laboratory software, among others).

Figure 2. Tweets since January 2008

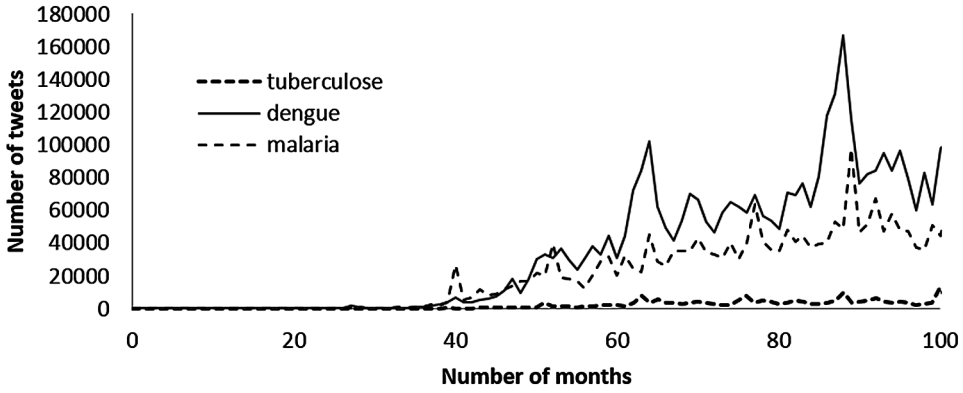


Table 4. Disproportionality analysis results

Disease/Drug/ADR	Reporting Ratio
HIV/lamivudine/rash	41.95414
Malaria/ chloroquine/itching	35.57355
Malaria/chloroquine/vomit	12.61881

- Use websites and social networks to disseminate information on drug safety and promote ADR reporting.
- Create data mining processes to search ADR on websites, social networks and EHR.

FUTURE RESEARCH DIRECTIONS

The authors believe that much work can be done to use informatics in improving pharmacovigilance.

As future work, pharmacovigilance websites can be explored to create a personal area for each person that submits an ADR, aiming to turn the ADR reporting act in a motivating and informative activity. It should provide technical information about the reported adverse reaction and the suspected drug, during the ADR report act, and give feedback. Another research plan is to use a pharmacovigilance facebook page to encourage ADR report by its members, conducting research work similar to those performed by Knezevic et al.

It should also be carefully developed ADR reporting forms adjusted to patients report. These forms should be simple and easy to fulfill, with accessible language (not too technical).

Authors see as a promising solution the integration in a single database all the suspected ADR detected within a healthcare institution. These ADR will then be sent to the Authority through regional pharmacovigilance centres. These centres will provide feedback related to the reported ADR.

An emerging research topic in pharmacovigilance is that the combination of information from multiple data sources may lead to more effective and accurate discovery of ADR. Depending on the data sources used, and how they are combined, it is believed that the resulting system could raise the statistical significance of results or facilitate new discoveries that are not possible using a single data source. It should be establish a database as a reference (gold) standard for adverse reactions, from the systematic exploration of heterogeneous data sources and more comprehensive than is recommended by Harpaz and colleagues.

CONCLUSION

Pharmacovigilance should use informatics to promote and complement spontaneous ADR report. Integration of pharmacovigilance databases with other healthcare IS seems to be an easy way to promote ADR reports among healthcare professionals. In addition, the trend of use of social networks has been exploited by pharmacovigilance with mechanism to detect adverse reactions among these networks.

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RESEARCH ARTICLE Open Access

How to promote adverse drug reaction reports using information systems – a systematic review and meta-analysis

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Abstract

Background: Adverse drug reactions (ADRs) are a well-recognized public health problem and a major cause of death and hospitalization in developed countries. The safety of a new drug cannot be established until it has been on the market for several years. Keeping drug reactions under surveillance through pharmacovigilance systems is indispensable. However, underreporting is a major issue that undermines the effectiveness of spontaneous reports. Our work presents a systematic review on the use of information systems for the promotion of ADR reporting. The aim of this work is to describe the state of the art information systems used to promote adverse drug reaction reporting.

Methods: A systematic review was performed with quantitative analysis of studies describing or evaluating the use of information systems to promote adverse drug reaction reporting. Studies with data related to the number of ADRs reported before and after each intervention and the follow-up period were included in the quantitative analysis.

Results: From a total of 3865 articles, 33 articles were included in the analysis; these articles described 29 different projects. Most of the projects were on a regional scale (62 %) and were performed in a hospital context (52 %). A total of 76 % performed passive promotion of ADR reporting and used web-based software (55 %). A total of 72 % targeted healthcare professionals and 24 % were oriented to patient ADR reporting. We performed a meta-analysis of 7 of the 29 projects to calculate the aggregated measure of the ADR reporting increase, which had an overall measure of 2.1 (indicating that the interventions doubled the number of ADRs reported).

Conclusions: We found that most of the projects performed passive promotion of ADR reporting (i.e., facilitating the process). They were developed in hospitals and were tailored to healthcare professionals. These interventions doubled the number of ADR reports. We believe that it would be useful to develop systems to assist healthcare professionals with completing ADR reporting within electronic health records because this approach seems to be an efficient method to increase the ADR reporting rate. When this approach is not possible, it is essential to have a tool that is easily accessible on the web to report ADRs. This tool can be promoted by sending emails or through the inclusion of direct hyperlinks on healthcare professionals' desktops.

Keywords: Adverse drug reactions report, Information systems, Pharmacovigilance

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Background

Adverse drug reactions (ADRs) are a well-recognized public health problem worldwide and a major cause of death and hospitalization in developed countries [1]. Rare and long-term ADRs are difficult to detect during the drug development stage. Detecting new ADRs not previously identified during clinical trials is only possible when the drug begins to be used by a large population after marketing authorization (MA). The safety of a new drug cannot be established until it has been on the market for several years [2]. As such, it is indispensable to keep drug reactions under close surveillance after commercialization through a pharmacovigilance system to continuously evaluate the drug's safety profile. In most countries, the pharmacovigilance system is based on spontaneous ADR reports made by healthcare professionals and consumers [3]. These reports can be made using paper, telephone, e-mail or through an on-line form and consist of a description of an adverse event apparently caused by a medicine. Spontaneous ADR reporting has been described as an efficient method to detect drug safety signs [4]; however, underreporting is a major issue that undermines the effectiveness of spontaneous reports. Several studies have suggested that less than 10 % of detected ADRs are effectively reported to medicine regulatory authorities [5, 6].

Worldwide, systems using informatics to promote ADR reporting or to detect the occurrence of ADRs in healthcare institutions have been tested and used, such as computer programs that allow voluntary and automated detection of ADR [7, 8] informatics tools created to analyse clinical databases [9] or websites that actively inform healthcare professionals [10].

In addition to signal detection, information and communication technologies can also be used to encourage and facilitate reporting of suspected ADR.

In the present work, a systematic review is presented on the use of information systems in pharmacovigilance. Our main goal is to describe the state of the art information systems for the passive or active promotion of adverse drug reaction reporting.

Methods

Eligible studies

Studies describing or evaluating the use of information systems to promote adverse drug reaction reports were selected.

Review team

The review team is composed of two pharmacists who are experts in pharmacovigilance (Inês Ribeiro Vaz (IV) and Ana Marta Silva (AS)) and the computer scientist Ricardo Cruz Correia (RC), who is an expert in medical informatics.

Search methods

Studies were searched in April 2014 in the bibliographic databases. We developed a search query that included the concepts adverse drug reaction, adverse drug reaction reporting system, pharmacovigilance and information system. Only articles written in English, Portuguese or French were included. We did not establish any criteria for the publication date.

Four distinct bibliographic databases were searched: Medline (via PubMed); ISI (ISI Web of Knowledge); IEEE (IEEE Xplore) and Scopus. The query search string used in Medline® was *((ADR OR "adverse drug reaction" OR "adverse drug reactions" OR "adverse drug event" OR "adverse drug events" OR "adverse dug effect" OR "adverse drug effects") OR "pharmacovigilance").* A similar query was used in the other databases and was adapted to the search engine.

Selection of studies for the review

The first selection was based on the study title and abstract (when available). Two reviewers on the review team (IV and AS) were involved in study selection and read all titles/abstracts. The study was considered eligible when at least one of the reviewers decided that the title/abstract mentioned the key concept of using information systems for ADR reporting. In cases of disagreement, a consensus meeting was held with the third reviewer (RC) to decide whether the article should be selected.

The second phase of study selection was based on the full text. The team leader (IV) reviewed each full-text article. In this stage, articles were excluded based on the following criteria: (1) the articles were only focused on medication errors; (2) the articles focused on ADR detection; (3) the articles were studies without any information system implemented; (4) the articles were studies concerning data quality; (5) the articles were studies focused on website usability; (6) the articles were only the authors' reflections on the theme; (7) the articles were studies only related to incidents that occurred in health institutions; (8) the articles were studies concerning signal detection and (9) the articles were studies concerning electronic transmission between the authority and other institutions (pharmaceutical companies or regional pharmacovigilance centres).

The articles remaining after this review were included in the final statistical analysis.

These articles were grouped into research projects to avoid the distortion created by multiple papers describing

the same project (Fig. 1). All statistical analyses were based on the projects and not on the articles.

Definition of variables

The variables examined in these reviews were related to the projects, papers and information systems described in each project.

We used the following data for project identification: (1) project number; (2) Information system name (if any); (3) country; (4) publication date; (5) type of study and (6) reference(s).

According to the description of the projects, the following variables were analysed:

1. Area covered by the project (i.e., region, country, or hospital)
2. Type of action promoted by the project (passive promotion of ADR reporting or active promotion of ADR reporting)
3. Type of software (i.e., web-based or mobile)
4. Type of institution (i.e., regulatory authority or universities)
5. Target (healthcare professionals or patients)
6. Type of medicine (all, vaccines, chemotherapy, or others)
7. Type of ADR (all/serious ADRs based on the World Health Organization seriousness criteria [11])

Statistical analysis

The inclusion criteria for the quantitative analysis were the availability of data related to the number of ADRs reported before and after each intervention and a follow-up period.

Studies that only disclosed the increased ADR rate and studies that reported zero ADRs before the project implementation were excluded because it was not possible to perform the analysis in these cases.

