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Improving Global Monitoring of Vaccine Safety : An Evaluation of the World Health Organization
Programme for International Drug Monitoring and Adverse Reactions Database on How They Serve
the Needs of Vaccine Safety

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**IMPROVING GLOBAL MONITORING OF VACCINE SAFETY:
AN EVALUATION OF THE WORLD HEALTH ORGANIZATION
PROGRAMME FOR INTERNATIONAL DRUG MONITORING
AND ADVERSE REACTIONS DATABASE
ON HOW THEY SERVE THE NEEDS OF VACCINE SAFETY**

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fulfillment of the requirements for the M.Sc. degree in Epidemiology

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ABSTRACT

The World Health Organization (WHO) Programme for International Drug Monitoring (PIDM) was developed for chemical rather than biological products. The ability of the PIDM to meet the needs of vaccine safety is of international public health importance. Three studies were conducted: 1) a survey of authorities responsible for reporting adverse events following immunizations (AEFIs); 2) an analysis of the WHO Adverse Reactions Database; and 3) a systematic review to identify and compare Bayesian methods used in drug and vaccine signaling. Communication between national surveillance authorities and lack of vaccine-specific terminologies are issues of concern. Many AEFI reports are not forwarded to the PIDM, and reporting timeliness and regularity should be improved. Few studies have examined the use of Bayesian methods in vaccine signaling. Vaccines should be recognized as a distinct group of drugs. Additional staff dedicated to AEFI reporting and vaccine signaling would be a valuable asset to the PIDM.

EXECUTIVE SUMMARY

The World Health Organization (WHO) Programme for International Drug Monitoring (PIDM) is an international adverse event monitoring system, responsible for the collection and assessment of adverse event reports from member countries around the world and the communication of information regarding drug and vaccine safety issues to regulatory and pharmacovigilance authorities of member countries. Administration of the programme is shared between the WHO Collaborating Centre for International Drug Monitoring (more commonly referred to as the Uppsala Monitoring Centre or simply the UMC) and WHO Headquarters.

The PIDM was initially developed for chemical rather than biological products. Very little has changed since its inception to take into consideration the unique characteristics of vaccines. While considerable achievements have been made in analysing drug-related adverse event reports, similar improvements have not been made in analysing vaccine-related reports. In June 2005, the Global Advisory Committee on Vaccine Safety called for a global consultation to address the need for improved monitoring and analysis of vaccine-related adverse event reports at the international level.

As part of the thesis, three manuscripts were prepared. The first manuscript was based on a survey of authorities responsible for adverse events following immunization (AEFI) surveillance in all countries participating in the PIDM. The objective of the survey was to gather evidence on: 1) the process and the product of national AEFI surveillance in member

countries; 2) the level of communication between national adverse drug reaction (ADR) and AEFI surveillance authorities; and 3) the acceptability and usefulness of the PIDM, the Brighton Collaboration's AEFI definitions, and the various internet-based services provided by the UMC. The survey identified critical elements that should be quickly addressed to improve global vaccine safety monitoring, in particular: communication between national ADR and AEFI surveillance authorities, ability to pay for advancing technology in developing countries, and proper use of services and terminologies.

The second manuscript resulted from a quantitative assessment of the WHO Adverse Reactions Database. The objectives of this analysis were: 1) to compare reporting patterns for ADRs and AEFIs; and 2) to identify potential problems that may hinder signaling of vaccine safety concerns. The analysis identified several issues of concern, in particular, many member countries do not forward any or all AEFI reports to the PIDM, and reporting timeliness and regularity need to be improved. Incomplete or absent AEFI reporting, and slow or irregular reporting, could prevent vaccine signals from being detected in a timely manner.

The third manuscript was based on a systematic review of the literature of Bayesian methods used for signaling drug and vaccine safety concerns. The objectives of this manuscript were: 1) to compare Bayesian methods that have been evaluated with respect to their utility in signaling drug and vaccine safety concerns; and 2) to comment on the use of the Bayesian Confidence Propagation Neural Network (BCPNN), the signaling method used by the PIDM, and specifically, the use of the BCPNN in identifying vaccine safety concerns.

Many studies have evaluated the utility of Bayesian methods, including the BCPNN, for signal detection and have found them effective for signaling drug safety concerns. Very few studies, however, have evaluated a Bayesian method for signal detection using AEFI reports, and no study has specifically evaluated the BCPNN method for signaling vaccine safety concerns. Recommendations for further study include testing the BCPNN and other Bayesian and non-Bayesian signaling methods with AEFI reports in order to assess the effectiveness of these tools in vaccine safety. The BCPNN may need to be customized for vaccine signal detection.

An overall evaluation of the PIDM and WHO database was conducted using the Centers for Disease Control and Prevention (CDC) outline for evaluating a public health surveillance system as a guide. The attributes that are most important to achieving the aims of the PIDM are acceptability, data quality, sensitivity, timeliness, and stability. In general, these attributes are not being adequately addressed for vaccines, which is affecting the usefulness of the PIDM as an international AEFI surveillance system.

The recommendations from this thesis can be summarized as follows:

1. It is essential that organizations and individuals involved in pharmacovigilance recognize vaccines as a distinct group of drugs. Vaccines should not be grouped with all other drugs and they require special consideration in pharmacovigilance. The annual meeting of National Pharmacovigilance Centres is an excellent opportunity to further this message by inviting both drug and vaccine safety authorities to attend the meeting annually and allotting a segment of each meeting to

discussions around vaccine safety issues. We recognize that this may require considerable effort on the part of the UMC to ensure that invitations are extended to both parties, however, meetings such as this present a unique opportunity to assist countries in improving the relationship between their ADR and AEFI surveillance authorities.

2. A staff person dedicated to AEFI reporting and vaccine signaling would be a valuable addition to the UMC team. The ideal candidate will be able to address concerns relating to deficiencies in the adverse event terminologies used to describe AEFIs, the lack of use of standardized AEFI definitions, the Anatomical Therapeutic Chemical classification of vaccines, and the use of the BCPNN and additional algorithms for vaccine signaling. Improvements to the programme that facilitate AEFI reporting and improve AEFI data quality should encourage better AEFI reporting. As the programme is ameliorated and more AEFIs are reported, vaccine signaling capabilities will also be improved.
3. It will be necessary to continue evaluating the PIDM. This thesis is only a first step.

CONTRIBUTION OF THE AUTHORS

Three manuscripts have been prepared for publication as part of this thesis. All manuscripts are co-authored by the student (ML), her co-supervisors, Dr Philippe Duclos and Dr George Wells, and an advisor to the thesis, Dr Wikke Walop. The student is the first author of all papers, having been primarily responsible for data collection, analysis, and writing of the manuscripts. Drs Duclos, Wells, and Walop provided valuable feedback throughout the process.

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ABBREVIATIONS USED IN THE TEXT

ADR	Adverse Drug Reaction
AEFI	Adverse Events Following Immunizations
AERS	(U.S. FDA) Adverse Event Reporting System
ATC	Anatomical Therapeutic Chemical (classification system)
BCG	Bacille Calmette-Guerin (vaccine)
BCPNN	Bayesian Confidence Propagation Neural Network
CAEFISS	Canadian Adverse Events Following Immunization Surveillance System
CDC	Centers for Disease Control and Prevention
CIOMS	Council for International Organizations of Medical Sciences
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
EBGM	Empirical Bayes Geometric Mean
FDA	(U.S.) Food and Drug Administration
GACVS	Global Advisory Committee on Vaccine Safety
GPS	Gamma Poisson Shrinker
GTN	Global Training Network
HCP	Healthcare Professional
IC	Information Component
ICD	International Classification of Disease(-9)
IMPACT	(Canadian) Immunization Monitoring Programme ACTIVE
ISPP	Immunization Safety Priority Project
IVB	Immunization, Vaccines, and Biologicals (Department)

JRF	(WHO/UNICEF) Joint Reporting Form on Immunization
MedDRA	(ICH) Medical Dictionary for Regulatory Affairs
MGPS	Multi-item Gamma Poisson Shrinker
NPC	National Pharmacovigilance Centre
PHAC	Public Health Agency of Canada
PIDM	(WHO) Programme for International Drug Monitoring
PRR	Proportional Reporting Ratio
ROR	Reporting Odds Ratio
SOC	System Organ Class
UMC	Uppsala Monitoring Centre
UN	United Nations
VAAESS	(Canadian) Vaccine Associated Adverse Events Surveillance System
VAERS	(U.S. FDA and CDC) Vaccine Adverse Event Reporting System
VSU	Vaccine Safety Unit
WHO	World Health Organization
WHO/HQ	WHO Headquarters
WHO-ART	WHO Adverse Reaction Terminology
WHO-DD	WHO Drug Dictionary

CHAPTER ONE: INTRODUCTION

1.1 Rationale

The World Health Organization (WHO) Programme for International Drug Monitoring (PIDM) is an international adverse event monitoring system. The PIDM is responsible for the collection and assessment of adverse event reports, including reports on adverse drug reactions (ADRs) and adverse events following immunizations (AEFIs), from member countries around the world, and the communication of information regarding drug and vaccine safety issues to regulatory and pharmacovigilance authorities of member countries.

The PIDM was initially developed for chemical rather than biological products, and very little has changed since its inception to take into consideration the unique characteristics of vaccines. Limitations of the PIDM with respect to AEFI reports include (1):

- a small number of AEFI reports in the database
- limited relevant case information available in AEFI reports
- difficulty associated with data mining using tools developed for drug-related issues
- problems communicating vaccine signals with national immunization authorities

In June 2005, the Global Advisory Committee on Vaccine Safety, acknowledging these limitations, called for a global consultation to address the need for improved monitoring and analysis of vaccine-related adverse event reports on an international level (1). Considering

the differences in characteristics between drugs and vaccines, the ability of the PIDM to meet the needs of vaccine safety is of great international public health importance (1, 2).

1.2 Outline and objectives

This thesis has been formatted as a manuscript-based thesis. Three manuscripts have been prepared, in addition to a background chapter (Chapter 2) and a general discussion and recommendations chapter (Chapter 6).

The following is an overview of the objectives of each chapter:

Chapter One

An introductory chapter meant to provide an overview of the organization of the thesis and the objectives of each chapter.

Chapter Two

To present necessary background information on vaccines, AEFIs, pharmacovigilance, and the PIDM, in order to appreciate the rationale for the thesis.

Chapter Three

A manuscript based on the results of a survey of the national AEFI surveillance authorities of countries participating in the PIDM. The objective of this survey was to gather evidence on: 1) the process and the product of national AEFI surveillance in member countries; 2) the

level of communication between national ADR and AEFI surveillance authorities; and 3) the acceptability and usefulness of the PIDM, the Brighton Collaboration's AEFI definitions, and the various internet-based services provided by the UMC.

Chapter Four

A manuscript resulting from a quantitative analysis of the WHO Adverse Reactions Database. The objectives of this analysis were: 1) to compare reporting patterns for ADRs and AEFIs; and 2) to identify potential problems that may hinder signaling of vaccine safety concerns.

Chapter Five

A manuscript based on a systematic review of the literature of Bayesian methods used for signaling drug and vaccine safety concerns. The objectives of this manuscript were: 1) to compare Bayesian methods that have been evaluated with respect to their utility in signaling drug and vaccine safety concerns; and 2) to comment on the use of the BCPNN, the signaling method used by the PIDM, and specifically, the use of the BCPNN for identifying vaccine safety concerns.

Chapter Six

A summary chapter meant to bring together the results of the survey, database analysis, and systematic review. Using the Centers for Disease Control and Prevention (CDC) outline for evaluating a public health surveillance system as a guide, the PIDM and WHO database were assessed on how they meet the needs of vaccine safety.

1.3 References

1. Global Advisory Committee on Vaccine Safety, 9-10 June 2005. Wkly Epidemiol Rec. 2005;80:242-7.
2. WHO consultation on global monitoring of adverse events following immunization, 9-10 January 2006. Wkly Epidemiol Rec. 2006;81:261-5.

CHAPTER TWO: BACKGROUND

2.1 Vaccines & Adverse Events Following Immunizations

Except for a few biological products, most drugs are chemical products. Vaccines are one example of biological drug products. For simplicity throughout this thesis, vaccines will be referred to as “vaccines”, while all other non-vaccine drugs will simply be referred to as “drugs”.

In spite of the many differences between vaccines and drugs, vaccines are commonly viewed as being similar to drugs. While some vaccines are used in the treatment of disease (e.g., Bacille Calmette-Guérin (BCG) vaccine in the treatment of bladder cancer) and are therefore somewhat akin to drugs, most vaccines are intended to prevent and control disease. Some of the special characteristics that differentiate those vaccines used for disease prevention from drugs are highlighted below:

- Vaccines are usually administered to large populations of healthy individuals
- Most vaccines are administered to infants and children
- Vaccine administration is often promoted or even made mandatory by governments
- A main issue in the safety and efficacy of vaccines is maintaining an adequate ‘cold chain’ (i.e., a system for keeping vaccines at the appropriate temperature, from the time of the start of manufacture until the time of use, in order to maintain vaccine quality and potency)

- Potential variation between different batches and lots of a vaccine necessitates lot-by-lot surveillance of vaccines at the post-marketing stage
- The public, in general, is less willing to accept the risks associated with vaccines

As a result of these differences, vaccines are held to extremely high safety standards (1).

Despite the safety measures taken, no drug or vaccine can be guaranteed completely safe.

Although AEFIs are usually mild, rare but serious events can occur. The terminology used in vaccine and drug safety, including the description of many adverse events, is largely ill-defined, and many terms are not interchangeable between drugs and vaccines. Adverse events that occur after immunization are referred to as “events”, a term that does not presume a causal relationship between the vaccine and the adverse event. Adverse events that occur following administration of a drug, on the other hand, are commonly referred to as “reactions”, which implies a causal relationship. An AEFI can thus be defined as “a medical incident that takes place after an immunization, causes concern, and is believed to be caused by the [vaccine or] immunization” (2). AEFIs include (2, 3):

- Vaccine reactions: Events caused by either the vaccine itself or by a preservative, stabilizer, or other vaccine component
- Programme errors: Events caused by an error in the preparation, handling, or the technique used during the administration of the vaccine
- Injection reactions: Events arising from anxiety about, or the pain from, the injection
- Coincidental events: Events that happen at the time of immunization or shortly afterwards but that are not caused by the vaccine or the programme

The frequency of AEFIs may be affected by the age of the patient, the type of vaccine administered, the number of vaccine doses administered, and other factors (Philippe Duclos, WHO, personal communication). Most reported AEFIs are coincidental events temporally associated with immunization. Young children, who are routinely immunized, have immature immune systems and are often sick with minor childhood ailments, such as the common cold. Many alleged links have been made between vaccines and certain chronic conditions, such as autism and hearing impairments. Many of these conditions first manifest themselves in young children and are often first diagnosed during childhood, coincidentally during the same time-period as when children are receiving their first immunizations (3-6).

The public expects that vaccines are safe and immunizations will not cause harm. As vaccine-preventable diseases are eradicated and the burden of infectious disease decreases, the public is losing sight of the risks of infectious diseases and thus the benefits of immunization. They are becoming increasingly focused on AEFIs, and in turn, becoming increasingly critical of vaccines. Rumours and misleading media reports can instil in the public feelings of distrust and apprehension towards immunization programmes and vaccines, which can result in a decrease in immunization coverage and a re-emergence of disease (7). In 1996, several cases of multiple sclerosis were reported among hepatitis B vaccinees in France (8). In response to the public's concern, the French Ministry of Health was forced to suspend the school-adolescent hepatitis B immunization programme, while maintaining a recommendation for infant and adolescent hepatitis B immunization (9). The government's withdrawal of the adolescent school-based programme was misinterpreted in the media as a ban on hepatitis B immunization and resulted in concern over the safety of

the vaccine in other countries (9). In 1998, in the UK, autism was alleged to occur following administration of the measles-mumps-rubella (MMR) vaccine (10). In spite of evidence that these allegations were unfounded (11), immunization rates in the UK have, and continue to, decrease, increasing the risk for an outbreak of measles (10). In 2003, rumours surfaced in Nigeria claiming that the oral polio virus vaccine, used in the effort to eradicate wild polio virus globally, was contaminated with anti-fertility substances (12). Immunization campaigns were suspended in Nigeria and, as a result, wild polio virus transmission resurfaced in several previously polio-free Nigerian states (13) and in 23 polio-free countries in the African Region and in countries as far as Indonesia (14). Developing post-marketing AEFI surveillance systems that focus on prevention, early detection, and a quick response to AEFIs (7) may help to avert the negative effects of bad press and rumours on immunization programmes and the health of communities.

2.2 Pharmacovigilance

Three terms -- ‘immunization safety’, ‘vaccine safety’, and ‘pharmacovigilance’ -- are often used interchangeably, though they in fact have different meanings.

Immunization safety is about “ensuring and monitoring the safety of all aspects of immunization, including vaccine quality, storage and handling, vaccine administration and the disposal of sharps” (7).

Vaccine safety is part of immunization safety and refers to ensuring the quality and safety of vaccine production and pharmacovigilance.

Pharmacovigilance refers to the early detection and appropriate and quick response to adverse events associated with vaccines in order to lessen the negative impact on immunization programmes and the health of individuals (Philippe Duclos, WHO, personal communication). Pharmacovigilance involves post-marketing surveillance of AEFIs and appropriate studies to test hypotheses following detection of a signal. The WHO defines a *signal* as “reported information on a possible causal relationship between an adverse event and a drug [or vaccine], the relationship being unknown or incompletely documented previously” (15).

This thesis will focus on vaccine pharmacovigilance, specifically in reference to AEFI surveillance within the WHO Programme for International Drug Monitoring.

Pre-market testing of new vaccines is insufficient for detecting all adverse events associated with vaccines. There are many reasons for this. Pre-market animal tests are inaccurate predictors of human safety. Human clinical trials are restricted by the limited number of subjects enrolled and the short duration of trials, which are intended to showcase a vaccine’s benefits rather than to detect adverse events. Such trials typically lack the power to detect AEFIs that occur at a rate of less than 1 in 1,000 (16). The specific terms used to describe the frequency of AEFIs are provided in Table 1.

Table 1. Description of terms used for the frequency of AEFIs in the population*

Term	Frequency
Very common	>1/10 immunizations (>10% of immunizations)
Common	>1/100 and <1/10 (>1% and <10%)
Uncommon	>1/1,000 and <1/100 (>0.1% and <1%)
Rare	>1/10,000 and <1/1,000 (>0.01% and <0.1%)
Very rare	<1/10,000 (<0.01%)

* Table adapted from CIOMS Working Group III. Guidelines for preparing core clinical safety information on drugs. Geneva (Switzerland): Council for International Organizations of Medical Sciences; 1995.

Pre-market tests with small sample sizes cannot fully explore the risk-benefit ratio of new vaccines. These vaccines must be under surveillance and tested after marketing in order to monitor changes in the risk-benefit ratio that may arise as more evidence about the vaccine's benefits and harms unfold. Furthermore, not all people on whom a vaccine will be used are represented in pre-market trials. For example, pregnant women, immunocompromised individuals, and people with a pre-existing condition that may put them at increased risk of adverse events, are not included in these pre-market trials. As a result, it is not known how these specific subpopulations may react to a particular vaccine, or how the risk-benefit ratio may be altered for these individuals (16).

Vaccines are produced in batches. Difficulties associated with vaccine manufacturing of biological products may result in the release of vaccine lots that are not fully potent or are more reactogenic (18). These may not be detected until after market release (18).

The deficiencies inherent in pre-market testing were highlighted by the rhesus rotavirus vaccine, released in the United States in 1998 (19-22). Pre-market testing, which included 10,000 children, failed to detect an association between the vaccine and intussusception (i.e., “a bowel obstruction in which one segment of bowel becomes enfolded within another segment” (22)). The signal was detected only after a large number of children were immunized. Following post-marketing studies that supported the signal and that determined that the risk-benefit ratio was unfavourable for American children, a recommendation was made that infants in the United States not be immunized against rotavirus. It is clear that post-marketing surveillance is a necessary step in evaluating the safety of vaccines.

The aims of post-marketing surveillance are to: 1) detect, correct, and prevent programmatic errors; 2) identify problems with specific vaccines or vaccine lots; 3) prevent false blame of coincidental events; 4) maintain public confidence by properly responding to parent and community concerns; 5) identify signals and generate hypotheses to be confirmed by appropriate studies, such as epidemiologic observational studies; 6) estimate rates of AEFIs in specific populations; and 7) adjust contraindications, information provided to the patient, and risk-benefit analyses, as appropriate (7, 18).

Post-marketing AEFI surveillance is usually performed by passive surveillance. Passive surveillance, as opposed to active surveillance, relies on healthcare professionals (HCPs) and others to report adverse events to the surveillance authority. Active surveillance, on the other hand, requires the surveillance authority to proactively collect reports. There are several methods of passive surveillance: spontaneous reporting, stimulated reporting, and mandatory reporting. Spontaneous reporting is the most common form of passive surveillance. HCPs and other appropriate reporters forward adverse event reports as they encounter them. Stimulated reporting is reporting that is encouraged by some means, intentionally or otherwise. Reporting may be stimulated by, for example, highlighting a safety concern in the news or through a targeted immunization campaign. Patients can be encouraged to report AEFIs to HCPs and manufacturers, and HCPs and manufacturers can be encouraged to report to local, regional, or national authorities. Mandatory reporting targets HCPs and manufacturers and requires them to report AEFIs by law. Physicians and public health nurses are usually the primary reporters of AEFIs to local, regional, and national AEFI surveillance authorities. In practice, nurses are generally better reporters than physicians, and reporting is not necessarily improved by mandatory reporting (Wikke Walop, Public Health Agency of Canada/University of Ottawa, personal communication).

Passive surveillance systems can provide an early warning of vaccine safety concerns.

Identified concerns can then be investigated more rigorously via appropriate studies.

Compared with the costs associated with treating adverse events, the cost of a surveillance system is quite small (23).

Most countries have a surveillance system in place for collecting post-marketing AEFI data. In Canada, the surveillance system has two components: the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS), formerly known as the Vaccine Associated Adverse Events Surveillance System (VAAESS), and the Immunization Monitoring Programme ACTive (IMPACT) (24). AEFIs reported through either programme are monitored by the Vaccine Safety Unit (VSU) of the Immunization and Respiratory Infections Division of the Public Health Agency of Canada (PHAC) (24). In Canada, ADRs and AEFIs are monitored separately. These two monitoring programmes were split to establish a specific reporting channel for AEFIs, and thereby improve the efficiency of vaccine safety monitoring (Philippe Duclos, WHO, personal communication).

CAEFISS is a passive reporting programme. The programme's new name emphasizes the fact that AEFIs are suspected events that occur following immunization, but are not necessarily caused by the immunization or the vaccine (24). Reporting is mandatory for HCPs in the provinces of Ontario, Saskatchewan, Nova Scotia, and Quebec, and for vaccine manufacturers in all provinces (24). HCPs report to local public health authorities, and sometimes to vaccine manufacturers, events that they feel might be associated with the administration of a vaccine. Reports received by local public health authorities are forwarded to provincial or territorial health authorities. Provincial and territorial health authorities and vaccine manufacturers, in turn, forward AEFI reports to the VSU, where reports are compiled in a national electronic database. Data from the database, along with lot-specific data obtained from vaccine manufacturers on the number of doses of their products distributed across the country, are used to estimate adverse event rates (24). While

differences in rates must be interpreted with caution, these data are useful for highlighting combinations that, upon further investigation, may signal a vaccine safety concern (24).

In contrast with CAEFISS, IMPACT is an active reporting programme (24). It is designed to highlight serious AEFI cases occurring in children across the country (24). A nurse monitor and a clinical investigator at each of the 12 paediatric hospitals that participate in the programme regularly review admission records to identify AEFI cases (24).

For AEFI surveillance data to be most useful, AEFI reports must be complete, accurate, and timely (5). Passive surveillance is limited by various factors including:

- under-reporting (i.e., not all AEFIs are reported)
- over-reporting (i.e., coincidental AEFIs are reported)
- biased reporting
- incomplete reports
- erroneous reports
- late reports
- inability to detect AEFIs that occur long after immunization
- lack of verification of reported diagnoses
- lack of use of standardized definitions
- inability to determine causality
- inability to calculate incidence rates and relative risks
- need for studies to test hypotheses

The extent of under-reporting varies tremendously from one country to another. It has been suggested that, in countries with established surveillance programmes, only 10% of physicians report ADRs, and only 10% of serious ADRs are reported (25). In general, the proportion of AEFIs reported to authorities is likely to be just as low as the proportion of ADRs. In Canada, however, because of IMPACT, most serious childhood AEFI cases are identified.