For each study with available data, the rate of ADRs reporting increase (quotient between ADR reports after and ADR reports before) and the respective 95 % confidence intervals were calculated. A rate of ADR reporting increase equal to 2 indicated that the ADR reports doubled after the intervention. Conversely, a rate of ADR reporting increase equal to 1

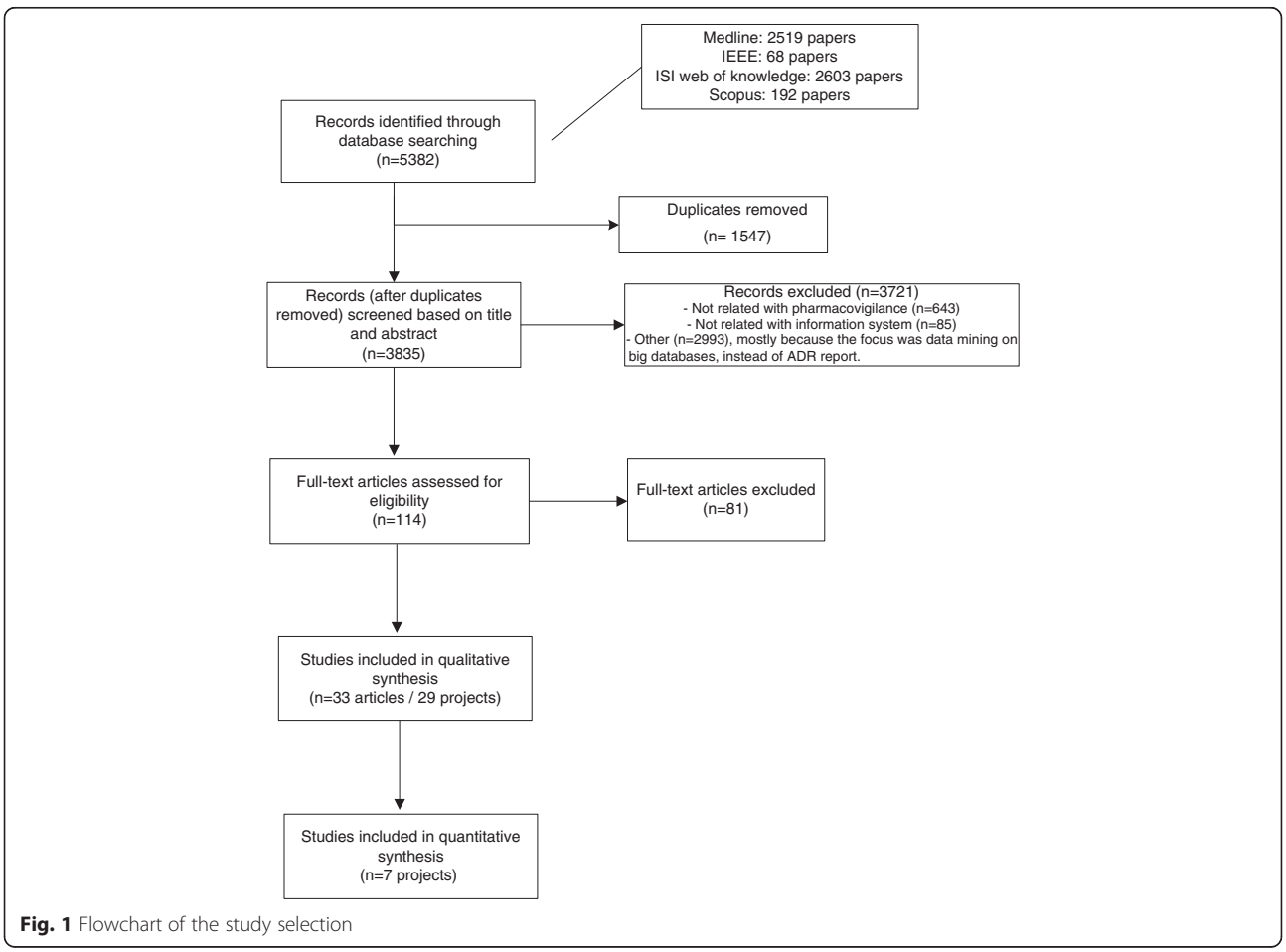

Fig. 1 Flowchart of the study selection

indicated that the number of ADR reports after the intervention was equal to the number of ADR reports before the intervention. The aggregated rate of the ADR reporting increase was calculated with the inverse variance method using a random effects model and a forest plot was presented. The confidence intervals, aggregated rate of ADRs and forest plot were performed using a Microsoft Excel spreadsheet. The description of the Microsoft Excel spreadsheet and the respective statistical methods used were described by Neyeloff [12].

Results

Our search method found 2519 articles in PubMed, 68 in IEEE, 2603 in ISI and 192 in Scopus. After eliminating duplicate articles, 3835 articles were selected.

Two reviewers (IV and AS) read all 3835 titles/abstracts. In cases of disagreement, which occurred with 151 articles, a consensus meeting was held with the third reviewer (RC) to decide whether the article should be selected.

A total of 643 studies were excluded because they were not related to pharmacovigilance, 85 were excluded because they were not related to information systems and 2993 were excluded for other reasons (mostly because their focus was on data mining in large databases instead of ADR reporting).

A total of 114 of the 3835 articles were selected in this first selection based on the title and abstract.

The team leader (IV) reviewed each of the 114 full-text articles. After this review, 33 articles remained for the final statistical analysis. At this stage, most of the articles were excluded because: (1) they were only related to medication errors; (2) they were focused on ADR detection; (3) they were studies without any information system implemented; (4) they were studies concerning data quality; (5) they were studies focused on website usability; (6) they were only authors' reflections on the theme; (7) they were studies only related to incidents that occurred at health institutions; (8) they were studies concerning signal detection or (9) they were studies concerning electronic transmission between the authority and other institutions (pharmaceutical companies or regional pharmacovigilance centres).

These 33 articles were grouped into 29 distinct research projects to avoid the distortion created by multiple papers describing the same project (Fig. 1.). All statistical analyses was based on projects and not on articles.

Table 1 lists all 29 projects, their country, the number of publications, the publication year and the journal. The country with the most published projects was the USA (11), followed by the United Kingdom (3).

Trends

There was an increasing trend in publication, especially after 2009 (Fig. 2).

Qualitative analysis

The qualitative variables analysed in each project are listed in Table 2 and described below. Globally, we found that there was an increase in the publication of projects over the study period, with 4 projects published before 2001, 4 projects between 2005 and 2007, 8 projects between 2008 and 2010 and 13 projects between 2011 and 2013.

Geographic area covered by the projects

Most of the projects were regional (62 %), followed by national projects (34 %). We found only 1 international project based on Facebook®. This international project was developed in the last time period (2011–2013).

Areas covered by the projects

Most of the projects (52 %) were developed in hospitals, followed by community projects (21 %). A total of 14 % covered primary care institutions and 10 % (3 projects) were developed for use in any type of healthcare institution. One project was dedicated to a multicentre clinical trial. We also found that all of the projects oriented to the community were developed in the last 3 years (2011–2013).

Types of actions promoted by the projects

The majority of the projects passively promoted ADR reporting (76 %); the remainder actively promoted reporting (24 %).

Types of software

More than half of the projects (55 %) used web-based technology and 41 % used electronic health records. Only one project used mobile phone technology. There was an increasing trend in software using web-based technology over all of the time intervals considered. The mobile technology appeared during the last time period.

Types of institutions promoting the studies

Most of the projects were promoted by hospitals and universities (31 % e*x aequo*). There were 4 projects developed by national institutions (not regulatory) and 5 projects implemented by regulatory authorities.

Targets

A total of 72 % of the projects were geared to healthcare professionals, 24 % to patients and one project was geared to both targets. Most of the projects targeting

Table 1 Project identification

Project number	System name (if any)	Country	Number of publications	Publication date(s)	References	Journals
4		USA	1	1992	[32]	Hospital pharmacy
28		France	1	2001	[26]	Fundamental & Clinical Pharmacology
11		Japan	1	2002	[33]	Yakugaku Zasshi-Journal of the Pharmaceutical Society of Japan
17		USA	1	2004	[34]	American Journal of Health-System Pharmacy
2		USA	3	2005, 2007	[25, 35, 36]	Journal of Clinical Oncology, Journal of American Medical Information Association
22		USA	2	2005, 2006	[28, 37]	Biosecurity and Bioterrorism-Biodefense Strategy Practice and Science, Health Expectations
10		USA	1	2007	[29]	Journal of the American Medical Informatics Association
9	MEADERS	USA	2	2007, 2010	[23, 38]	Annals of Family Medicine, AMIA Annual Symposium proceedings
21		Spain	1	2008	[39]	Annals of Pharmacotherapy
7		Sweden	1	2009	[15]	European Journal of Clinical Pharmacology
5		Canada	1	2010	[40]	International Journal of Medical Informatics
13		Canada	1	2010	[27]	Vaccine
18		USA	1	2010	[41]	Pharmacoepidemiology and Drug Safety
19		United Kingdom	1	2010	[42]	Archives of Disease in Childhood
23	ALIAS	USA	1	2010	[43]	Contemporary Clinical Trials
27		Taiwan	1	2010	[14]	Value in Health
8		United Kingdom	1	2011	[44]	Journal of Psychiatric and Mental Health Nursing
12		Serbia	1	2011	[20]	Drug Safety
14		France	1	2011	[13]	Therapie
15		USA	1	2011	[21]	Paediatrics
6		United Kingdom	1	2012	[45]	Drug Safety
16		Korea	1	2012	[46]	Yonsei Medical Journal.
20		Portugal	1	2012	[16]	Drug Safety
25		USA	1	2012	[47]	2012 Ninth International Conference on Information Technology: New Generations
1		Cambodge	1	2013	[22]	Journal of Medical Internet Research
3		Netherlands	1	2013	[18]	Studies in health technology and informatics
24	SALUS	France	1	2013	[48]	Studies in health technology and informatics
26		Spain	1	2013	[49]	International Journal of Clinical Pharmacy
29		Denmark	1	2013	[17]	European Journal of Hospital Pharmacy-Science and Practice

patient ADR reporting were developed in the last years considered (2011–2013).

Types of medicine

Most of the projects (72 %) covered all medicines, but 17 % were specific to vaccines. There were also projects specific to reporting ADRs due to chemotherapy, human albumin and radiopaque agents (1 project for each of these medicines).

Types of ADR

Only a small percentage of the projects were specific for serious adverse drug reactions. The majority (93 %) covered all ADR.

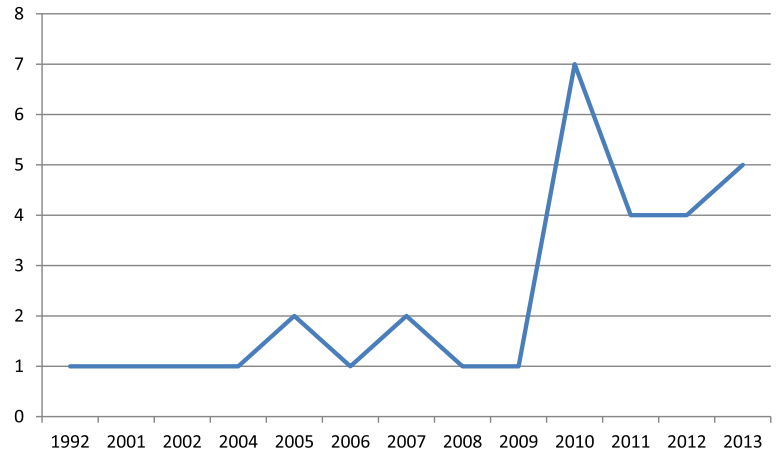

Fig. 2 Number of publications by year

Quantitative analysis

From the 29 projects analysed, seven projects met the criteria for inclusion in the quantitative analysis (meta-analysis). The criteria used were the availability of data related to the number of ADR reported before and after each intervention and a follow-up period.

From the seven projects included in the quantitative analysis, six had the same follow-up period (12 months) and only one (project 14) differed on this item (18 months of follow-up). The results are described in Table 3.

We performed a meta-analysis with these seven projects to calculate the aggregated measure of the ADR reporting increase. The overall measure was 2.1, which indicated that the interventions performed in the analysed projects doubled the number of ADR reports (Fig. 3).

Projects 14, 7 and 6, which had similar ADR reporting increases, used different approaches. The authors of project 14 assessed an online ADR reporting form, in project 7 the authors send repeated e-mails with ADR information to healthcare professionals and project 6 evaluated the inclusion of a reporting system inside the clinical information system.

Four of the information systems that contributed to the improvement of ADR reporting used web-based technology. Two used an online reporting form (Project 14 [13] and Project 27 [14]) to facilitate ADR reporting. A Swedish group opted to evaluate the effect of repeated emails to health care professionals that contained attached ADR information (Project 7 [15]). A Portuguese study tested the inclusion of hyperlinks to the online ADR reporting form on hospitals' electronic patient records (Project 20 [16]) to facilitate access to the ADR form.

Three projects explored the use of electronic health records to directly report the ADRs (projects 29, 6 and 17). Among these, project 29 [17], which had the best result in terms of the ADR reporting increase, was a system that completed the ADR report whenever a physician required assistance.

Discussion

Although a limited number of projects was included in our work (n = 29), our data suggest that the number of projects that aimed to promote ADR reporting using information technologies increased over time.

Study selection was performed as a manual review; this approach caused a huge workload because we obtained more than 3000 articles. An optimized query would reduce the workload but lose sensitivity.

As expected, most of the projects that aimed to promote adverse drug reactions reporting were developed in hospitals and tailored to healthcare professionals. In fact, most of the serious ADRs were detected in hospitals and reported by healthcare professionals [18]. For example, in Europe direct reporting (ADRs reported by patients) has only been allowed for every country since 2012 [19]. This finding may also explain why most of the projects that targeted direct ADR reporting were developed in the last 3 years of the study period (2011–2013) [18, 20–22].

Most of the authors chose to develop systems for the passive promotion of ADR reporting because busy healthcare professionals only submit their suspected ADR if it does not increase their workload [23, 24]. Active promotion of ADR reporting is difficult and not always ethically acceptable because no material reward can be given to the reporters. Thus, projects that aimed to actively promote ADR reporting involved teaching sessions [25] or e-mails containing ADR information [15, 18, 26, 27].

Our results suggested that there was an increasing trend in the use of web-based software to promote ADR reporting, which could be explained by the

Table 2 Qualitative analysis of the projects

Variable	Time period				Total (%)	Project numbers
	<2004 (4 projects)	2005–2007 (4 projects)	2008–2010 (8 projects)	2011–2013 (13 projects)		
Geographic area covered by the project						
Regional	4	3	5	6	18 (62)	2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 20, 21, 22, 26, 27, 28, 29
National	0	1	3	6	10 (34)	1, 3, 6, 9, 15, 18, 19, 23, 24, 25
International	0	0	0	1	1 (3)	12
Area covered by the project						
Hospital	4	2	5	4	15 (52)	2, 4, 5, 8, 11, 13, 17, 18, 20, 21, 22, 26, 27, 28, 29
Community	0	0	0	6	6 (21)	1, 3, 12, 14, 15, 16
Primary care	0	2	1	1	4 (14)	6, 7, 9, 10
Other healthcare institutions *(different from hospitals or primary care)*	0	0	1	2	3 (10)	19, 24, 25
Clinical trials	0	0	1	0	1 (3)	23
Type of action promoted by the project						
Passive promotion of ADR reporting	3	3	6	10	22 (76)	4, 5, 6, 8, 9, 10, 11, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 29
Active promotion of ADR reporting	1	1	2	3	7 (24)	1, 2, 3, 7, 12, 13, 28
Type of software						
Web-based	1	3	6	6	16 (55)	2, 3, 5, 7, 9, 12, 13, 14, 15, 16, 19, 20, 22, 23, 27, 28
System inside the Electronic Health Record	3	1	2	6	12 (41)	4, 6, 8, 10, 11, 17, 21, 24, 25, 26, 18, 29
Mobile	0	0	0	1	1 (3)	1
Type of institution promoting the study						
Hospital	2	1	3	3	9 (31)	2, 4, 8, 17, 18, 21, 26, 27, 29
University	1	1	3	4	9 (31)	5, 10, 11, 12, 13, 19, 20, 24, 25
National institution	0	2	0	2	4 (14)	1, 9, 15, 22
Regulatory authority	1	0	1	3	5 (17)	6, 7, 14, 16, 28
Other[a]	0	0	1	1	2 (7)	3, 23
Target						
Healthcare professionals	4	2	7	8	21 (72)	4, 6, 7, 8, 9, 10, 11, 13, 14, 16, 17, 18, 19, 21, 23, 24, 25, 26, 27, 28, 29.
Patients	0	2	1	4	7 (24)	1, 2, 3, 5, 12, 20, 22
Healthcare professionals and patients	0	0	0	1	1 (3)	15
Type of medicine						
All	4	1	5	11	21 (72)	3, 4, 5, 6, 7, 8, 9, 11, 12, 14, 16, 17, 18, 19, 20, 21, 24, 25, 26, 28, 29
Vaccines	0	2	1	2	5 (17)	1, 10, 13, 15, 22
Chemotherapy	0	1	0	0	1 (3)	2
Human albumin	0	0	1	0	1 (3)	23
Radiopaque agents	0	0	1	0	1 (3)	27

Table 2 Qualitative analysis of the projects *(Continued)*

Type of ADR						
All	4	4	8	11	27 (93)	2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29
Serious	0	0	0	2	2 (7)	1, 3

[a] Other institutions are: Clinical trial team (project 23) and website producer (project 3)

dissemination of internet use. Nevertheless, mobile technology was also appearing.

Most of the retrieved projects covered all medicines and ADR, whereas only a few were specific. However, we found 5 projects dedicated to vaccine adverse reactions [21, 22, 27–29] and in the last 3 years two projects were developed to specifically report serious ADR [18, 22].

The institutions that primarily promoted this work were universities and hospitals because universities have the know-how to perform these actions and hospitals have specific needs to be solved. However, regulatory authorities have been increasing their involvement in the development of this type of project.

A limitation of this study is that a grey literature search was not performed. However, we think that this lack does not cause a large bias because regulatory authorities are less likely to produce this type of project. When regulatory authorities are involved in projects of this scope, they usually associate with universities and hospitals that have a greater incentive to publish.

Based on our quantitative analysis, we can conclude that all of the projects analysed increased the ADR reporting numbers (most by approximately two-fold). We found two projects that increased ADR reporting by more than two-fold [14, 17], perhaps because their basal values were much lower compared with the other five projects. A similar effect was noted previously in two other studies when the same population of health care professionals was exposed to the same educational interventions two different times [30, 31]. After the first intervention, the authors achieved a much higher effect and ADR reporting increased compared to the second intervention due to the differences in the initial values.

In our quantitative analysis, we found a limitation concerning the aggregation of the information because we found only 7 studies that provided data concerning its impact on the increase in ADR reporting. These data were not available for the other studies even after we contacted the authors. However, we did not identify any variable that could distinguish these 7 projects from the other 22 projects. We must reiterate the importance of providing quantitative data when publishing studies focused on interventions that aim to promote ADR reporting.

Worldwide underreporting of ADR is a major concern, and many institutions are aware that it is feasible to use information systems to improve ADR reporting. The most commonly used platform is web-based and exhibits an increasing trend, but interventions inside electronic health records also have the potential to improve pharmacovigilance activities and particularly ADR reporting. Direct ADR reporting is being increasingly taken into account when the aim is to improve information on drug safety.

Based on our results, we believe that it would be useful to adopt a system to assist healthcare professionals with completing ADR reporting within electronic health records because this approach seems to be an efficient method to increase the ADR reporting rate. When this approach is not possible, it is essential to have a tool that is easily accessible on the web to report ADR. This tool can be promoted by sending emails or through the inclusion of direct hyperlinks on healthcare professionals' desktops.

Table 3 Intervention effect on ADR reporting increase

Study	ADR reports before	ADR reports after	Rate	CI lower	CI upper
Project 14	287	415	1,44	−0,18	3,07
Project 7	89	111	1,25	−0,51	3,00
Project 29	30	162	5,4	4,56	6,24
Project 6	3279	4716	1,44	−0,20	3,072
Project 17	118	294	2,49	1,25	3,73
Project 27	20	62	3,1	1,99	4,21
Project 20	82	212	2,58	1,37	3,80

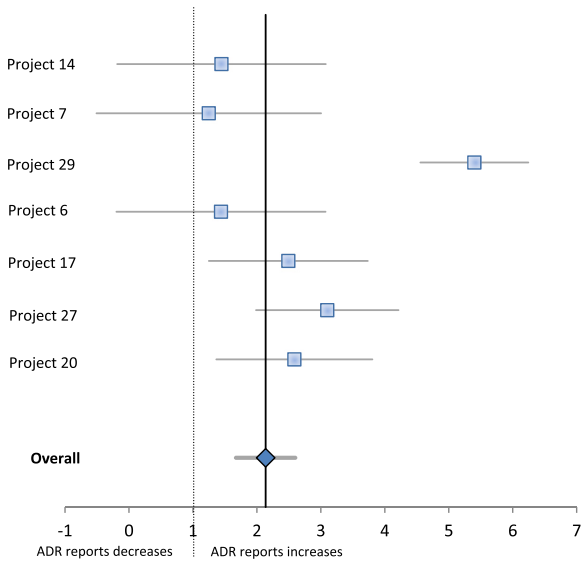

Fig. 3 Rate (ADR reports after/ADR reports before) of ADR report increase (95 % IC)

Conclusions

Our systematic review allowed us to note some facts about interventions that aim to improve ADR reporting using information systems. According to our aggregation analysis, these interventions doubled the number of ADR reports. We also found that most projects passively promoted ADR reporting (facilitating the reporting process) and the countries involved in this type of project were Northern America countries (USA and Canada), European countries and in a smaller number Far East countries.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

IV and RC were responsible for the development of the query. IV also performed data collection and was the team leader for article screening and the writing of the manuscript. AS performed the article screening. RC was involved on the article selection when there was disagreement between the other two reviewers (IV and AS). CS performed the quantitative analysis. All four authors were involved in the writing of the manuscript, discussion and the revision of the whole article. All authors read and approved the final manuscript.

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Promoting adverse drug reaction reporting: comparison of different approaches

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ABSTRACT

OBJECTIVE: To describe different approaches to promote adverse drug reaction reporting among health care professionals, determining their cost-effectiveness.

METHODS: We analyzed and compared several approaches taken by the Northern Pharmacovigilance Centre (Portugal) to promote adverse drug reaction reporting. Approaches were compared regarding the number and relevance of adverse drug reaction reports obtained and costs involved. Costs by report were estimated by adding the initial costs and the running costs of each intervention. These costs were divided by the number of reports obtained with each intervention, to assess its cost-effectiveness.

RESULTS: All the approaches seem to have increased the number of adverse drug reaction reports. We noted the biggest increase with protocols (321 reports, costing 1.96 € each), followed by first educational approach (265 reports, 20.31 €/report) and by the hyperlink approach (136 reports, 15.59 €/report). Regarding the severity of adverse drug reactions, protocols were the most efficient approach, costing 2.29 €/report, followed by hyperlinks (30.28 €/report, having no running costs). Concerning unexpected adverse drug reactions, the best result was obtained with protocols (5.12 €/report), followed by first educational approach (38.79 €/report).

CONCLUSIONS: We recommend implementing protocols in other pharmacovigilance centers. They seem to be the most efficient intervention, allowing receiving adverse drug reactions reports at lower costs. The increase applied not only to the total number of reports, but also to the severity, unexpectedness and high degree of causality attributed to the adverse drug reactions. Still, hyperlinks have the advantage of not involving running costs, showing the second best performance in cost per adverse drug reactions report.

DESCRIPTORS: Drug-Related Side Effects and Adverse Reactions. Forms and Records Control. Drug Monitoring. Adverse Drug Reaction Reporting Systems. Pharmacovigilance.

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INTRODUCTION

Adverse drug reactions (ADR) are inherent to medicine use[20], and most of them can only be detected after the commercialization of the drug[14]. In fact, during clinical trials, rare reactions are hardly detected, as well as the ones associated with chronic utilization of the drug. It is also difficult to predict the drug effect among special populations (pregnant women, children, older adults), as they usually do not participate in the clinical research.