The likelihood of reporting an AEFI is influenced by the vaccine, the type and severity of the event, the time since immunization, and the amount of publicity over the suspected AEFI (26, 27). It has been said that “under-reporting is both a technical and a psychological issue” (25). A variety of factors, both encouraging and discouraging, may play a role in a HCP’s decision to report an adverse event. The following may influence a HCPs decision to report (25, 28, 29):

- seriousness of the reaction
- abnormality of the reaction
- involvement of a new drug or vaccine
- confidence in the diagnosis of an adverse event
- fear of litigation for diagnosing an adverse event
- fear of appearing foolish for reporting an adverse event
- fear of admitting to having caused harm
- ambition to publish cases rather than to report
- patient confidentiality
- feeling too busy to report

- ignorance of where or how to report
- belief that all marketed products are safe

Under-reporting may be lessened by encouraging HCPs to report regularly and by making the criteria and procedure for reporting as clear and simple as possible (25). Both ethically and practically-speaking, it is better not to financially reward HCPs for submitting AEFI reports. A financial reward programme would likely sacrifice the quality of AEFI reports and set a difficult precedent for other surveillance programmes to follow.

The variety of definitions and categorizations of AEFIs makes meaningful comparisons between databases virtually impossible, limiting the amount of AEFI data available to evaluate the safety of vaccines. Standardized definitions will make case reports within and between databases more comparable. As definitions are standardized and similar pharmacovigilance databases are linked, the increase in volume of useable data will permit faster signal detection and hypothesis testing.

A causal relationship between a vaccine and an adverse event is often erroneously assumed based only on a temporal association between an immunization and an adverse event (18).

An AEFI surveillance database includes data only on vaccinated individuals who have experienced suspected adverse events; no data is available on vaccinated individuals who have not experienced adverse events or on non-vaccinees. Because most of the population is immunized, finding a suitable control group is difficult; non-immunized individuals may be systematically different from vaccinated individuals and may introduce a bias if used as

controls. Because different age groups experience different background risks of illness, different vaccines administered to different age groups should not be compared. For example, sudden infant death syndrome (SIDS) refers to the unexpected and sudden death of an apparently healthy child less than one year of age (30). Children receive many of their primary immunizations before the age of one (31). Because SIDS, by definition, can occur only during the first year of life, the same time-period when children receive their first immunizations, comparing vaccines administered in infancy with those administered later in childhood for the incidence of SIDS will lead investigators to draw misleading conclusions about the safety of these vaccines. Epidemiologic evaluations of causality and calculations of attributable and relative risks, therefore, cannot be made from AEFI reports alone.

Studies, including epidemiologic studies, are required to test hypotheses resulting from the analysis of surveillance data. The two most common epidemiologic designs are the cohort study and the case-control study. Cohort studies are appropriate when an outcome occurs frequently and shortly after immunization. Case-control studies are preferred when an outcome is rare (and most AEFIs that are investigated are rare) and occurs long after immunization. Randomized controlled trials are not usually conducted post-licensure because of ethical, logistical, and scientific limitations (18). The emergence of computerized large linked population databases, linking, for example, immunization registries with hospitalization records, will facilitate epidemiologic evaluations of causality (1, 27).

Cooperation and communication between all parties involved in vaccine safety is necessary. Adverse event reporting should be encouraged. HCPs and the community should be informed of serious vaccine safety issues in the context of the benefits and harms of both disease and immunization to the individual and to the community. Feedback is important in motivating HCPs and others to report. Family physicians, paediatricians, nurses, and pharmacists have regular, direct contact with the public and therefore play an important role in risk communication. The likelihood of better quality and timelier reports will be increased by making reporting as easy as possible, by keeping HCPs informed of why their participation is important, and by providing HCPs with feedback from the system. Patient confidentiality must be respected, particularly in light of the fact that individual consent for the collection of personal data is often not sought. The success of a surveillance system depends, in large part, on the willingness of patients and HCPs to report. If AEFI surveillance data are not used responsibly, reporters are unlikely to continue reporting and the surveillance system will fail as a result (25).

2.3 International Pharmacovigilance

Every immunization carries the risk of adverse events that should be balanced against the benefits of immunization and the risks associated with infectious disease. AEFIs reported in one part of the world may differ significantly from AEFIs reported in another part of the world following administration of the same vaccine (1). Because risk-benefit ratios and the perception of risk can differ in different parts of the world, risk-benefit assessments should be country-specific. Surveillance must, therefore, be available in every country where

vaccines are introduced (18). A surveillance system should be tailored to the country and be integrated into the country's existing pharmacovigilance or public health programme (7). Considerable progress has been made in AEFI post-marketing surveillance, with more countries establishing surveillance systems and placing more importance on AEFI reporting (7, 18).

The large proportion of malnourished and immunocompromised persons in many developing countries presents an additional challenge in vaccine safety. Because high-risk individuals are usually not included in pre-market testing of vaccines, the type and frequency of AEFIs experienced by these specific groups of individuals cannot be accurately predicted. Additional population-specific testing is required to evaluate the risks and benefits of immunization in these specific populations. The Global Advisory Committee on Vaccine Safety, for example, has suggested that population based studies be conducted to test the safety and effectiveness of live BCG vaccine in HIV-positive infants living in regions with a high endemic rate of TB (33).

While the risks associated with immunization may be considered acceptable from a public health point-of-view, they may be less acceptable to the individuals being immunized. Serious consequences for the population, however, can result when high vaccine coverage rates are not achieved (18). In Greece, in 1993, a major rubella epidemic occurred, affecting women of childbearing age (34). The epidemic resulted in the birth of the largest number of babies with congenital rubella syndrome recorded in the country's history (34). Immunizing children at one year of age will interrupt transmission of the virus, however, if immunization

coverage is low, adolescents and young women are at increased risk of infection during pregnancy (34). Infection during pregnancy can result in spontaneous abortion, stillbirth, and congenital rubella syndrome in newborn infants (34).

The WHO has a pivotal role to play in AEFI surveillance and response to global vaccine safety concerns. Some of the WHO's activities are described below.

Global Advisory Committee on Vaccine Safety (GACVS): Both real and rumoured vaccine safety concerns must be appropriately addressed in order to minimize the negative impact on immunization programmes and the resultant resurgence of infectious diseases. The ability of national advisory committees to collectively address international vaccine safety concerns can be hindered by their national interests and perspectives (18). As a result, the WHO has established the GACVS to independently assess serious vaccine safety issues of global importance (7, 18).

Global Training Network (GTN): The WHO developed the GTN to improve vaccine quality and use globally. The GTN provides the staff of national regulatory authorities, control laboratories, vaccine manufacturers, and immunization programmes with educational resources and training, including a course in AEFI monitoring (7, 18, 32, 35, 36). The network currently consists of 15 training centres located around the world (37).

Collaborating to create large linked population databases: In spite of great improvements in AEFI surveillance activities, many countries, particularly developing countries, still lack the capacity and tools to properly evaluate surveillance data via epidemiologic or laboratory investigations, including the means to organize large linked population databases (7, 18). International collaboration in signal detection and hypothesis testing is therefore essential (18). In collaboration with the WHO, the International Vaccine Institute (an international centre of research, training, and technical assistance for vaccines needed in developing countries (38)) plans to create large linked population databases in developing countries in Asia. Thus far, one such programme has been introduced in Vietnam (19).

Ensuring the safety of United Nations (UN) vaccines: Vaccines provided through the UN are aimed at preventing diseases specific to developing countries, and are particularly important to countries that cannot otherwise afford vaccines (18). The WHO assesses candidate vaccines to ensure that they are safe, effective, and meet the needs of immunization programmes (18). Vaccines produced in developing countries are often wrongly assumed to be of lesser quality even though they undergo the same scrutiny as vaccines produced anywhere in the developed world (18). The global supply of vaccines relies heavily on the production of vaccines in developing countries (18).

Immunization Safety Priority Project (ISPP): The ISPP, launched by the WHO's Vaccines and Biologicals Department (now known as the Immunization, Vaccines, and Biologicals (IVB) Department), was created to ensure the safety of all immunizations administered in national immunization programmes (7). The ISPP advocated for the safety of vaccines, the safety of injections, and the safety of disposal; "A safe injection is not only one that does not harm the recipient but also one that does not harm the healthcare worker [or] the community" (7). In 2005, the project was mainstreamed into the IVB Department's regular departmental activities.

Supporting the Brighton Collaboration: The Brighton Collaboration is a voluntary, international collaboration of experts working to develop standardized AEFI case definitions and AEFI monitoring guidelines in order to assist in the development, evaluation, and dissemination of high quality vaccine safety information (18). The group's aim is to develop 50 to 100 definitions; so far, six definitions have been finalized and 18 others are in development (Philippe Duclos, WHO, personal communication).

The WHO Programme for International Drug Monitoring: An international database of AEFI reports from several countries can strengthen an association, signaling vaccine safety concerns before they become apparent in individual countries.

2.4 The WHO Programme for International Drug Monitoring

The WHO Programme for International Drug Monitoring (PIDM) is an international adverse event monitoring system. It was developed following the thalidomide disaster of 1961, where babies, whose mothers had taken a supposedly “safe” sleeping pill during pregnancy, suffered amelia (i.e., born without one or more limbs (39)) and phocomelia (i.e., born with very short or absent long bones and a flipper-like appearance of the hands or feet (39)) (23). After a pilot project in the United States in 1968, the PIDM was set-up at WHO Headquarters (WHO/HQ), Geneva in 1971, and then moved to Uppsala, Sweden in 1978 (23). Today, administration of the programme is shared between the WHO Collaborating Centre for International Drug Monitoring (more commonly referred to as the Uppsala Monitoring Centre or simply the UMC), which retains responsibility for daily operations, and WHO/HQ, which is responsible for policy issues (40). Since 2002, the UMC has financed all of its activities through the sale of publications and services resulting from its regular activities (23).

The PIDM is responsible for the collection and assessment of adverse event reports from member countries around the world, and the communication of information regarding drug and vaccine safety issues to regulatory and pharmacovigilance authorities of member countries. National Pharmacovigilance Centres (NPCs) of member countries submit individual case reports of suspected ADRs and AEFIs to the UMC. At the UMC, case reports are stored in a common database known as the WHO Adverse Reactions Database.

A country wishing to join the PIDM must have a NPC appointed by the national health authority (e.g., Ministry of Health) that will represent the country in the PIDM, and the NPC must have the ability to submit case reports to the UMC according to current WHO guidelines (Sten Olsson, UMC, personal communication). The NPC can be responsible for national ADR surveillance, national AEFI surveillance, or both. Generally, the UMC communicates only with one national surveillance authority in each country. If two surveillance authorities exist, as in the case where ADR and AEFI surveillance are conducted by separate authorities, the UMC usually communicates with the authority designated as the NPC. It is the responsibility of the NPC to communicate with any other national surveillance authorities in the country. All national surveillance authorities may submit adverse event reports to the UMC. As of March 2006, the PIDM had grown to include 79 member countries and 19 associate countries (i.e., countries waiting to synchronize their national reporting formats with that of the UMC) (41). The WHO database contains over 3.5 million case reports (41).

National reporting schemes vary from country to country. Reports are usually made by HCPs and submitted to the NPC via local and regional surveillance centres (23). Some NPCs assess reports before sending them to the UMC (23). Once at the UMC, no further assessment is made on the individual reports (23). Although NPCs are requested to submit their case reports to the UMC quickly and regularly, reporting frequency varies between countries and within countries over time (23).