Because of these limitations, post-marketing surveillance is essential, which is why most countries have pharmacovigilance centers to monitor detected ADR. The fundamental tool used by these centers is the spontaneous reporting of ADR by healthcare professionals and consumers. This method consists in describing an adverse episode suspected to be caused by one or more drugs and provides valuable information to the regulatory health authorities, which is important for the decisions about marketed medicines. The biggest problem of this method is the underreporting, i.e., ADR are detected but not reported to national regulatory health authorities. Most developed countries face this situation[15,19]. Worldwide, many approaches have been completed to fight the major problem of ADR underreporting, such as regular visits to health professionals[10], questionnaire studies[2], educational interventions (including workshops, meetings and presentations)[4,12,16], among others.

This study aimed to describe several approaches that intended to improve ADR reporting and determine the cost-effectiveness of each one of them.

METHODS

From its creation (in 2000) to 2003, Northern Pharmacovigilance Centre, a Portuguese regional pharmacovigilance center, had an extremely low rate of ADR reports, about 43 per year/million inhabitants. We realize this value is very low when compared with the World Health Organization (WHO) recommendation for an Optimal National Centre, which is at least 200 reports per year/million inhabitants[a].

To reach its objectives, in 2004 the Centre established a collaboration protocol (*protocol approach*) with the immunoallergology department of a central hospital (located on the same street as the Centre) to collect every suspected case of ADR emerged in appointments related to drug allergies. This collaboration includes regular visits of the pharmacovigilance staff to the immunoallergology department to collect the detected cases in ADR report forms, under the physician supervision. Then, the form is signed by the physician and follows the normal course of all the ADR spontaneous reports. This approach was replicated two more times, in 2007 and 2009, in two other immunoallergology departments, one from a specialized hospital (pediatric hospital, located 6 km from the Centre) and another from a central hospital (located 11 km from the Centre). These three protocols remain active.

A study conducted in 2004 provided educational interventions (*educational approach*) for physicians and pharmacists[4,8]. Those interventions were based on a previous case-control study that identified the reasons for underreporting[6,7]. The educational approach includes workshops about pharmacovigilance at health care professionals' working places.

Since the effect of educational interventions decreased over time, the authors of the previously described work promote reinforcement interventions (*educational and telephone approach*). We started a new study in 2007, also among physicians and pharmacists. This study consisted not only in outreach interventions (workshops), but also in telephone interviews[9,17]. The phone interviews followed a script about ADR and the importance of reporting. Details are described in a previous publication[17].

[a] Governo de Portugal, INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde. *Farmacovigilância em Portugal*. Lisboa: INFARMED; 2004.

We propose a new approach: the inclusion of a hyperlink (*hyperlink approach*) to an online ADR reporting form on hospitals' electronic patient records (EPR). The main aim of this study, performed from 2006 to 2010, was to evaluate the impact of these hyperlinks on the number of spontaneous ADR reports[18]. The inclusion of hyperlinks began in December 2007 and continued over the following five months. The temporal distribution of all these approaches is shown in Figure 1.

In the present work, we analyzed the number of ADR reports obtained with each one of the described approaches. We know exactly which ADR reports were originated at the three departments participating in the protocol intervention and analyzed them separately. Four physicians were involved.

The first educational intervention (in 2004) involved three hospitals, 26 healthcare centers, and 73 pharmacies. About 900 health care professionals attended these interventions[4]. About 340 health care professionals (physicians and pharmacists) attended the second intervention (second workshop + telephone, both in 2007). Five health care centers, two hospitals, and 40 pharmacies received the telephone intervention, and 16 health care centers, two hospitals, and 23 pharmacies received the second educational intervention.

For the hyperlinks, we estimated 15,000 health care professionals potentially affected by the intervention, as this is the total number of professionals working at the 12 participating hospital centers (corresponding to 22 hospitals). It was the first exposure to any intervention for eight of these hospital centers.

The variables analyzed were: type of approach, ADR relevance, initial costs of the interventions, running costs of the interventions, and costs per ADR report. Each of these variables is described as follows.

- Type of approach: hyperlink, protocol, educational, and telephone approach.
- Number of ADR reports obtained with each intervention: the difference between ADR reports received two years after the intervention and ADR reports received two years before the intervention.
- ADR relevance: we adopted the following criteria: (1) ADR severity; (2) ADR expectedness; and (3) causality attributed to the ADR report. A serious ADR is any untoward medical occurrence that results in death, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is life-threatening[2]. An unexpected ADR is the one in which the nature or severity is not consistent with domestic labeling or market authorization, or expected from characteristics of the drug[2]. We considered an ADR more relevant if one of the two highest degrees of causality was attributed to it: (1) definitive or certain, or (2) probable (the medicine was the likely causative agent of an observed adverse reaction)[b].
- Initial costs of the interventions: we consider as initial costs the expenses needed for implementing the approach, as educational material and staff working hours. These costs are described in Table 1.

[b] World Health Organization; Uppsala Monitoring Centre Uppsala. Uppsala: Uppsala Monitoring Centre Uppsala [updated 2015 Aug 18; cited 2013 Aug 9]. Available from: http://www.who-umc.org/DynPage.aspx?id=22682

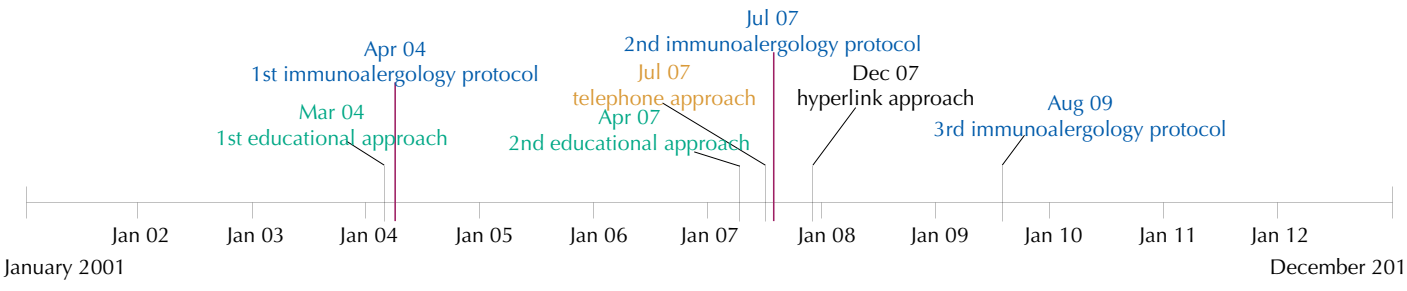

Figure 1. Timeline of the studied approaches.

- Running costs of the interventions: annual running costs are the expenses needed for continuing the projects, as fuel, material and staff working hours. These costs are described in Table 1. We did not consider the normal (daily) costs of ADR report processing, as we only meant to compare the costs involved in obtaining ADR reports.
- Costs per ADR report: costs by ADR report were estimated by adding initial costs and running costs. Initial costs per ADR report were obtained by dividing initial costs by the difference between ADR reports received two years after the intervention and ADR reports received two years before the intervention (which we consider to be the number of notifications obtained with each intervention). Running costs were obtained by dividing the running costs of the two-year intervention by the number of notifications obtained with each intervention. To assess the cost-effectiveness of each intervention, we considered the sum of these costs (initial + running costs) as the total cost of each ADR obtained in the two years following each intervention.

The pharmacovigilance center website uses a web server and has audit trails that read each site visit since 2006. These audit trails are processed using the Webalizer program (www.webalizer.org) to estimate site hits, user logins and visits. ADR reports obtained by these approaches are included in a database. We collect them by selecting the report date and origin.

We presented the total number of reports received in each quarter during the period studied. For each health institution, ADR reports made before and after the intervention, if any, were measured.

To examine whether each intervention increased the ADR report trend, an interrupted time series analysis using autoregressive integrated moving average (ARIMA) was performed using quarter data of ADR reports, as well as each intervention (first and second educational approach, telephone approach, and hyperlink approach) as dichotomous variables (before and after intervention).

We performed an additional analysis with the hyperlinks approach, to consider the institutions exposed to any type of intervention for the first time. With this sub-analysis we intended to isolate the ADR reports obtained with each intervention.

This study was approved by the local Ethics Committee of the Faculdade de Medicina of the Universidade do Porto (Process PCEDCSS-FMUP 08/2014, approved in May 7, 2014).

Table 1. Estimated costs of each approach.

Approach	Initial costs		Annual running costs	
	Value	Description	Value	Description
Protocol approach	150 €	Pharmacovigilance and clinical service staff working hours	240 €	Fuel, material, and pharmacovigilance and clinical staff working hours
Hyperlink approach	2,120 €	Pharmacovigilance and software development staff working hours	-	-
Educational approach	200 €	Educational material and pharmacovigilance staff working hours	2,500 €	Fuel, material, and pharmacovigilance staff working hours
Telephone approach	400 €	Telephone calls during the pilot study and pharmacovigilance staff working hours	800 €	Telephone calls, material, and pharmacovigilance staff working hours

RESULTS

We found an increasing trend in the number of ADR reports received by the Northern Pharmacovigilance Centre during the studied period: 2000-2012. The number of annual ADR reports increased from the year in which the first interventions were made (2004) to the end of the study period (Figure 2).

Excluding the ADR reports obtained with the protocol approach, the only intervention that significantly increased the ADR report trend was the first educational approach, in the first quarter of 2004 ($p < 0.001$).

We did not find a significant increase in the ADR report trend in the second educational approach in second quarter of 2007 ($p = 0.203$). The telephone approach also failed to significantly increase ADR reporting in the third quarter of 2007 ($p = 0.243$). With the hyperlink approach we observed a slight increase in ADR reporting, although without statistical significance ($p = 0.193$).

All the approaches increased the number of ADR reports, when we compare the two years before with the two years after the interventions. We noted the biggest increase with the protocol approach (321 ADR reports obtained), followed by the first educational approach, with 265 ADR reports obtained, and by the hyperlink approach, with 136 ADR reports. For the hyperlink approach, we isolated the institutions exposed to an intervention for the first time; these cases obtained 141 ADR reports.

According to the initial costs involved, our results suggest that the protocol approach is the most cost-effective, costing 0.47 € per ADR report, followed by the first educational and telephone approach, costing 0.78 € per ADR report. Analyzing running costs, the hyperlinks approach is the most favorable, having none. On the other hand, we can conclude that the second educational approach is the intervention that entails more costs, with 123.81 € per report (Table 2).

Regarding the relevance of ADR reports, we analyzed the severity, expectedness and degree of causality attributed to the reports. Regarding serious ADR, the protocol approach was the most cost-effective, costing 2.29 € per report. The hyperlink approach obtained the second lowest value (30.28 € per report), having no running costs. We found similar results for the relevance criterion of causality assessment. Concerning ADR expectedness, the best result belonged to the protocol approach (5.12 € per report), followed by the first educational approach (38.79 € per report) (Table 3).