The *WHO-Drug Dictionary* (WHO-DD) is used to identify drugs and vaccines and the *WHO-Adverse Reaction Terminology* (WHO-ART) is used to describe ADRs and AEFIs. The PIDM is able to link the terminology used in WHO-ART with that used in the *International Conference on Harmonization Medical Dictionary for Regulatory Affairs* (MedDRA), another adverse event terminology used by many reporting countries (23). MedDRA is a compilation of WHO-ART, the *Coding Symbols for Thesaurus of Adverse Reaction Terms* (COSTART), and the International Classification of Disease (ICD) -9. In order to be entered into the database, a report must contain, at minimum, an identified reporting country, a unique report identification number, a suspected product, and an adverse event (23, 42). In order to maximize the usefulness of reports in signal detection, NPCs are encouraged to ensure that the data in their reports are as accurate and complete as possible (23). Every incoming report is checked by UMC staff for proper syntax, inter-field coherence, duplication of reports, and use of accepted product names and adverse event terms (23, 42). Reports with rejected values are flagged, examined by UMC staff, and corrected (23, 42). If a new product or adverse event term, not yet classified in the WHO-DD or WHO-ART, is reported, UMC staff update the WHO-DD or WHO-ART to include the new product or term. The completeness of reports is graded on a scale of 0 (poor, i.e., does not contain an identified reporting country, a report identification number, a product, and an adverse event) to 5 (very good, i.e., contains an identified reporting country, a report identification number, a product, and an adverse event, as well as information on age, gender, date of onset of reaction, treatment dates, patient outcome, drug dosage, and route of administration). Grading helps UMC staff highlight well documented cases and cases that

are missing data (23, 42). It is also used in signal detection and for statistical purposes (23, 42).

Since 1998, a Bayesian Confidence Propagation Neural Network (BCPNN) has been used for routine data mining of the database (23, 42). The BCPNN is transparent, time-efficient, flexible for different kinds of searches, and can handle large amounts of data, including incomplete data (23, 43). The Information Component (IC), calculated with the BCPNN, is a measure of the strength of an association between a product and an adverse event (23, 43). The IC is used to identify combinations of products and adverse events that stand out from the background data and are, statistically, highly associated (23, 43). A positive IC value indicates that a combination is reported more often than would be expected based on the rest of the reports in the database (23). A negative IC value indicates that the combination is reported less often than statistically expected (23). An IC value of zero indicates that there is no quantitative dependency between a particular product and adverse event (23). The standard deviation for each IC value is calculated. The larger the number of case reports in the database pertaining to product X, adverse event Y, and the specific X-Y combination, the narrower the confidence interval around the IC value (23).

The database is scanned quarterly using the BCPNN. All combinations of products and adverse events in the database, as well as the statistical figures generated by the BCPNN, are listed in the 'Combinations Database' (23). UMC staff review the Combinations Database and identify those combinations with a positive lower 95% confidence limit of the IC value (23). The first quarter that a combination has a positive lower 95% confidence limit of the

IC value, it is copied into the ‘Associations Database’ (23). Combinations found in the Associations Database are those that are considered statistically worth investigating. These combinations undergo a filtering process based on pre-defined algorithms designed to narrow down the number of associations to a more manageable subset that will include those of greatest concern (23). UMC staff perform a search of the literature for information on these identified associations (23). An association that is not found in the literature or is not adequately defined is sent to an international expert who assesses the evidence for the relationship between the product and the adverse event (23). If, after review by an expert, the association is considered a ‘signal’, a summary of the association is included in the UMC’s publication ‘SIGNAL’ (23). This is a restricted access document made available to NPCs of countries participating in the PIDM, and when appropriate, to product manufacturers, to enable a quick response to important signals (23). In addition, NPCs have access to the outputs from the quarterly scans of the database, and access to both an e-mail conferencing facility (i.e., *Vigimed*) and an online search facility for searching the WHO database (i.e., *Vigisearch*) (23, 44).

Unlike national post-marketing surveillance systems (e.g., Canada’s CAEFISS), the PIDM is unique because it is an international database, operated independently of any specific country. Because data from all participating countries are compiled into one large database, it increases the statistical power to detect sooner associations based on infrequently reported events.

The PIDM was initially developed for chemical rather than biological products. Very little has changed since its inception to take into consideration the unique characteristics of vaccines, in particular: the same drug classification system is used to categorize drugs and vaccines; adverse reaction terminologies have not been expanded to include all symptoms of AEFIs; and ADR and AEFI case reports are analysed in the same way. Considering the differences in characteristics between drugs and vaccines, the ability of the PIDM to meet the needs of vaccine safety is of great international public health importance (45, 46).

The UMC has made considerable achievements in analysing drug-related adverse event reports, however similar improvements have not been made in analysing vaccine-related reports. Limitations of the PIDM with respect to AEFI reports include (45):

- a small number of AEFI reports in the database
- limited relevant case information available in AEFI reports
- difficulty associated with data mining using tools developed for drug-related issues
- problems communicating vaccine signals with national immunization authorities

In June 2005, the Global Advisory Committee on Vaccine Safety, acknowledging these limitations, called for a global consultation to address the need for improved monitoring and analysis of vaccine-related adverse event reports on an international level (45).

It is expected that results of this evaluation will be used by the WHO and UMC to guide further research and action to improve international AEFI surveillance.

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CHAPTER THREE: A SURVEY OF NATIONAL CENTRES PARTICIPATING IN THE WHO PROGRAMME FOR INTERNATIONAL DRUG MONITORING

The following is a manuscript prepared for publication, based on a survey of the national AEFI surveillance authorities of countries participating in the PIDM. The objective of this survey was to gather evidence on: 1) the process and the product of national AEFI surveillance in member countries; 2) the level of communication between national ADR and AEFI surveillance authorities; and 3) the acceptability and usefulness of the PIDM, the Brighton Collaboration's AEFI definitions, and the various internet-based services provided by the UMC.

A copy of the letter from the Ottawa Hospital Research Ethics Board, approving this project, is provided in Appendix A.

A copy of the questionnaire that was sent to the National Pharmacovigilance Centres is provided in Appendix B.

This manuscript was co-authored by the student (ML), her co-supervisors, Dr Philippe Duclos and Dr George Wells, and an advisor to the thesis, Dr Wikke Walop. The student is the first author of this paper, having been primarily responsible for data collection, analysis, and writing of the manuscript. Drs Duclos, Wells, and Walop provided valuable feedback throughout the process.

Improving global monitoring of vaccine safety: a survey of national centres participating in the WHO Programme for International Drug Monitoring

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This manuscript includes one (1) table and two (2) figures.

Abstract

The World Health Organization (WHO) Programme for International Drug Monitoring (PIDM) was established following the thalidomide disaster of 1961. The PIDM has made considerable achievements in analyzing drug-related adverse event reports, however more limited progress has been made in analysing vaccine-related reports. In June 2005, the Global Advisory Committee on Vaccine Safety, acknowledging these limitations, called for a global consultation to address the need for improved monitoring and analysis of vaccine-related adverse event reports on an international level. In preparation for this consultation and as part of a larger study designed to evaluate the PIDM, a survey of the National Pharmacovigilance Centres of all countries participating in the PIDM was conducted. Forty-four percent of countries reported having a separate surveillance system for adverse events following immunizations (AEFIs) and 74% reported forwarding AEFI reports regularly to the PIDM. Half of the respondents knew of the Brighton Collaboration, a major international initiative aimed at the standardization of AEFI definitions. The survey identified critical elements that should be quickly addressed to improve global vaccine safety monitoring. Communication between national adverse drug reaction (ADR) and AEFI surveillance authorities, ability to pay for advancing technology in developing countries, and proper use of services and terminologies are issues of concern.

Keywords

pharmacovigilance, Programme for International Drug Monitoring, vaccine, survey

Introduction

The World Health Organization (WHO) Programme for International Drug Monitoring (PIDM) is an international adverse event monitoring system developed following the thalidomide disaster of 1961 (1). Administration of the PIDM is the joint responsibility of the WHO Collaborating Centre for International Drug Monitoring, more commonly referred to as the Uppsala Monitoring Centre (UMC), and the WHO Headquarters (WHO/HQ) (2).

Countries participating in the PIDM submit adverse drug reaction (ADR) reports, including adverse events following immunization (AEFI) reports, to the UMC through their National Pharmacovigilance Centre (NPC). Once received by the UMC, reports are stored in the WHO Adverse Reactions Database. Participation in the PIDM has increased significantly since its inception in 1968. The PIDM began with only 10 countries, Canada being one of the founding members. As of March 2006, the PIDM had grown to include 79 member countries and the WHO database contained over 3.5 million reports (3).

The UMC uses the *WHO Drug Dictionary* (WHO-DD) to identify drugs and vaccines. The Anatomical Therapeutic Chemical (ATC) classification system is used to divide drugs and vaccines into groups “according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties” (4).

Several terminologies exist for describing adverse events. The WHO Adverse Reaction Terminology (WHO-ART), the *International Conference on Harmonization Medical*

Dictionary for Regulatory Affairs (MedDRA), and the *Coding Symbols for Thesaurus of Adverse Reaction Terms* (COSTART) are used by member countries of the PIDM. The UMC is able to link these terminologies so that reports coded with different terminologies are comparable.

The Brighton Collaboration is an international voluntary collaboration of professionals and organizations aiming to develop standardized, widely disseminated and globally accepted AEFI definitions and AEFI monitoring guidelines for data collection, analysis, and presentation (5). The CIOMS/WHO Working Group on Vaccine Pharmacovigilance, a recent collaboration of the Council for International Organizations of Medical Sciences (CIOMS) and the WHO, aims: 1) to propose standardized definitions relevant for monitoring the safety of vaccines (e.g., “AEFI”, “vaccine failure”); 2) to contribute to the efforts of the Brighton Collaboration by assisting in the development, review, evaluation, and approval of AEFI definitions; and 3) to collaborate with the CIOMS Working Group on Standardised MedDRA Queries to ensure that proposed queries will be applicable to vaccines (6). The CIOMS/WHO Working Group on Vaccine Pharmacovigilance and the Brighton Collaboration are expected to make significant progress in the standardization of AEFI definitions and vaccine safety terminology.

Participating countries have access to various internet services provided by the UMC, including *Vigibase Online* (i.e., an online adverse event report management system), *Vigisearch* (i.e., an online search facility for searching data in the database), and *Vigimed* (i.e., an e-mail conferencing facility exclusively for PIDM member countries) (1, 7). These

services are intended to improve adverse event reporting, both within a country and to the UMC, allow NPCs to search the WHO database, and facilitate discussion among NPCs. Signals identified by the PIDM are included in the UMC's publication SIGNAL. This is a restricted access document made available to NPCs of countries participating in the PIDM and, when appropriate, to product manufacturers.

Except for a few biological products, most drugs are chemical products. Vaccines are one example of biological drug products. In spite of the many differences between vaccines and drugs, vaccines are commonly viewed as being similar to drugs. While some vaccines are used in the treatment of disease (e.g., Bacille Calmette-Guérin (BCG) vaccine in the treatment of bladder cancer) and are therefore somewhat akin to drugs, most vaccines are intended to prevent and control disease. Some of the special characteristics that differentiate vaccines used for disease prevention from drugs are: vaccines are usually administered to large populations of healthy individuals; most vaccines are administered to infants and children; vaccine administration is often promoted or even made mandatory by governments; a main issue in the safety and efficacy of vaccines is maintaining an adequate 'cold chain' (i.e., a system for keeping vaccines at the appropriate temperature, from the time of the start of manufacture until the time of use, in order to maintain vaccine quality and potency); potential variation between different brands and lots of a vaccine necessitates lot-by-lot surveillance of vaccines at the post-marketing stage; and the public is, in general, less willing to accept the risks associated with vaccines.

A country wishing to join the PIDM must have a NPC responsible for national ADR surveillance, national AEFI surveillance, or both. The NPC must adhere to the criteria set out in the UMC publication 'Joining the WHO Programme for International Drug Monitoring' (2). Generally, the UMC communicates only with one national surveillance authority in each country. If two surveillance authorities exist, as in the case where ADR and AEFI surveillance are conducted by separate authorities, the UMC usually communicates with the authority designated as the NPC. It is the responsibility of the NPC to communicate with any other national surveillance authorities in the country. All national surveillance authorities may submit adverse event reports to the UMC.

The PIDM was initially developed for chemical rather than biological products. Very little has changed since its inception to take into consideration the unique characteristics of vaccines, in particular: the same drug classification system is used to categorize drugs and vaccines; adverse reaction terminologies have not been expanded to include all symptoms of AEFIs; and ADR and AEFI case reports are analysed in the same way. Considering the differences in characteristics between drugs and vaccines, the ability of the PIDM to meet the needs of vaccine safety is of great international public health importance (8, 9).

A survey of authorities responsible for AEFI surveillance in all countries participating in the PIDM was conducted as part of a larger study designed to evaluate the PIDM on how it serves the needs of vaccine safety. The objective of this survey was to gather evidence on: 1) the process and the product of national AEFI surveillance in member countries; 2) the level of communication between national ADR and AEFI surveillance authorities; and 3) the

acceptability and usefulness of the PIDM, the Brighton Collaboration's AEFI definitions, and the various internet-based services provided by the UMC.