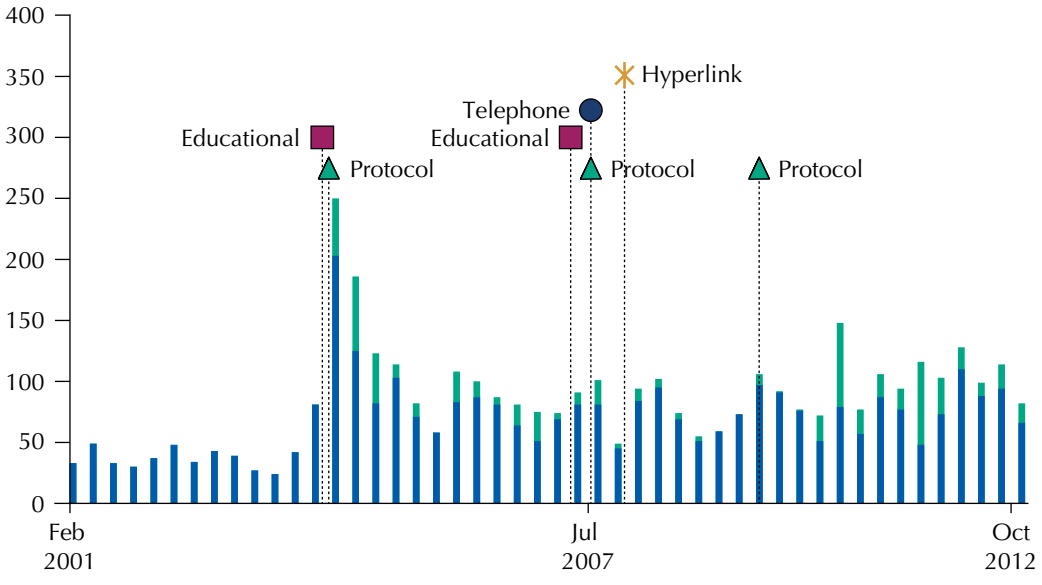

Figure 2. Total number of adverse drug reaction reports received in the Northern Pharmacovigilance Centre during the studied period, per trimester (in green, those obtained with protocols).

Table 2. Number and costs of adverse drug reaction reports obtained with each intervention.

Approach	Intervention	Adverse drug reaction reports				Costs (€) per report		
		Before		After				
		2 years	1 year	1 year	2 years	Initial costs	Running costs (2 years)	Total
Protocols		0	0	204	117	0.47	1.49	1.96
Hyperlinks		153	120	277	132	15.59	0.00	15.59
Hyperlinks NPE*		68	47	146	110	15.03	0.00	15.03
Educational	1st workshop	36	24	257	68	0.78	19.53	20.31
	Pharmacies	2	8	110	25	1.60	40.00	41.60
	Health care centers	25	7	102	17	2.29	57.47	59.77
	Hospitals	9	9	45	26	3.77	94.34	98.11
Phone Interview		47	26	87	34	8.33	33.33	41.67
	Pharmacies	23	10	37	14	22.22	88.88	111.11
	Health care centers	3	1	8	2	66.67	266.67	333.33
	Hospitals	21	15	42	18	16.67	66.67	83.33
Educational	2nd workshop	54	40	106	30	4.76	119.05	123.81
	Pharmacies	39	25	69	18	8.70	217.39	226.09
	Health care centers	10	13	26	6	22.22	555.55	577.78
	Hospitals	5	2	11	6	20.00	500.00	520.00

* NPE: Not previously exposed. Considering only the institutions without any previous intervention.

Table 3. Number and costs of serious, unexpected, and classified with a high degree of causality adverse drug reaction reports obtained with each intervention.

Approach	Intervention	Adverse drug reaction reports				Costs (€) per report		
		Before		After				
		2 years	1 year	1 year	2 years	Initial costs	Running costs (2 years)	Total
Serious								
Protocols		0	0	180	94	0.54	1.75	2.29
Hyperlinks		113	96	193	86	30.28	0.00	30.28
Educational	1st workshop	12	15	111	42	1.59	32.68	34.27
Phone interview		29	19	55	21	14.29	57.14	71.43
Educational	2nd workshop	37	23	44	8	-	-	-
High degree of causality								
Protocols		0	0	165	66	0.65	2.08	2.73
Hyperlinks		114	86	232	109	15.03	0.00	15.03
Educational	1st workshop	14	17	169	47	1.08	27.03	28.11
Phone interview		40	17	65	26	11.76	47.06	58.82
Educational	2nd workshop	37	27	74	22	6.25	156.25	162.50
Unexpected								
Protocols		0	0	70	53	1.22	3.90	5.12
Hyperlinks		63	40	69	37	706.67	0.00	706.67
Educational	1st workshop	10	7	111	40	1.49	37.30	38.79
Phone interview		17	11	22	7	400.00	1,600.00	2,000.00
Educational	2nd workshop	24	17	28	6	-	-	-

DISCUSSION

Although there is some overlap of interventions, making it difficult sometimes to differentiate the gains from each one of them, our results show that, in general, all interventions increased the number of ADR reports when comparing two years before with two years after.

Protocols in hospital immunoallergology departments seem to be the most efficient intervention. In fact, this intervention is the one that allows obtaining ADR reports with lower costs involved, with an increase not only in the total number of ADR reports, but also in the severity, unexpectedness, and high degree of causality attributed to the ADR.

Nevertheless, these protocols have the disadvantage of increasing the reports of ADR in patients of a specific population (patients with allergies), which can bias the global pharmacovigilance data. We started to establish these protocols at the request of one of the immunoallergology departments, but we are trying to establish similar protocols in other departments (as oncology departments, hospital pharmacies, among others), to solve the bias issue.

On the other hand, the hyperlink approach has the great advantage of not involving running costs, and seems to have the second best performance in costs per ADR report. Even when we consider only the hospitals exposed to an intervention for the first time (to avoid the overlap effect), this behavior remains.

We also concluded that the first educational intervention was much more efficient than the second one. In fact, the second intervention seemed to be counterproductive, as shown by the results of serious and unexpected ADR reports (these numbers decreased after the intervention). We already had this conviction since this intervention was performed. In fact, in most health care institutions where the second intervention took place, we found professionals less receptive than in the first intervention, as they already knew the subject and did not seem to believe they needed another workshop about it.

Unfortunately, we are not able to compare our results with other authors' results, as we failed to find any study addressing the issue of ADR report costs. Many studies proposed strategies to improve ADR reports[1,11,13] and some authors have already studied the costs of an ADR[3,5]. However, no one had studied the costs involved in obtaining ADR reports before, which is the novelty of our work.

Although there might be some overlap and eventual contamination among the interventions, we believe that this did not introduce an important bias in our conclusions. First, we knew exactly which reports were originated at the departments participating in the protocols. Moreover, we included in our results the ADR reports obtained after the hyperlink inclusion in the hospitals that had an intervention for the first time. Thus, we could infer that the gain in ADR reports after hyperlink inclusion was caused by this intervention. Furthermore, there is no problem of overlapping for the first educational approach (workshops in 2004) because this was the first intervention made. The only interventions for which we cannot resolve the overlapping limitation is the second educational intervention and the phone intervention. However, these two interventions were planned as complementary to the first one.

We believe that our work can help pharmacovigilance centers worldwide choose the best set of interventions to promote adverse drug reactions report. This choice must be based on the particular characteristics of each center, such as available staff and budget, geographic location, proximity to hospitals, among others.

Based on our results, we recommend the implementation of protocols with hospital immunoallergology departments, as they seem to be the most cost-effective intervention, followed by hyperlinks to ADR reporting forms, and the promotion of educational interventions to health care professionals for the first time.

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SHORT COMMUNICATION

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Promoting Spontaneous Adverse Drug Reaction Reporting in Hospitals Using a Hyperlink to the Online Reporting Form

An Ecological Study in Portugal

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Abstract

Background: Spontaneous adverse drug reaction (ADR) reporting has been described as an efficient method to detect drug safety signals. However, under-reporting is a major issue undermining the effectiveness of spontaneous reports. Among hospitalized patients, ADRs are a particularly serious problem because these patients are often treated with more than one drug, and these drugs are often new and aggressive.

Objective: To promote spontaneous ADR reporting by healthcare professionals working in hospitals in the northern regions of Portugal, we propose the inclusion of a hyperlink to an online ADR reporting form on hospitals' electronic patient records (EPRs). The main aim of this study was to evaluate the impact of these hyperlinks on the number of spontaneous ADR reports to the Northern Pharmacovigilance Centre (UFN – Unidade de Farmacovigilância do Norte). We also assess the number of daily UFN website visits before and after the inclusion of the hyperlinks.

Methods: An ecological study was performed in northern Portuguese hospitals from 2006 to 2010. The hyperlinks were included in either EPRs or on computer desktops. The median of spontaneous ADR reports (total and online) per month and the respective ranges were presented before and after the intervention in all hospitals in this study. The comparisons were performed using the Mann-Whitney U-test.

Results: Sixteen hospital centres were involved in the study (27 hospitals). Eleven centres (18 hospitals) included the hyperlinks. Considering the hospitals with hyperlink access to the EPRs, the median ADR reports per month significantly increased, from two (range 0–12) to five reports (range 1–17). The median of ADR reports per month using the online form also increased

significantly, from one (range 0–5) before the intervention to four (range 1–17) after it. Moreover, serious ADRs increased 3-fold, and non-previously described ADRs increased 4.5-fold. None of these significant increases were observed in the hospitals where the hyperlink was not installed. We also found a significant increase in daily UFN website visits, from ten before the intervention to 27 after it ($p < 0.001$).

Conclusion: The increase in ADR reporting shows that the inclusion of hyperlinks to online ADR reporting forms is an easy and cost-effective way to change health professional behaviours with regard to spontaneous ADR reports.

Introduction

Adverse drug reactions (ADRs) are a well recognized public health problem worldwide and a major cause of death and hospitalization in developed countries.[1] In fact, rare and long-term ADRs are difficult to detect during the drug development stage. Only when the drugs begin to be used by a large population after marketing authorization is it possible to detect new ADRs not previously identified during clinical trials. In reality, the safety of a new drug cannot be established until it has been on the market for several years.[2] As such, it is essential to keep reactions to drugs under close surveillance, especially after marketing, through a pharmacovigilance system.

In Portugal, this system is based on spontaneous ADR reports made by healthcare professionals.[3] These reports can be made using paper, telephone, e-mail or through an online form,[4] and they consist of a description of an adverse event supposedly caused by a medicine. Spontaneous ADR reporting has been described as an efficient method for detecting drug safety signals.[5] However, under-reporting is a major issue undermining the effectiveness of spontaneous reporting. Several studies suggest that less than 10% of detected ADRs are effectively reported to medicine regulatory authorities.[6,7] In addition, the spontaneous ADR report rate in northern Portugal was 90 reports/million inhabitants in 2009, which is highly unsatisfactory according to the WHO recommendations (200 reports/million inhabitants[8]).

Worldwide, systems using informatics to promote ADR reporting or to detect ADRs that have occurred in healthcare institutions have been tested and are currently being used. Computer programs that allow voluntary and automated detection of ADRs,[9,10] informatics tools created to analyse clinical databases,[11] or websites that actively inform healthcare professionals[12] are examples of such systems.

Among hospitalized patients, ADRs are a particularly serious problem. In fact, these patients are often treated with more than one drug, and these drugs are often new and aggressive. Despite these treatments, there is currently no specific system for monitoring or reporting ADRs in Portuguese hospitals. We believe that making the reporting system easier would considerably increase the number of reported ADRs.

With the intention of promoting spontaneous ADR reporting by healthcare professionals working in hospitals, we proposed the inclusion of a hyperlink to an online ADR reporting form (part of the Northern Pharmacovigilance Centre [UFN] website) on the electronic patient records (EPRs) or on the desktops of hospital computers. With this system, we expected to reach not only the physicians but also the pharmacists and nurses working at these hospitals. In Portuguese hospitals, pharmacists have an important role in ADR detection and reporting because physicians discuss with them the adverse events that occurred during medical treatment, asking for alternative drugs available at the pharmacy. In addition, some pharmacists are part of the clinical visit and frequently detect ADRs themselves.

Aim

Our main aim was to evaluate the impact of the hyperlinks installed in Portuguese hospitals on the number of ADRs reported by these hospitals using the hyperlink versus those that did not, and we also evaluated the number of visits to the UFN website.

Methods

Intervention

Hyperlinks to the ADR online reporting UFN form were proposed to the 18 northern Portuguese hospitals. The hyperlinks can be included either in healthcare professional-specific software (typically EPRs or pharmacy-specific applications used by doctors, nurses and pharmacists) or on hospital computer desktops (see figure 1 for examples of both situations). Notably, most of the Portuguese EPRs are web-based, so the hyperlink automatically opens the UFN form in a new browser window.

The online reporting UFN form requires the health professional to log in with their personal account. Patient data are collected in an anonymous way (only the initials of the patient name are required, aiming to help the health professional identify each case) and are secured in an Oracle database with appropriate access restrictions.

In the beginning of October 2007, a letter was sent to the chief physicians of these 18 northern Portuguese hospitals suggesting the inclusion of the hyperlink. If there was no response within 2 weeks, clinical administration boards were reminded by telephone. Thirteen centres forwarded this announcement to the respective computer departments, and only one hospital forwarded it to the pharmaceutical department. Five of the centres failed to respond by the end of 2010. After approval by the hospital board and after being forwarded to the respective departments, UFN made a third contact to explain technical specifications and to send the specific hyperlink for each hospital.

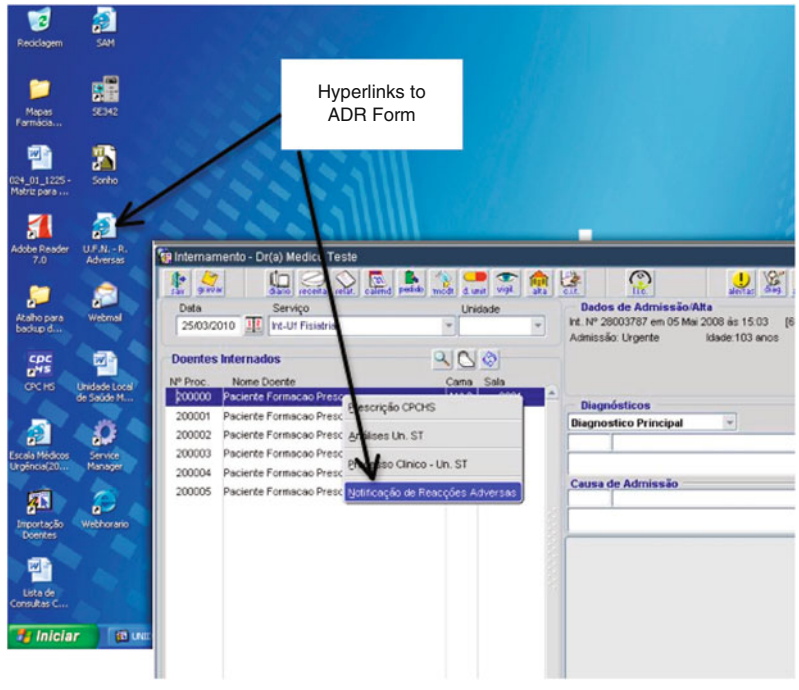

Fig. 1. Examples of hyperlinks on a computer desktop (back image) and in an electronic patient record (front image).

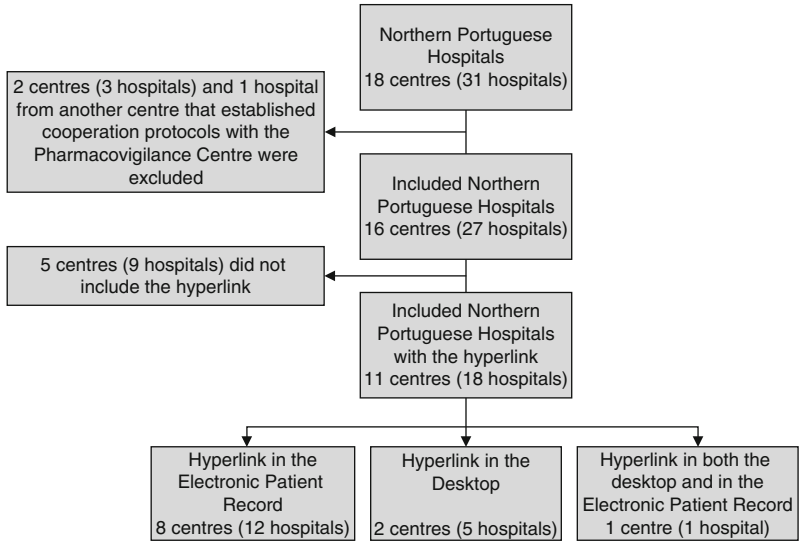

Fig. 2. Diagrammatic representation of the hospitals and hospital centres of northern Portugal that were included and excluded from the study.

Study Design and Data Collection

An ecological study was carried out in northern Portuguese hospitals from 2006 to 2010. The number of spontaneous ADR reports and online spontaneous ADR reports originating from hospitals were analysed before and after the above-mentioned intervention, without a control group. Five hospital centres implemented the hyperlink in December 2007, and the other six implemented it over the course of the next 5 months. We looked at the 23 months before and the 31 months after implementation in each hospital.

The UFN website uses an Apache web-server and has a record of the web logs related to the site visits since January 2006. These logs were initially processed using Webalizer software (www.webalizer.org) to calculate site hits, user logins and visits.

Telephone interviews with the computer departments of each hospital were performed to collect where each institution installed the hyperlink to the UFN website, and screen-shots illustrating the interventions were taken.

Variables

The main variables collected for analysis were as follows:

- Date – date and time of the ADR report.
- Hospital – institution where the ADR was detected.
- Health professional – type of health professional that reported the ADR (doctor, nurse, pharmacist or other).
- Seriousness – seriousness of the ADR, grouped as 'Serious' or 'Non-serious' according to the WHO criteria.
- Previous knowledge – whether the ADR was previously described in the Summary of Product Characteristics for the drug or not.

Bias

From the initial 18 centres (31 hospitals) we excluded four hospitals that established other cooperation protocols with UFN to avoid a possible confounder bias (see figure 2). For the other 16 centres, we believe that there were no external interventions that could potentially explain the observed results.

Statistical Methods

The number of spontaneous ADR reports and online spontaneous ADR reports per month were compared between the two periods (before and after the intervention). The number of ADR reports per quarter, before and after the installation

of the hyperlinks, is presented graphically (see figure 3). The number of ADR reports per quarter in the excluded hospitals and in the hospitals that did not participate (those that did not install the hyperlinks) is presented in figure 4.

Median values of the number of daily UFN website visits were reported because of the skewed distribution of the data. The number of daily UFN website visits was compared before and after the intervention using the Mann-Whitney U-test. The significance level was set at $p < 0.05$.

Results

Participants

Of the 16 centres involved in the study, 11 centres (18 hospitals) included the hyperlinks. Eight centres included the hyperlink only in the EPRs, two centres included the hyperlink on the computer desktops, and one included it both on the desktops and in the EPRs (see figure 2). Of the 18 hospitals involved, one is a university hospital, and three are specialized hospitals

Main Results

Considering the 16 centres that implemented the project, the median number of ADR reports per month significantly increased after project implementation. In fact, before the intervention the median of total ADR reports per month was 2, ranging from 0 to 12, and 31 months after the intervention the median was 5, ranging from 1 to 17 ($p = 0.043$). Four months after the project was implemented the median number of reports per month was 4.

Considering only the reports using the online form, before the project was implemented the median total online ADR reports per month was 1, ranging from 0 to 5, and after the intervention, this number was 4, ranging from 1 to 17 ($p = 0.009$).

Figure 3 shows the number of ADR reports per quarter before and after the intervention. Figure 4 presents the number of ADR reports per quarter in the excluded hospitals and in the hospitals that did not install the hyperlinks.

The 11 centres included reported 17 serious ADRs in 23 months using the online form before the intervention, and 69 in 31 months (a 3-fold increase) after the intervention. These centres reported seven non-previously described ADRs using the online form before the intervention and 42 after (increase of 4.5-fold).

The hospital with the largest increase in ADR reports submitted online was the one that included the hyperlink both in the EPRs and on the computer desktops, with a mean of three online reports per year before the intervention and 18 after. The three hospitals that included the hyperlink on

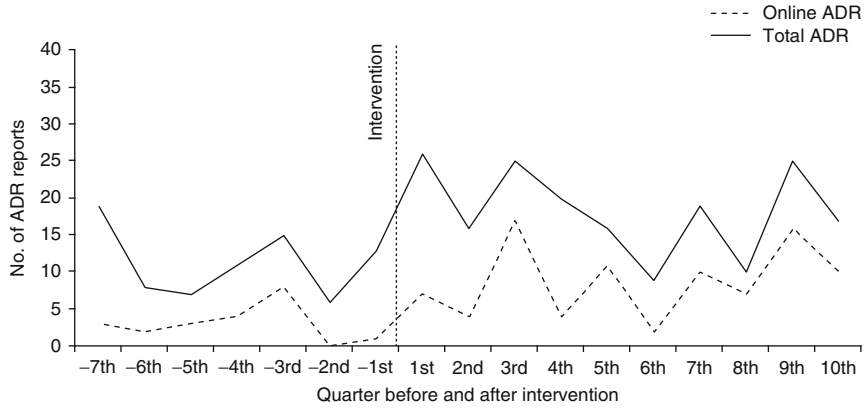

Fig. 3. Evolution of adverse drug reaction (ADR) reports (total and only online) in hospitals with the intervention. The quarters were adjusted for the time of intervention. Five hospital centres implemented the hyperlink in December 2007, two in January 2008, one in February, one in March, one in April and one in May.

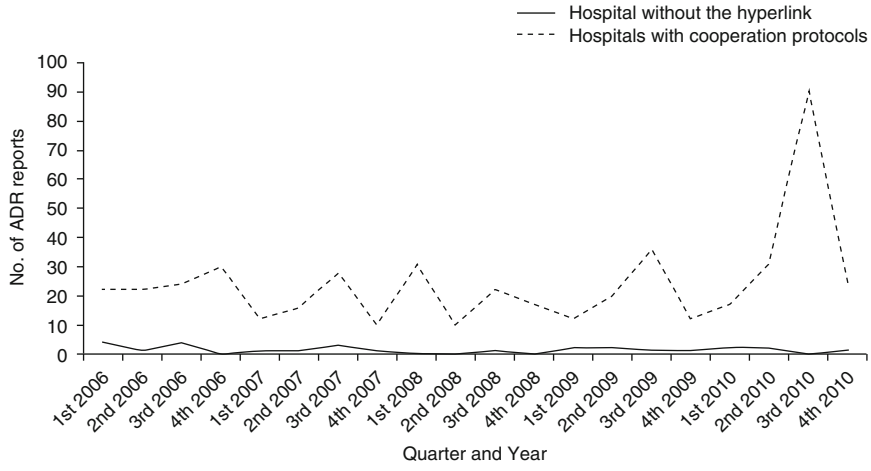

Fig. 4. Evolution of adverse drug reaction (ADR) reports in the excluded hospitals (with cooperation protocols) and in the hospitals that did not install the hyperlinks.

the desktops (including the one that simultaneously included it in the EPRs) were in the top five of the hospitals with higher increases in ADR reports submitted online.

There were no ADR reports sent in both paper and online formats by the same professional.

Other Analysis

There was a significant increase in daily UFN website visits after the intervention ($p < 0.001$). Before the intervention there was a median of ten daily UFN website visits, and after the intervention, the median increased to 27 visits.