Methods

At the time of survey in July 2005, 76 countries were participating as full members in the PIDM. This included five countries from the WHO African Region, 13 countries from the WHO Region of the Americas, six countries from the WHO Eastern Mediterranean Region, 38 countries from the WHO European Region, four countries from the WHO South-East Asia Region, and 10 countries from the WHO Western Pacific Region.

A questionnaire was developed in collaboration with interested parties, including the WHO, the UMC, and the Public Health Agency of Canada. The questionnaire was mailed to the UMC's contact person at the NPC of each of the 76 countries during the fourth week of July 2005. Contact persons were requested to forward the questionnaire and its accompanying cover letter to the authority most responsible for AEFI surveillance within their country, if this was not the NPC. A reminder was sent out during the second week of October 2005 following a presentation of preliminary survey results made in September 2005 at the *Twenty-eighth Annual Meeting of Representatives participating in the WHO Programme for International Drug Monitoring* in Geneva, Switzerland.

The questionnaire included 25 questions and addressed: 1) which countries are forwarding AEFI reports to the UMC; 2) how AEFI reports are forwarded to the UMC; 3) what types of

AEFI reports are forwarded to the UMC; 4) which terminologies are used to code AEFI reports; 5) the usefulness of the communications services provided by the UMC; and 6) overall impressions of the PIDM and WHO database with respect to AEFI surveillance and vaccine safety. In addition to questions relating to reporting practices, respondents were asked one question about the Brighton Collaboration. This question was designed to assess global awareness and acceptability of the Brighton Collaborations' AEFI definitions. Descriptive statistics including counts and percentages were calculated. Frequency distributions were prepared where appropriate.

Ethical approval was obtained from the Ottawa Hospital Research Ethics Board.

Results

A summary of responses to the questions is presented in Table 1. Responses to open questions and additional results are presented in the text below. For open-ended questions, where more than two respondents gave a response, the number giving the response is presented in the text. For clarity, survey questions have been grouped into six focus areas: countries forwarding AEFI reports to the UMC; methods of forwarding reports to the UMC; types of AEFI reports forwarded to the UMC; terminologies used to code AEFI reports; utility of communication services provided by the UMC; and overall impressions of the PIDM and WHO database.

Response rate

Thirty-six of 76 (47%) countries responded to the survey, a response rate consistent with previous surveys of NPCs (Sten Olsson, UMC, personal communication). Fifty-three percent of survey responses came from member countries in the WHO European Region. Twenty-three percent of member countries in the WHO Region of the Americas responded to the survey while 50-60% of member countries in each of the remaining five WHO Regions responded to the survey (Figure 1).

Countries forwarding AEFI reports to the UMC

Four of the six countries that do not forward AEFI reports to the UMC have separate surveillance systems for ADRs and AEFIs (one country did not indicate whether its ADR and AEFI surveillance systems are separate or not).

Countries not forwarding AEFI reports to the UMC cited the following reasons: do not know about the UMC; do not have any AEFI reports to forward; not required to report AEFIs; no responsible authority for reporting AEFIs; and AEFI data not compatible with the UMC's reporting format.

Factors hindering or limiting AEFI reporting to the UMC include: insufficient or absent funding; internet and telecommunications too expensive; shortage of staff and competing demands on staff; time required to format reports; and reports not forwarded by the vaccine authority to the NPC.

Respondents suggested that specific AEFI reporting instructions should be created and include specific guidelines on how to handle programmatic errors, coincidental events, injection reactions, and vaccine batch problems.

Methods of forwarding reports to the UMC

Factors impeding regular reporting of AEFIs to the UMC include: a shortage of staff; competing demands; an absence of reports to send; just starting to report; currently setting up a new reporting schedule following a database change; and insufficient financial resources to purchase *Vigibase Online*.

Two respondents who felt that the workload associated with AEFI reporting to the UMC is unmanageable cited as their primary concerns a lack of time and staff to address AEFIs. One of these countries indicated that their AEFI surveillance is separate from their ADR surveillance (the other did not indicate if it was separate or not). Both countries indicated that AEFI reporting within their country is not mandatory and that reporting to the UMC does not occur regularly. Both countries indicated, however, that they do forward AEFI reports to the UMC, be it in an irregular manner.

Respondents who had indicated that the workload is manageable also noted that: there is a shortage of staff; reporting is time consuming; reporting is manageable so long as it is in the same format as ADRs; and reporting AEFIs is no more unmanageable than for ADRs.

Types of AEFI reports forwarded to the UMC

Healthcare professionals are the primary reporters of AEFIs. All 36 countries accept AEFI reports from physicians. Most countries accept reports from at least one other source as well (Figure 2). Sixteen of 36 countries (44.4%) indicated that they accept consumer reports.

Seven of 36 countries (19.4%) indicated that one or more population subgroup(s) is(are) systematically excluded from their country's AEFI surveillance system. Five of the seven countries exclude recipients of travelers' vaccines; two exclude the private sector; five exclude the military sector; and one excludes vaccines administered outside the Expanded Programme on Immunization (i.e., a WHO programme that aims to eliminate sickness and death from childhood diseases for which a safe and effective vaccine is available by developing national immunization programmes to deliver immunizations to all children and adults who require them (10)). One of the seven countries did not indicate which group(s) is(are) excluded.

Among the 30 countries that forward AEFI reports to the UMC, 26 (92.9%) submit all AEFI reports. One country submits only serious reports and unexpected reports. One country indicated that it does not submit all AEFI reports or only serious AEFI reports, but did not specify which reports it does submit. Two countries did not indicate what type of reports they submit.

Respondents indicated that some AEFI reports are not submitted to the UMC because: they are considered 'non-cases', are unlikely associations, or are not deemed 'certain',

‘probable’, or ‘possible’ following causality assessment; they are duplicate reports; they are not well investigated or the minimum amount of information on the case is unavailable; or they were not forwarded by the Expanded Programme on Immunization.

Terminologies used to code AEFI reports

Twenty-seven of 36 countries (75.0%) are using WHO-ART to code adverse events in AEFI reports; seven countries (19.4%) are using MedDRA; and one country (2.8%) is using COSTART. One additional country indicated that it is using a method other than WHO-ART or MedDRA but did not specify which terminology it is using.

Countries that have not adopted the Brighton Collaboration’s AEFI definitions cited the following reasons: need to consider further the implications and feasibility of adopting the definitions; do not want to treat the monitoring and reporting of ADRs and AEFIs separately; and have not yet decided whether to apply the definitions or not.

Utility of communication services provided by the UMC

Reasons why countries are not satisfied or only partially satisfied with *Vigimed* include: a lack of responses to their queries; a lack of detail in responses; and misuse of *Vigimed* when *Vigisearch* should be used instead. Respondents suggested: creating an archiving system by topic and consolidating associated responses (*4 respondents made this suggestion*); updating email addresses; restricting enquiries to questions that cannot be answered through *Vigisearch*; and using *Vigimed* to exchange information on signals detected.

Respondents who indicated that they are dissatisfied with *Vigisearch* cited the following reasons: it can be slow and difficult to use; it is difficult to search by ATC classification; and the frequency of connection breaks or the system being down for maintenance. Suggested improvements included: organizing a training programme on how to use *Vigisearch*; faster search capability; indicating how many reports were received for a particular substance; easier access to the total number of reports by AEFI; more search parameters (e.g., seriousness, reporter qualification); easier searching by ATC classification; ability to identify the number of programmatic errors; permitting analyses for medication-error events; batch-related searching; access to more than 30 case reports; and printable tables.

Overall impressions of the PIDM and WHO database

Narrative comments were invited on respondents' overall impressions of the PIDM and WHO database with respect to AEFI surveillance and vaccine safety. Twenty-six of 36 respondents provided comments in response to this question. Respondents' overall impressions were generally positive. Most respondents indicated that the programme and database were "sufficient", "useful", or "excellent". Some respondents made criticisms of the database, such as the AEFI data are of poor quality and the AEFI portion of the database is too small. Others indicated that they have made very little use of the database for AEFIs and therefore could not comment further about the programme or database.

Discussion

Some countries participating in the PIDM combine ADR and AEFI surveillance under one authority; others separate them. Separate surveillance systems can make communication and collaboration between ADR and AEFI surveillance authorities more difficult. If communication between authorities is hindered, AEFI reports may not be forwarded to the UMC. When a single authority is responsible for ADR and AEFI surveillance, vaccines may be grouped with drugs and specific vaccine considerations may not be addressed (e.g., AEFIs may not be adequately described because drug-specific terminology may be used). Two survey respondents made clear that there was a lack of communication and collaboration between their ADR and AEFI surveillance authorities. One respondent was from a country's national AEFI surveillance authority and indicated that the AEFI surveillance authority did not know about the UMC. The other respondent was from a country's national ADR surveillance authority and indicated that the country had no AEFI reports to forward to the UMC. This respondent further explained that the drug authority had been in contact with the Expanded Programme on Immunization manager in the country and had been told that there were no reports requiring the drug authority's attention.

Several survey respondents indicated that some AEFI reports may be screened, ruled-out, and not submitted to the UMC. While it is appropriate not to send duplicate reports to the UMC, it is inappropriate to withhold reports because they have not been investigated beyond the UMC's minimal data requirements. Assessments of causality on individual reports are not necessary. Because there is no standardized method of assessing causality on individual

reports and because each reporting country can perform its own causality assessments, it is likely that the standard categories for the likelihood of causal associations (such as “probable” or “possible”) are applied differently by different countries. Rather, surveillance authorities should investigate cases quickly and forward complete reports to the UMC in a timely manner. Further reporting bias will be introduced if cases are not submitted to the UMC. Complete and timely case reports are needed in order to quickly detect vaccine signals of possible international concern. The signaling process will be compromised if reports are not forwarded or are delayed.

Theoretically, *Vigibase Online* should facilitate more timely and regular reporting of adverse events to the UMC. The effectiveness of the system, however, will depend on several factors: 1) countries must have the means to purchase the system and the computer technology to operate it; 2) national surveillance authorities must make their healthcare professionals and other reporters aware of the system and of how to use it; and 3) national surveillance programmes must employ appropriate numbers of trained staff who are able to process incoming reports quickly. In spite of the presumed benefits of using *Vigibase Online* and other internet applications, the operating costs may prevent some countries from fully participating in the PIDM, even when the initial costs can be overcome. The impact of *Vigibase Online* on the timeliness of reporting and, in turn, the efficiency of signal detection has not been formally evaluated.

WHO-ART and MedDRA, the two most common adverse event terminologies used by PIDM-participating countries to code AEFI reports, were not designed with the specific

needs of AEFI surveillance in mind. Consequently, adequately describing AEFIs can be difficult. Respondents to our survey reported that there are terms that cause problems for describing AEFIs and that there are AEFI terms missing from these terminologies. This problem could be remedied by a review of the adverse event terminologies for the inclusion of AEFI-specific symptoms.

Fifty percent of countries responding to our survey had heard of the Brighton Collaboration and most of the countries were aware of the proposed definitions and intended to apply the definitions to their national AEFI surveillance system. While it is clear that the Brighton Collaborations' definitions are generally accepted, further promotion of the definitions is needed to encourage more countries to adopt them. As AEFI definitions and vaccine safety terminology are standardized and more countries use the standardized vocabularies, AEFI surveillance data will become more comparable between countries and will better facilitate international surveillance.

Open questions provide the opportunity for respondents who feel strongly about an issue to voice their concerns. The thoughts and concerns raised by respondents who answered these questions may not represent the opinions of all AEFI surveillance authorities questioned. The answers provided, however, are useful because they may lead investigators to interesting insights and potential focus areas for future research.

The results of this survey are limited by the small number of surveys returned. While the response rate to this survey was consistent with earlier surveys of NPCs, results may not be

completely representative of all countries currently participating in the PIDM. Furthermore, in some cases, the questionnaire was completed and returned by someone other than the country's AEFI surveillance authority.

Survey respondents have generally found the PIDM and WHO database to be useful. There is, however, a definite need for activities to strengthen vaccine safety data, such as the standardization of AEFI definitions and vaccine safety terminology. Communication between drug and vaccine authorities of member countries is paramount and should be addressed.