Discussion

Our results show that the inclusion of hyperlinks to an online ADR reporting form in the EPRs does change health professional behaviours in ADR reporting. In reality, there was an increase in ADR reporting in the hospitals involved in this project, in the total number of ADR reports (more than 2-fold), in the number of ADR reports submitted online (4-fold), in serious ADRs reported online (3-fold) and in non-previously described ADRs (more than 4-fold). Additionally, daily visits to the UFN website increased approximately 3-fold after the intervention.

A similar intervention based on changing the EPRs of a hospital to facilitate ADR reporting is presented in Ortega et al.[13] Compared with our ADR reporting growth, the measured impact was higher in their study as they moved from zero to 1.6 ADRs per month in just one hospital. We argue that this difference may be due to the fact that they were able to fine-tune the EPRs to increase ADR reporting because they had more control over its application, while in our case we were limited to placing hyperlinks in existing heterogeneous EPRs. Therefore, our approach seems more easily implementable because hospitals are known to have many different information systems[14] and a national pharmacovigilance institution is probably not able to impose the changes described in Ortega et al.[13] to most commercial EPRs.

In the study by Figueiras et al.,[15] which was performed in the same region as our study, an educational intervention to improve physician reporting is described, namely by performing outreach visits to groups of health professionals. Their results present a very impressive increase (10-fold) in ADR reporting in the intervention group, and a 6-fold increase in the reporting of serious ADRs. When compared with our results, it is clear that the educational intervention has proven to be much more effective, but also requires more resources (human and financial).

Also, the effectiveness of these interventions appears to decrease through time. In the study by Pedrós et al.,[16] an educational (periodic meetings) and economic incentives-based intervention strategy was initiated in 2003. Their results present an increase of 5.6-fold in all ADRs and a 2-fold increase in serious ADR reports. Their impact is similar to our study, but again used more financial resources.

When compared with other types of interventions, such as solely educational[15] or educational combined with economic incentives,[16] our intervention seems to have less impact although it is more long lasting and less expensive.

As an additional outcome, we can see that the hospital with the highest increase in ADR reports submitted online was the one that simultaneously included the hyperlink in the EPRs and on the computer desktop. According to our results for hyperlink placement, the computer desktop is likely more efficient than the EPR homepage. It is our opinion that these improvements could also be effective in other countries because they are more related to generic usage of graphic user interfaces than to local practices.

Notably, making the ADR forms easily accessible might also promote future ADR reporting initiatives that can take advantage of the visibility of the hyperlink to the users. Therefore, we argue that our solution is cost effective, appropriate for widespread use in many healthcare institutions, and can consistently increase ADR reporting over time.

Limitations

In some hospitals, we found that although the hyperlink was included, the professionals did not know about it. In the near future, we aim to increase the knowledge of the hyperlink by more actively informing health professionals using flyers sent to the hospitals, posters and an e-mail showing specifically how to find the hyperlink. Another problem detected was the inability to use the hyperlink in some hospitals because the users did not have permission to access to the internet.

Future Work

To solve the problem of not being able to access the Internet, we are now developing Web-services[17] to be used by other systems available on hospital intranets. With this tool, it will not be necessary to access the UFN website and healthcare professionals can simply use the existing information systems as proposed in Ortega et al.[13] With this future work, we expect to eliminate all the technical obstacles to ADR reporting, further increasing the reporting rate. Meanwhile, we also aim to implement this project in northern Portugal primary-care healthcare centres and to provide the hyperlink to general practitioners and nurses.

Conclusions

The inclusion of hyperlinks on computer desktops and in EPRs to online ADR reporting forms is an easy and cost-effective way to change health professionals' behaviours with regard to spontaneous ADR reports. In fact, daily visits to the UFN website significantly increased after the inclusion of the hyperlinks, but even more importantly, the amount and relevance of ADR reports significantly increased after the inclusion of the hyperlink in the hospitals involved in this project.

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Inês Ribeiro-Vaz was responsible for most of the intervention and data collection. Cristina Santos performed the statistical analysis. Altamiro Costa-Pereira and Ricardo Cruz-Correia supervised the writing of the paper. Ricardo Cruz-Correia also conceptualized the intervention.

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Using Web Services to Link Electronic Clinical Records to Pharmacovigilance Databases

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Abstract

Purpose: Adverse Drug Reaction (ADR) reporting is an efficient method to assess the safety of drugs. However, underreporting is a major issue undermining the effectiveness this method. Among patients with Inflammatory Bowel Disease (IBD), ADR are a serious problem, because these patients are often treated with new and potent drugs. Electronic registries usually include information on ADR, recorded by physicians. To promote ADR reporting by gastroenterologists working in a multicentre IBD study group, we proposed the utilisation of a web service in their usual Electronic Health Records (EHR) to collect ADR. The aim of this work was to describe the impact of this intervention on the number of ADR reported to the regulatory authority through a regional pharmacovigilance centre.

Methods: A study was performed between 2013 and 2015. A web service was created and implemented in an EHR in use. We analysed the trends and type of ADR reported through this service.

Results: From April 2013 to February 2015, 167 ADR reports were sent to the Northern Pharmacovigilance Centre through the web service, comprising 10% of the total ADR reports received in the same period. Of these, 118 cases were serious (one was life-threatening). In the northern region of Portugal, GEDII physicians reported 9 ADR during the 23 months previous to web service implementation and 121 ADR during the 23 months after web service implementation, i.e. an increase of 81%.

Conclusions: This solution allowed for reporting 167 ADR during the first 23 months of implementation, simply by clicking a button included in the usual EHR used by gastroenterologists. These results suggest that information systems (IS) should facilitate the reporting of ADR.

Keywords: Adverse Drug Reactions; Inflammatory Bowel Disease; Pharmacovigilance; Electronic Health Records

Introduction

All medicines have adverse effects, some of them unknown until the drug is commercialised. Thus, it is crucial to implement strategies to monitor drug safety. Pharmacovigilance is the activity of drug surveillance, after its launch onto the market, with the main goal of public health protection, ensuring that the drug benefit outweighs its risks. Worldwide, pharmacovigilance systems are mostly based on spontaneous ADR reports made by healthcare professionals and consumers. Spontaneous ADR reporting has been described as an essential method to detect drug safety signals; however, underreporting is a major issue undermining the effectiveness of spontaneous reports. Several studies suggest that fewer than 10% of detected ADR are effectively reported to medicine regulatory authorities (e.g. Food and Drug Administration - FDA, European Medicines Agency - EMA, etc.) [1,2].

It is known that, one of the main reasons why healthcare professionals do not report ADR is due to an increase in their workload [3,4]. So, in order to reduce ADR reporting efforts, Information Systems (IS) to promote ADR reporting or to detect ADR in healthcare institutions have been tested and used, such as software for voluntary and automated detection of ADR, tools that analyse clinical databases or web-sites that actively inform healthcare professionals [5]. Information and communication technologies can also be used to facilitate and promote ADR reporting, such as the creation of on-line reporting forms and the development of tools to collect safety data from Electronic Health Records (EHR), among others [6,7].

In Portugal, there is a multi centre research project, in the field of gastric diseases (Study Group of Inflammatory Bowel Disease – GEDII) [8] whose members use the same electronic health record to collect patient information. As these patients are often treated with new and potent drugs (e.g. immunomodulating agents), the EHR has a field related to medication and ADR. Since the group members already fill in this field, it was considered an advantage to create a tool to send the data to the pharmacovigilance system.

Aim

The aim of this work was to implement and describe the implementation of a web service in an EHR to collect ADR reports and analyse the number of ADR reports sent to the Portuguese regulatory authority (INFARMED), through a regional pharmacovigilance centre.

Methods

Intervention

The multi-centre research project, the Study Group of Inflammatory Bowel Disease – GEDII [8], has its own Electronic Health Record (EHR) to collect patient information, with a field related to medications and ADR.

The GEDII members asked for collaboration with the Northern Pharmacovigilance Centre (UFN in Portuguese) and the Health Information and Decision Sciences Department (CIDES) of the Faculty of Medicine to develop a tool to allow for easy reporting of ADR included in the EHR to the pharmacovigilance system. The two entities had, at the time, released a new information service (a web service) to collect suspected adverse reactions directly from prescription and medical records. This system was easily adapted to the EHR used by the GEDII group.

The Northern Pharmacovigilance Centre, as part of the Portuguese Pharmacovigilance System, receives ADR reports from healthcare professionals (and, since 2012, from consumers as well) through an on-line form, a paper form, e-mail and by telephone. Since 2013, UFN has also received ADR reports through the web service.

The web service anonymises patient data (converting the full name of the patient into initials), according to the data protection standards of the Portuguese Pharmacovigilance System. Figure 1 shows the information flow from the electronic health record to the pharmacovigilance system.

To use this service, there is a button asking the doctor if he/she will allow the information to be sent to the pharmacovigilance database (see Figure 2). If the physician does not allow for this information to be sent to the system, it will only be stored in the health record.

Study design and data collection

The web service was implemented in the GEDII electronic health record (used only by gastroenterologists) in April 2013. There are 15 hospitals using this information system, covering a total of 4031 patients. The database has 39 registered users, which means that, potentially, 39 physicians could report ADR through this information system [8].

In order to use this web service, it is necessary to access a specific URL, provided by the Northern Pharmacovigilance Centre and CIDES. The service was incorporated in the GEDII software to collect the ADR already stored by the physicians in the system. Each physician, in the context of the patient, sends the ADR to the Regional Pharmacovigilance Centre.

After the ADR report is received by the Regional Pharmacovigilance Centre, their technical staff process the report according to the pharmacovigilance guidelines [9], sending it to the Portuguese Regulatory Authority (INFARMED).

If the doctor does not want to send the information to the pharmacovigilance system, it will only be stored in the medical history.

To analyse the trends and type of ADR reported through this service, we performed a descriptive analysis on the number and seriousness of ADR reported. The seriousness was assessed using the World Health Organisation [10] seriousness criterion [11]. According to this criterion, a serious ADR is any untoward medical occurrence that at any dose: results in death, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity or is life-threatening.

Results

From April 2013 to February 2015, physicians from GEDII reported 167 ADR through the described web service.

Of the 167 reported ADR, 118 (71%) were serious ADR, considering the World Health Organisation seriousness criterion [11]. One of the cases was life-threatening and none were fatal.

To calculate the increase in ADR reporting in this period, we used data from the northern region, which is the delimited area of the Northern Pharmacovigilance Centre, as we did not have access to national ADR reporting data. Thus, considering the physicians from the GEDII group that work in at the northern region of Portugal, 9 ADR were reported during the 23 months prior to web service implementation and 121 ADR were reported during the 23 months after web service implementation, i.e. an increase of 81%.

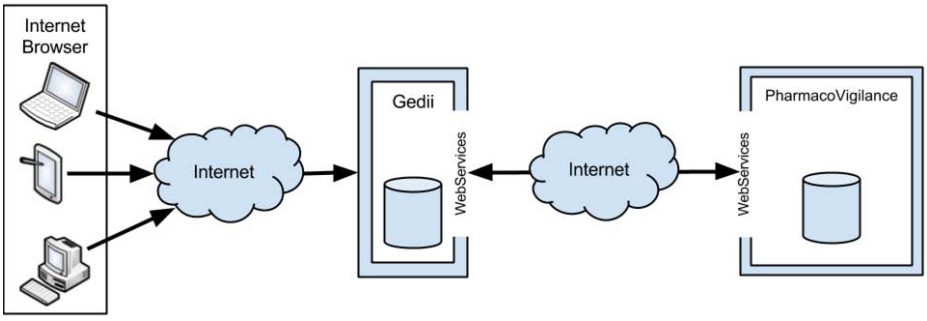

Figure 1: Information flow

Drugs involved in the Reported ADR

Most of the cases had one only suspected drug, but in six cases there were two suspected drugs involved.