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Table 1. Survey responses to closed questions

Question	Yes (%)	Responded: Did not respond
<i>Countries forwarding AEFI reports to the UMC</i>		
Does your country have separate surveillance systems for reporting ADRs and AEFIs?	15 (44)	34:2
Does your country forward AEFI reports to the UMC?	30 (83)	36:0
Are there financial or other considerations that hinder or limit reporting of AEFIs to the UMC?	7 (20)	35:1
Are the UMC's instructions for AEFI reporting clear?	20 (95)	21:9
Are the UMC's instructions for AEFI reporting adequate?	21 (91)	23:7
<i>Methods of forwarding reports to the UMC</i>		
Does reporting to the UMC occur at regular intervals?	20 (74)	27:3
Is the workload associated with AEFI reporting to the UMC manageable?	26 (93)	28:2
<i>Types of AEFI reports forwarded to the UMC</i>		
Are vaccine programme errors (i.e., "medication errors") reported to the UMC?	14 (47)	30:0
Are vaccine failures reported to the UMC?	18 (62)	29:1
Are individual AEFI reports ever screened, ruled-out as cases, and not submitted to the UMC?	9 (32)	28:2
Does any assessment and classification (e.g., definite, probable, possible) of causality of the relationship between a reported AEFI and vaccine administration take place at the national level before AEFI reports are forwarded to the UMC?	25 (83)	30:0
<i>Terminologies used to code AEFI reports</i>		
Are you planning to switch to MedDRA?	11 (44)	25:4
Are there specific terms that cause problems for classifying AEFI?	7 (23)	30:6
Are there terms missing from the coding terminology you are using?	5 (18)	28:8
Have you heard of the Brighton Collaboration?	18 (51)	35:1
Will you be applying the definitions proposed by the Brighton Collaboration to your national AEFI surveillance system?	15 (75)	20:1
<i>Utility of communication services provided by the UMC</i>		
Have you heard of Vigibase Online?	30 (83)	36:0
Are you planning to switch to Vigibase Online?	11 (41)	27:3
Have you used Vigimed for your vaccine-related queries?	16 (44)	36:0
Are you satisfied with the number of responses you have received to your queries?	15 (94)	16:0
Have you used Vigisearch to find vaccine-related data in the WHO database?	19 (53)	36:0
Are you satisfied with the results of your search?	16 (89)	18:1
Do you receive the UMC's SIGNAL publication?	29 (81)	36:0
Is the SIGNAL publication useful?	30 (100)	30:1

Notes:

- i) The number of respondents 'eligible' to respond to each question varied depending on each respondent's response to earlier questions.
- ii) Percentages were calculated for the number of respondents giving a 'yes' answer out of the number of respondents who answered the question.
- iii) Seven countries were already using MedDRA at the time of survey. These countries were considered a 'yes' to the question: "Are you planning to switch to MedDRA?"
- iv) Two respondents indicated that they had not heard of the Brighton Collaboration. Respondents were referred to the Brighton Collaboration's website (<http://www.brightoncollaboration.org>) in the questionnaire. Both of these respondents indicated that they would be applying the Brighton Collaboration's AEFI definitions.
- v) Five countries were already using *Vigibase Online* at the time of survey. These countries were considered a 'yes' to the question: "Are you planning to switch to *Vigibase Online*?"
- vi) Two respondents indicated that they did not regularly receive the SIGNAL publication but that they have received some issues; based on the issues they have received, both respondents indicated that the publication was useful.

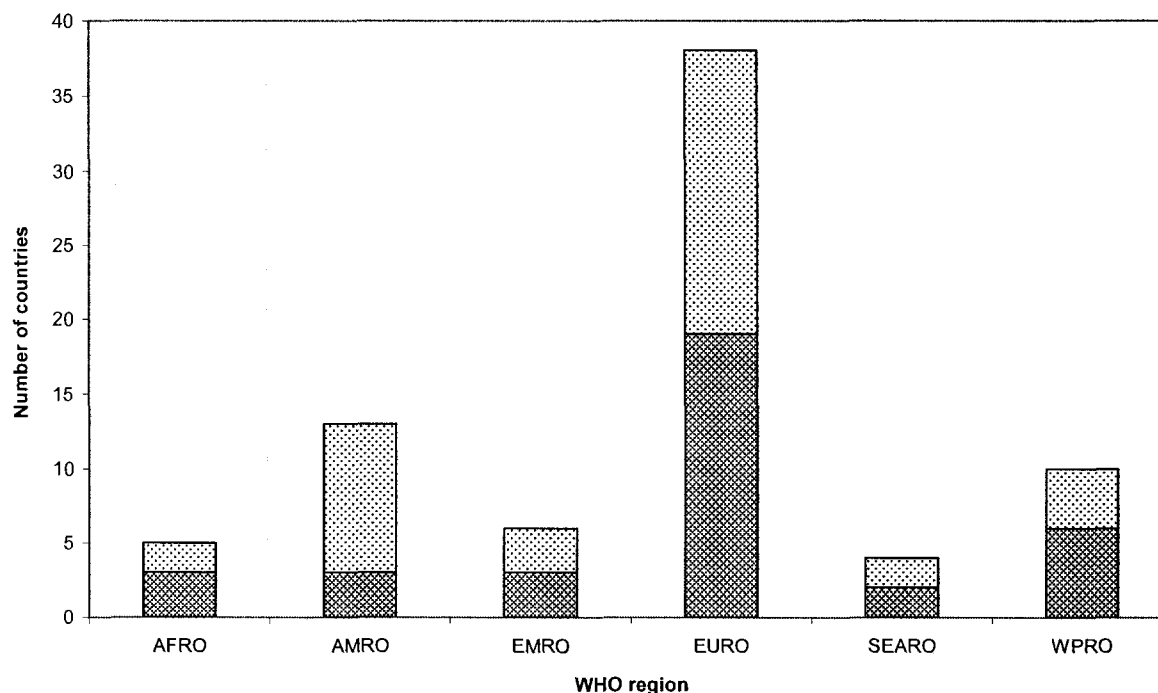


Figure 1. Proportion of PIDM member-countries responding to the survey by WHO Region

The six WHO regions: African Region (AFRO), Region of the Americas (AMRO), Eastern-Mediterranean Region (EMRO), European Region (EURO), South-East Asia Region (SEARO), Western Pacific Region (WPRO). The height of each bar represents the total number of countries from each WHO Region participating in the PIDM; the darker portion of each bar represents the number of countries responding to the survey.

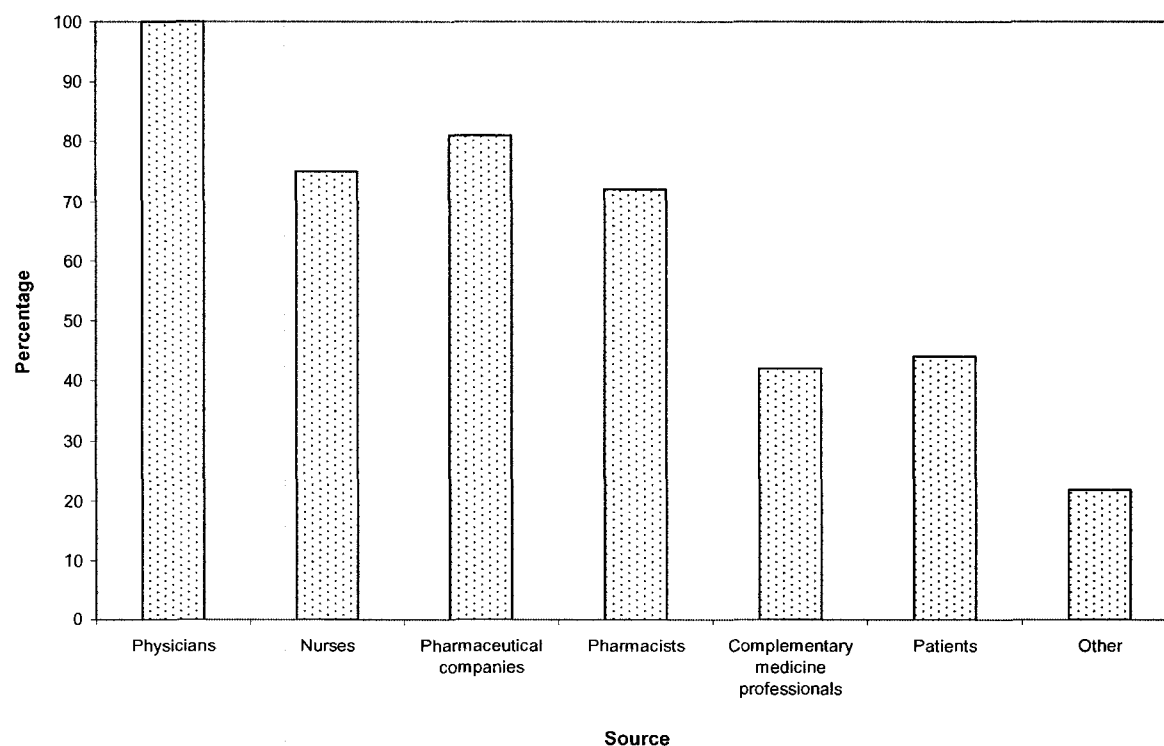


Figure 2. Sources of AEFI notification within member countries

The horizontal axis gives the nature of the source. The vertical axis gives the percent of responding countries that allow AEFI reporting from a given source. Questionnaire respondents indicated that 'Other' may include: state or territory health departments, local government clinics, anti-vaccination lobby groups, dentists, coroners, regional hygiene inspectors, epidemiologists, or 'anyone'

CHAPTER FOUR: A QUANTITATIVE ANALYSIS OF ADVERSE EVENT REPORTS IN THE WHO ADVERSE REACTIONS DATABASE

The following is a manuscript prepared for publication, based on an analysis of the WHO database. The objectives of this analysis were: 1) to compare reporting patterns for ADRs and AEFIs; and 2) to identify potential problems that may hinder signaling of vaccine safety concerns. While the previous manuscript identified many of the strengths and weaknesses of the PIDM from the point-of-view of national AEFI surveillance authorities, this manuscript quantitatively examines the AEFI reports in the WHO database.

Please refer to Appendix A for a copy of the letter from the Ottawa Hospital Research Ethics Board, approving this project.

A detailed description of the WHO database data obtained from the Uppsala Monitoring Centre is provided in Appendix C.

This manuscript was co-authored by the student (ML), her co-supervisors, Dr Philippe Duclos and Dr George Wells, and an advisor to the thesis, Dr Wikke Walop. The student is the first author of this paper, having been primarily responsible for data collection, analysis, and writing of the manuscript. Drs Duclos, Wells, and Walop provided valuable feedback throughout the process.

Improving global monitoring of vaccine safety: a quantitative analysis of adverse event reports in the WHO Adverse Reactions Database

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Abstract

The World Health Organization (WHO) Programme for International Drug Monitoring (PIDM) was initially developed for chemical rather than biological products. The PIDM has made considerable achievements in analyzing drug-related adverse event reports, however, more limited progress has been made in analysing vaccine-related reports. In June 2005, the Global Advisory Committee on Vaccine Safety, acknowledging these limitations, called for a global consultation to address the need for improved monitoring and analysis of vaccine-related adverse event reports on an international level. In preparation for this consultation and as part of a larger study designed to evaluate the PIDM, the WHO Adverse Reactions Database was quantitatively assessed. The United States, Canada, and the United Kingdom have contributed 82% of AEFI reports in the database. Most AEFI reports concerned individuals who were not taking any drugs at the time of immunization. The mean difference between onset date and report date of AEFI reports was 872.3 days (2.4 years). The analysis identified several issues of concern, in particular, many member countries do not forward any or all AEFI reports to the PIDM, and timeliness and regularity of reporting need to be improved. Incomplete or absent AEFI reporting, and slow or irregular reporting, could prevent vaccine signals from being detected in a timely manner.

Keywords

pharmacovigilance, Programme for International Drug Monitoring, vaccine, database

Introduction

The World Health Organization (WHO) Programme for International Drug Monitoring (PIDM) is an international adverse event monitoring system developed following the thalidomide disaster of 1961 (1). After a pilot project in the United States beginning in 1968, the PIDM was set-up at WHO Headquarters (WHO/HQ), Geneva in 1971, and moved to Uppsala, Sweden in 1978 (1). Today, administration of the programme is shared between the WHO Collaborating Centre for International Drug Monitoring, more commonly referred to as the Uppsala Monitoring Centre (UMC), and WHO/HQ (2).