Of the reported ADR, 106 cases (63%) were presumably due to azathioprine, 23 cases (14%) to infliximab, 14 cases (8%) to adalimumab and 9 (5%) cases to methotrexate (Figure 3).

All of these drugs are classified as antineoplastic and immunomodulating agents, according to the WHO Anatomical Therapeutic Chemical (ATC) classification system [12]. Azathioprine, infliximab and adalimumab are immunosuppressants and methotrexate is an antimetabolite.

Discussion

Worldwide, many systems use electronic health records to facilitate adverse event reporting, with the same goal as our work, which is to not overload healthcare professionals with additional administrative work to report ADR [7, 13, 14]. These systems can be included in the EHR and be easily completed [13] or can actively help in form filling with the automatic input of certain information already included in the EHR [7]. During the ALIAS (Albumin in Acute Stroke Trial) experience, authors decided to integrate an electronic safety reporting module into the existing web-based system to deal with safety reporting obligations of a multicentre clinical trial [15]. This system pre-populates the reporting form with the existing information, which needs to be completed and validated by clinical staff. The ASTER pilot study also brought an important contribution to the development of these systems, as it triggered ADR within the EHR, collected patient data, populated the ADR reporting form and made the report available to the physician for review [16]. This work is different from ours, because it asks the clinician to provide additional information on the adverse event and then submits the report. All these systems incur extra work on the part of physicians, which is difficult to eliminate. The novelty of our work is the detail of allowing the physician to report ADR without any additional administrative work beyond the usual clinical registry. In addition, the EHR remained the same, without the need to change the physicians' routine. This system adapts to the routines of the healthcare professionals and not *vice versa*, which can explain the increasing of ADR reporting among the studied group.

It is also important to note that most of the reported ADR were serious. In fact, the studied group deals with innovative and powerful drugs those often cause serious adverse events. This finding reinforces the importance of our work, as Pharmacovigilance Systems seek mainly information about serious (and unexpected) ADR [17].

Our study has some limitations, such that it only included gastroenterologists. However, this web service is available to be used in several software. Even so, it is currently in use only in two software systems: the one described in this study and an electronic prescription software system. Another issue is that our study does not have a control group, which limits the conclusions drawn. For this reason, the only comparison that the authors were able to perform was for the number of ADR reports made by the same group of gastroenterologists before the web service implementation.

Conclusions

The simple solution described in our work allowed for

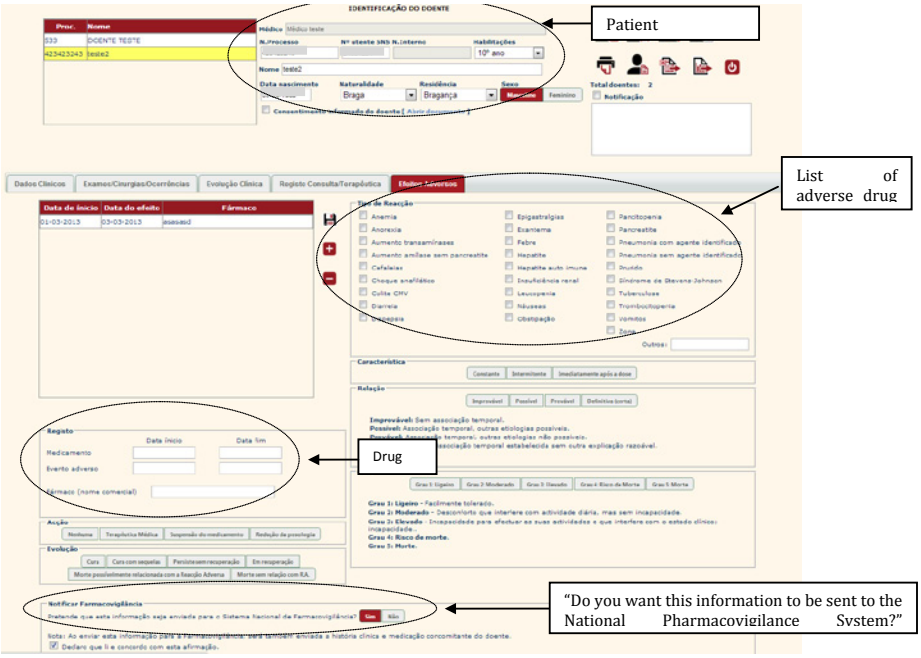

Figure 2: Screen shot of the ADR section on the GEDII electronic health record

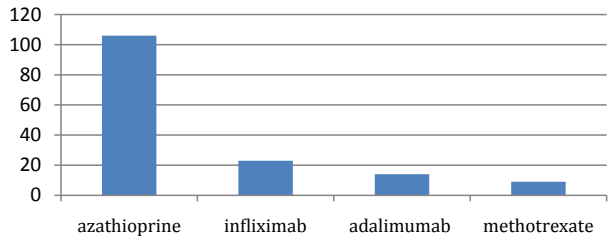

Figure 3: Drugs involved in the reported ADR

reporting 167 ADR during the first 23 months of implementation, simply by clicking a button included in the usual electronic health record used by gastroenterologists. Our results suggest that doctors would report more ADR if they do not have to take on any further workload to do it. We propose that IS used to support multicentre studies should be used to report detected ADR.

Author Contributions

Inês Ribeiro-Vaz was responsible for data collection and writing the paper. Ricardo J C Correia conceptualised the intervention and supervised writing of the paper.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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U.PORTO
FMUP FACULDADE DE MEDICINA
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COMITÉ DE ÉTICA DO DEPARTAMENTO DE CIÊNCIAS SOCIAIS E SAÚDE DA FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

PCEDCSS-FMUP 08/2014

Sobre o protocolo relativo ao estudo "***UTILIZAÇÃO DOS SISTEMAS DE INFORMAÇÃO COMO FACILITADORES E MOTIVADORES DA NOTIFICAÇÃO ESPONTÂNEA DE REAÇÕES ADVERSAS A MEDICAMENTOS (RAM)*** ", de que é investigadora principal a Sr.ª Dr.ª Ines Vaz, no âmbito do Programa Doutoral em Investigação Clínica e Serviços de Saúde da Faculdade de Medicina da Universidade do Porto.

A – Relatório

1. O Comité de Ética do Departamento de Ciências Sociais e Saúde da FMUP apreciou o processo relativo ao pedido de parecer dirigido a este Comité pela Investigadora Fernanda Inês de Carvalho Pereira Ribeiro Vaz, licenciada em Farmácia, a exercer as funções de receção, validação, processamento e avaliação de Notificações Espontâneas de Reações Adversas a Medicamentos comercializados (RAM) na Unidade de Farmacovigilância do Norte (UFN), pertencente ao Departamento de Ciências da Informação e da Decisão em Saúde da FMUP. Este trabalho é realizado no âmbito do Programa Doutoral em Investigação Clínica e Serviços de Saúde (PDICSS) da FMUP, sob a orientação dos Senhores Professores Ricardo João Cruz Correia, Jorge Manuel Silva Junqueira Polónia e Cristina Maria Nogueira Costa Santos.

2. Fazem parte do processo em análise os seguintes documentos: requerimento de Pedido de Parecer ao Comité de Ética da FMUP; projeto do estudo, que inclui título descritivo e objetivo, identificação da investigadora, entidade de origem, introdução/justificação do trabalho, metodologias, não referindo o cronograma e os recursos/orçamento/protocolo financeiro/origem do financiamento; *curriculum vitae* da investigadora; declaração de que o trabalho será elaborado de acordo com as normas de proteção de dados e de confidencialidade a que o Sistema Nacional de Farmacovigilância está obrigado; autorização do Prof. Doutor Altamiro da Costa Pereira, Diretor Departamento de Ciências da Informação e da Decisão em Saúde da FMUP, onde se insere a UFN, local onde será levado a cabo o trabalho.

3. O trabalho tem como objetivo "Avaliar várias intervenções implementadas na UFN, relativamente ao seu impacto na notificação de RAM" e compreende quatro diferentes estudos:

Estudo 1 - Comparar, com base nas notificações de 10 anos de RAM da UFN, o impacto de quatro intervenções na sua notificação (1- protocolos com imunoalergologia; 2-intervenções educativas; 3 –telefonemas e 4- *hyperlinks* para notificação *online*), através dos custos de cada intervenção e do nº de notificações ganhas com cada uma e seu custo,

Estudo 2 - Criar a área do notificador no site da UFN para lhe fornecer, no ato da notificação, informação técnica;

Estudo 3 - Desenhar e implementar uma rede Bayesiana de apoio à avaliação de causalidade das notificações de RAM com *feedback* para o notificador;

Estudo 4 (metodologia a definir, dado não estar incluído no plano de estudos) - Comparar o impacto que a criação do perfil da UFN no *Facebook* terá nas notificações de RAM, com base

nas notificações que as pessoas que "gostam" da página da UFN faziam antes e depois de se juntarem à referida página, utilizando, para isso, o seu nome tal como apresentado no *Facebook*.

B – Identificação das questões com eventuais implicações éticas

1. Reconhece-se relevância e pertinência do trabalho e interesse prático para os serviços de saúde.
2. Trata-se de um trabalho sem envolvimento de utentes.
3. A confidencialidade dos dados é estritamente garantida pela investigadora.
4. Relativamente aos estudos 1,2 e 3 não é explícito no protocolo se irá ser elaborado algum instrumento de recolha de dados específico para este projeto, ou se serão apenas descritos os procedimentos de rotina de um Serviço.

Contudo a investigadora informou posteriormente que não será construída qualquer instrumento de recolha de dados, sendo o impacto das intervenções aferido pela medição dos indicadores normais da UFN.

5. Relativamente ao estudo 4 pretende-se constituir uma base de dados identificada, não anonimizada. Ora o tratamento de dados sensíveis e a criação de bases de dados com esta informação é proibido e só pode ser realizado após parecer positivo da Comissão Nacional de Proteção de Dados (ver Lei da Proteção de Dados Pessoais, Lei n.º 67/98, de 26 de Outubro).

Contudo a investigadora informou posteriormente que será criada uma lista nominativa com as pessoas que fizeram "gosto" da página do *Facebook* da UFN, informação que é pública por estar no *Facebook* e a que cada pessoa aderiu por sua livre iniciativa. Esta lista nominativa será posteriormente comparada com a dos notificadores da UFN, tendo a investigadora assegurado que nenhum dado pessoal será publicado, sendo os dados publicados de forma agregada.

C – Conclusões

1. Face ao exposto o Comité de Ética do Departamento de Ciências Sociais e Saúde da FMUP delibera dar parecer favorável à realização do mesmo.
2. Contudo, dado não estar explícito o cronograma e os recursos/orçamento/protocolo financeiro/origem do financiamento do trabalho, o Comité de Ética do Departamento de Ciências Sociais e Saúde da FMUP entende que os mesmos são da responsabilidade do Diretor Departamento de Ciências da Informação e da Decisão em Saúde da FMUP, na medida em que autoriza a realização do trabalho no âmbito das atividades de rotina da UFN, serviço que tutela.

Aprovado em reunião do dia 07/05/2014, por unanimidade.

O Presidente do Comité de Ética
Prof. Doutor Rui Nunes

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O Relator do Parecer
Prof. Doutor Alberto Hespanhol