Countries participating in the PIDM submit adverse drug reaction (ADR) reports, including adverse events following immunization (AEFI) reports, to the UMC through their National Pharmacovigilance Centre (NPC). Once received by the UMC, reports are stored in the WHO Adverse Reactions Database. This computerized database stores case reports in a hierarchical manner to allow for easy searching and analysis of the database (3).

Participation in the PIDM has increased significantly since its inception in 1968. The PIDM began with only 10 countries, Canada being one of the founding members. As of March 2006, the PIDM had grown to include 79 member countries and the WHO database contained over 3.5 million reports (4).

One of the primary functions of the PIDM is to identify new adverse event signals from data in the WHO database. The WHO defines a signal as “reported information on a possible causal relationship between an adverse event and a drug [or vaccine], the relationship being

unknown or incompletely documented previously” (5). Following an automated signal detection process using a Bayesian Confidence Propagation Neural Network (BCPNN), and expert review of identified combinations of products and events of interest, identified ‘signals’ are included in the UMC’s publication SIGNAL. This is a restricted access document made available to NPCs of countries participating in the PIDM and, when appropriate, to product manufacturers. Participating countries also have access to various internet services provided by the UMC, including *Vigibase Online* (i.e., an online adverse event report management system), *Vigisearch* (i.e., an online search facility for searching data in the database), and *Vigimed* (i.e., an e-mail conferencing facility exclusively for PIDM member countries) (1, 6).

Except for a few biological products, most drugs are chemical products. Vaccines are one example of biological drug products. In spite of the many differences between vaccines and drugs, vaccines are commonly viewed as being similar to drugs. While some vaccines are used in the treatment of disease (e.g., Bacille Calmette-Guérin (BCG) vaccine in the treatment of bladder cancer) and are therefore somewhat akin to drugs, most vaccines are intended to prevent and control disease. Some of the special characteristics that differentiate those vaccines used for disease prevention from drugs are: vaccines are usually administered to large populations of healthy individuals; most vaccines are administered to infants and children; vaccine administration is often promoted or even made mandatory by governments; a main issue in the safety and efficacy of vaccines is maintaining an adequate ‘cold chain’ (i.e., a system for keeping vaccines at the appropriate temperature, from the time of the start of manufacture until the time of use, in order to maintain vaccine quality

and potency); potential variation between different batches and lots of a vaccine necessitates lot-by-lot surveillance of vaccines at the post-marketing stage; and the public, in general, is less willing to accept the risks associated with vaccines.

The PIDM was initially developed for chemical rather than biological products. Very little has changed since its inception to take into consideration the unique characteristics of vaccines, in particular: the same drug classification system is used to categorize drugs and vaccines; adverse reaction terminologies have not been expanded to include all symptoms of AEFIs; and ADR and AEFI case reports are analysed in the same way. Considering the differences in characteristics between drugs and vaccines, the ability of the PIDM to meet the needs of vaccine safety is of great international public health importance (7, 8).

The WHO database was quantitatively assessed as part of a larger study designed to evaluate the PIDM on how it serves the needs of vaccine safety. The objectives of this analysis were: 1) to compare reporting patterns for ADRs and AEFIs; and 2) to identify potential problems that may hinder signaling of vaccine safety concerns.

Methods

Data from the WHO database were obtained directly from the UMC in the form of Excel tables and a data listing. The Excel tables summarized all case reports (i.e. all AEFI reports and all non-AEFI reports) in the WHO database as of 30 May 2005. The first table provided the total number of reports submitted to the UMC by each country per year. The second

table provided the total number of reports submitted to the UMC by patient age. The data listing included all AEFI reports in the WHO database as of 30 May 2005. This listing included data on the following variables: report identification number, reporting country, date of onset of the adverse event(s), date the report was entered into the WHO database, age of the patient, name of the vaccine(s) administered, Anatomical Therapeutic Chemical (ATC) classification of the vaccine(s) administered, adverse event(s), System Organ Class (SOC) affected by the adverse event(s), whether the patient was taking any drugs at the time of the immunization, basis of the event (i.e., the reporting country's indication as to whether the administered vaccine is suspect, concomitant, or interacting in the adverse event), and causal designation (e.g., probable, possible).

Some analyses used data collected from 1968 - 30 May 2005. For other analyses, it was decided that a more accurate picture of current reporting practices would be gained by limiting the analysis to more recently collected data, from 1996 – 30 May 2005. Where an analysis was limited to the last 10 years, this is clearly indicated in the results and associated figures.

Where AEFI reports have been compared to all other reports in the database (e.g., non-vaccine drugs, herbals), all other reports are simply referred to as 'Other'.

The United Nations' country population size data were used in calculating average reporting rates (9). The population less than five years of age was used since most immunizations are administered to children before the age of five. For each country reporting AEFIs to the

UMC between 1996 - 30 May 2005, the number of AEFI reports occurring in children less than five years of age was divided by the number of children in the country who were less than five years, for each of the ten years. Each country's yearly AEFI reporting rates were summed and divided by the number of years between 1996 and 2005 that the country reported AEFIs to the UMC. This average reporting rate was used to compare how well countries are reporting to the UMC.

Data from the WHO/UNICEF Joint Reporting Form on Immunization (JRF) were obtained from the WHO, Department of Immunization, Vaccines, and Biologicals, for the years 2001, 2002, and 2003 (latest available data). The JRF is an annual survey undertaken by the WHO and UNICEF to collect information on national immunization programmes, including estimates of the incidence of vaccine preventable diseases and estimates of vaccine coverage rates (10). These data were used to compare the number of AEFIs reported to the UMC and on the JRF, from 2001-2003, as a measure of the level of communication between ADR and AEFI surveillance authorities in participating countries. Only those countries that began participation in the PIDM prior to 2001 were included in this comparison.

For calculations on timeliness of reporting, the full date of onset of AEFIs and the full date of reporting to the UMC were used. Where the full date was not provided (i.e., a report contained only the month and year or only the year), the first day of the month (e.g., 01-07-2001) or the first day of the year (e.g., 01-01-2003) was used.

Descriptive statistics, including counts, proportions, and rates, were calculated using the SAS® 9.1 statistical software package.

Ethical approval was obtained from the Ottawa Hospital Research Ethics Board.

Results

Evolution of the PIDM

Ten industrialized countries participated in the PIDM in 1968. By 30 May 2005 (last available data at time of analysis), the number of participating countries had grown to 75 and the database contained over 3.3 million case reports. Figure 1 presents the evolution over time of the number of participating countries and the total number of reports in the WHO database.

Countries participating in the PIDM

The United States is the greatest contributor of reports to the database, followed by the United Kingdom, Germany, and Canada. All four of these countries have been members of the PIDM since 1968, which accounts, in part, for their substantial contributions to the database.

The number of AEFI reports submitted to the UMC by country ranged from a high of 117,743 reports to a low of 0 reports. The United States, Canada, and the United Kingdom

have contributed the greatest number of AEFI reports to the database. Together, these three countries provided 223,913 of the 272,748 AEFI reports in the database (82.1%).

Thirty-six percent of Canada's reports to the database were AEFI reports; among the countries that have contributed greater than 1,000 AEFI reports to the database, no other country's AEFI reports accounted for a greater proportion of their total contribution to the database. Austria (27.1%) and New Zealand (15.5%) contributed the next greatest proportions (Figure 2). Of the countries with 100 to 1,000 AEFI reports in the database, no country's AEFI reports accounted for more than 11% of their contribution to the database. For the country with the smallest proportion of AEFI reports, their AEFI reporting represented 0.6% of their contribution to the database.

The average number of reports of AEFIs occurring between 1996 and 30 May 2005, by country and population size for children less than 5 years of age, is illustrated in Figure 3. Canada, New Zealand, and Sweden have the highest rates of AEFI reporting.

There was a substantial discrepancy between the number of AEFIs reported to the UMC and the number of AEFIs reported on the JRF for many countries. The total number of AEFIs reported on the JRF from 2001-2003 exceeded the number of AEFI reports to the UMC over the same time period by 68,003 reports. The greatest difference between the two sources for any one country over three years varied from 10,263 cases not reported on the JRF to 46,080 cases not reported to the UMC. Several countries failed to report or reported 'zero' AEFIs in any one of the three years to both the UMC and on the JRF; four countries failed to report

or reported zero AEFIs to both the UMC and on the JRF during all three years. Only two countries, each only in one of the three years, reported the same number of AEFIs to both the UMC and on the JRF.

Age of individuals with reported AEFIs

The age distribution of individuals on AEFI reports differed significantly from that on all ‘other’ reports in the database. Most immunizations are administered to infants and young children while most other products are given to adults, and in particular, older adults (Figure 4).

Most AEFI reports (259,014) concerned individuals who were not taking any drugs at the time of immunization (called here ‘Vaccine’ reports). The remaining AEFI reports (13,734) concerned individuals who were taking one or more medications (called here ‘Mixed’ reports). For AEFI reports that provided the age of vaccinees (246,877), the proportion of ‘Vaccine’ to ‘Mixed’ reports increased with increasing age (Figure 5). The total difference in the proportion of ‘Mixed’ reports between the <1 year and the 65+ years age groups was 13% (almost a 5-fold difference).

Types of adverse events reported in AEFI reports

Reports of AEFIs occurring between 1996 and 30 May 2005 most commonly involved the following SOCs: 1) ‘body as a whole - general disorders’, 2) ‘application site disorders’, 3) ‘skin and appendages disorders’, and 4) ‘central and peripheral nervous system disorders’

(Figure 6). Adverse events reported under these four SOCs include, for example, anaphylactic reaction, injection site reaction, rash, and paralysis, respectively.

The WHO has labelled 544 adverse event terms as “critical”. Critical terms are “adverse reaction terms referring to, or possibly being indicative of, serious disease states, which have been regarded as particularly important to follow up” (11). Among those countries contributing greater than 1,000 reports of AEFIs occurring between 1996 and 30 May 2005, the percentage of critical terms varied from a high of 18.3% to a low of 3.5%. France, Italy, and Denmark reported the highest percentage of critical terms by country at 18.3%, 14.6%, and 11.5%, respectively (Figure 7).

Eighty-two percent of reports of AEFIs occurring between 1996 and 30 May 2005 had not undergone an evaluation of individual causality (98,775 of 119,968 reports). Of the 21,193 reports that had some indication of causality, 4,200 reports (19.8%) included at least one adverse event term reported with a “certain” likelihood of causal association with the administered vaccine. A “certain” event is defined as “a clinical event ... that occurs in a plausible time relation to drug [or vaccine] administration, and which cannot be explained by concurrent disease or other drugs or chemicals” (12). Of the 4,200 “certain” terms, 231 (5.5%) were also “critical” terms.

Figures 8 and 9 illustrate the number of reports of AEFIs occurring between 1996 and 30 May 2005 by vaccine type and ATC classification, respectively. The ATC classification system, developed by the WHO Collaborating Centre for Drug Statistics Methodology, in

Oslo, Norway (13), is used to divide drugs and vaccines into groups “according to the organ or system on which they act, and their chemical, pharmacological and therapeutic properties” (14). An AEFI report may include one or more vaccine(s) and can be included under one or more ATC classification(s).

Timeliness of AEFI reporting to the UMC

The minimum interval between the date of onset of AEFIs and the date of reporting to the UMC, for AEFI reports entered into the WHO database between 1996 and 30 May 2005, was 19 days. The maximum interval was 3,258 days. Three AEFI reports had onset dates later than report dates. The mean difference between onset date and report date was 872.3 days (2.4 years).

Discussion

Participation in the PIDM has increased significantly over the programme’s 38-year history. In 1968, 10 developed countries – Australia, Canada, Denmark, Germany, Ireland, Netherlands, New Zealand, Sweden, the United Kingdom, and the United States – founded the programme. By 30 May 2005, the programme had grown to include 75 countries, representing all six WHO Regions, and included developed, developing, and least developed countries, as well as countries with economies in transition (15).

Several analyses were performed to describe the AEFI reports found in the database and to identify the countries from which reports have come. Three analyses are particularly

notable: 1) an analysis of the number of AEFI reports submitted by country; 2) an analysis of the proportion of AEFI reports submitted by country; and 3) an analysis of the average yearly AEFI reporting rate, by country, for the population less than 5 years of age, over the last 10 years.

The first analysis highlighted the fact that three countries have contributed a substantial majority (82.1%) of the AEFI reports in the WHO database. Furthermore, as of 30 May 2005, 12 member countries had not submitted any AEFI reports to the UMC. This unevenness of reporting compromises the representativeness of the WHO database. It is expected that all member countries regularly forward their reports to the UMC and no country should systematically exclude any group of AEFI reports. The ability of the PIDM to signal vaccine safety concerns will be restricted as a result of countries not forwarding some or all of their AEFI reports to the UMC. The PIDM will only be able to signal concerns related to those vaccines for which reports have been received, and signaling of these issues may be delayed because of the relatively low volume of AEFI reports in the database. Identification of important vaccine safety concerns may be delayed or altogether missed as a result of a systematic reporting bias.

The latter two analyses take into consideration differences in population size of different countries and the length of time that countries have participated in the PIDM. Both of these analyses are helpful in identifying which countries are more frequent reporters of AEFIs.

None of these three analyses, however, measures the quality of reports (e.g., the completeness or accuracy of reports) or whether any particular country reports mostly critical or non-critical AEFIs. It was not in the scope of this study to assess these additional dimensions, however, a future study should focus on these assessments.

The NPC is usually the national ADR surveillance authority for a country. In some cases, the NPC is also the national AEFI surveillance authority; in other cases, a separate national authority monitors AEFIs. The NPC could monitor only AEFIs. All national surveillance authorities may submit AEFI reports to the UMC. The JRF is sent to the national immunization programme in each country, which may or may not be the country's national AEFI surveillance authority. There is a clear and sizable discrepancy between the number of AEFIs reported on the JRF and to the UMC, during the period 2001-2003, by those countries participating in the PIDM. It is difficult to interpret this comparison between JRF and UMC data because of the delay in reporting to the UMC that this analysis has shown; we cannot say for certain whether all of these cases that are apparently not reported to the UMC are significantly delayed or are in fact never reported. A survey of AEFI surveillance authorities of countries participating in the PIDM, however, made it clear that collaboration and communication between drug and vaccine safety authorities is lacking in many countries (Letourneau et al., to be submitted). Poor relationships between drug and vaccine safety authorities likely play a role in this reporting discrepancy for several countries.

There is an apparent trend of increasing numbers of 'Mixed' AEFI reports (i.e., reports of AEFIs in patients who are also taking one or more drugs) with increasing age, however, the

trend was not as strong as expected. It is possible that older patients taking several medications, who experience an AEFI, assume that their experience is another symptom of disease or a side-effect of a medication. It is also possible that HCPs reporting AEFIs in older patients (i.e., patients who are 65+ years of age) neglect to include information on medications that patients are taking. Not sending AEFI reports, particularly those pertaining to critical adverse events, and sending incomplete or inaccurate reports may cause vaccine signals to be missed or delayed. While all AEFI reports should be submitted to the UMC, it is the AEFI reports pertaining to critical terms that are most likely to contribute to the detection of important vaccine safety concerns. While it was not in the scope of the current study, a future study should examine whether the proportion of 'Mixed' reports is actually much greater when non-critical terms are removed from the analysis.

It is generally understood that minor local and systemic reactions, such as injection site pain and fever, may occur following immunization. Serious reactions are expected to occur less frequently. Adverse events involving the central or peripheral nervous system, such as paralysis and convulsions, were the fourth most commonly reported SOC of AEFIs in the WHO database between 1996 and 30 May 2005. It is possible that AEFI reports of events involving the central and peripheral nervous system are the result of stimulated reporting. Media reports in recent years have frequently highlighted vaccine-event combinations of a serious nature. In addition, some countries use AEFI reporting forms that specifically ask the reporter to indicate whether the patient experienced a particular serious neurological AEFI. There is generally no indication of the quality of these, or any other, AEFI reports.

Assessments of causality on individual reports are not very informative from an international pharmacovigilance perspective. Despite standard categories for the likelihood of causal associations (such as “probable” or “possible”), there is no standardized method of assessing causality on individual reports. Because each reporting country can perform its own causality assessments, it is likely that the standard categories are applied differently by different countries. It is the rate of reporting and the quality of reports, rather than the assessment of causality on individual reports, that will most contribute to the timely detection of vaccine signals.

In the process of reviewing the number of AEFI reports by vaccine type and ATC classification, we identified several issues of concern: 1) Many vaccines are found under more than one name in the database; 2) Several different vaccines are classified under a single ATC code; 3) Several vaccines are included under more than one ATC code; 4) The hierarchical nature of the ATC coding system, and in particular, of vaccine codes, may make searching the database difficult. For example, the diphtheria-tetanus-inactivated poliomyelitis vaccine is found under the ATC codes “tetanus” and “poliomyelitis” but not under the ATC code “diphtheria”; 5) Some vaccine ATC codes appear inappropriately named.

Because the rules for assigning ATC codes were developed on the basis of chemical products, the classification system is not well-suited for biological products such as vaccines. Specific ATC coding rules for vaccines should therefore be developed.

Countries participating in the PIDM are requested to forward adverse event reports as quickly as possible. Not all member countries forward AEFI reports to the UMC. Among those countries that do forward AEFI reports, reporting timeliness varies between countries and often within a country over time. It is expected that countries using the UMC's online report management software *Vigibase Online* will be able to report more regularly and more quickly to the UMC. However, with so few countries currently using this method (Letourenau et al., to be submitted), it is difficult to assess the impact of this service on the ability of the PIDM to detect vaccine safety concerns. For an international AEFI surveillance system to be of real benefit to the *international* community, complete and timely reports must be received from *all* countries participating in the programme. The greater the number of countries participating in the PIDM and submitting high-quality AEFI reports to the UMC, the greater the opportunity to quickly detect vaccine signals.

This analysis identified several issues of concern, in particular, many member countries do not forward any or all AEFI reports to the PIDM and reporting timeliness and regularity need to be improved. This study is the first attempt at an analysis of the WHO database for the purpose of evaluating how the PIDM serves the needs of vaccine safety. Additional analyses will be necessary to further assess various dimensions of the database.

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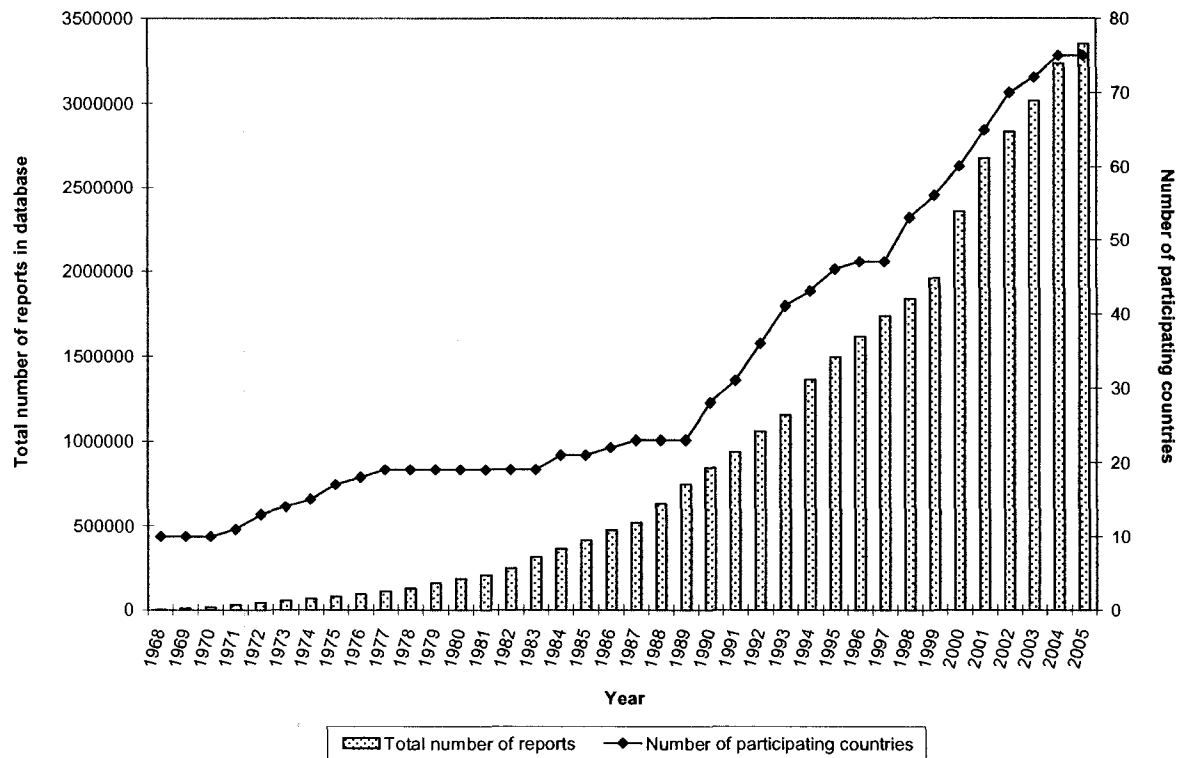


Figure 1. Evolution of the number of countries participating in the WHO Programme for International Drug Monitoring and the number of adverse event reports in the WHO Adverse Reactions Database, 1968 - 30 May 2005.

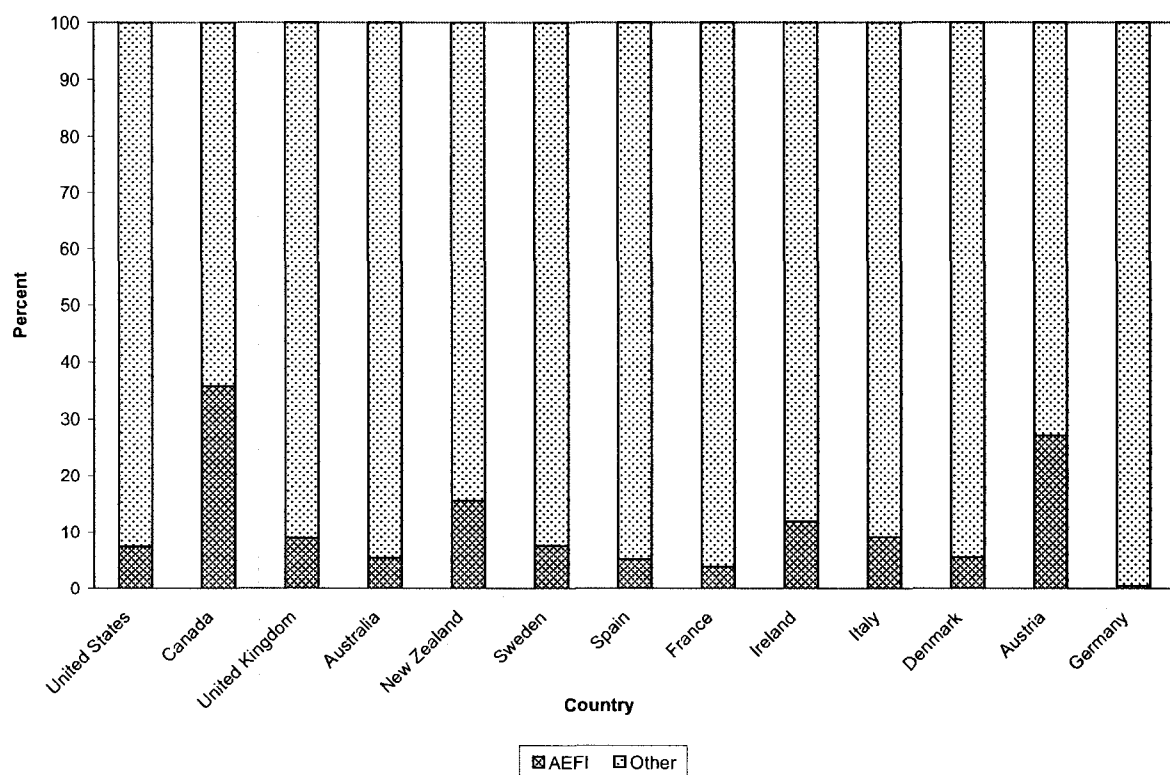


Figure 2. Proportion of AEFI reports versus ‘Other’ reports in the WHO database, by country, for countries with >1000 AEFI reports in the database, submitted by 30 May 2005. ‘Other’ reports refer to all non-vaccine-related reports in the database (e.g., non-vaccine drugs, herbals).

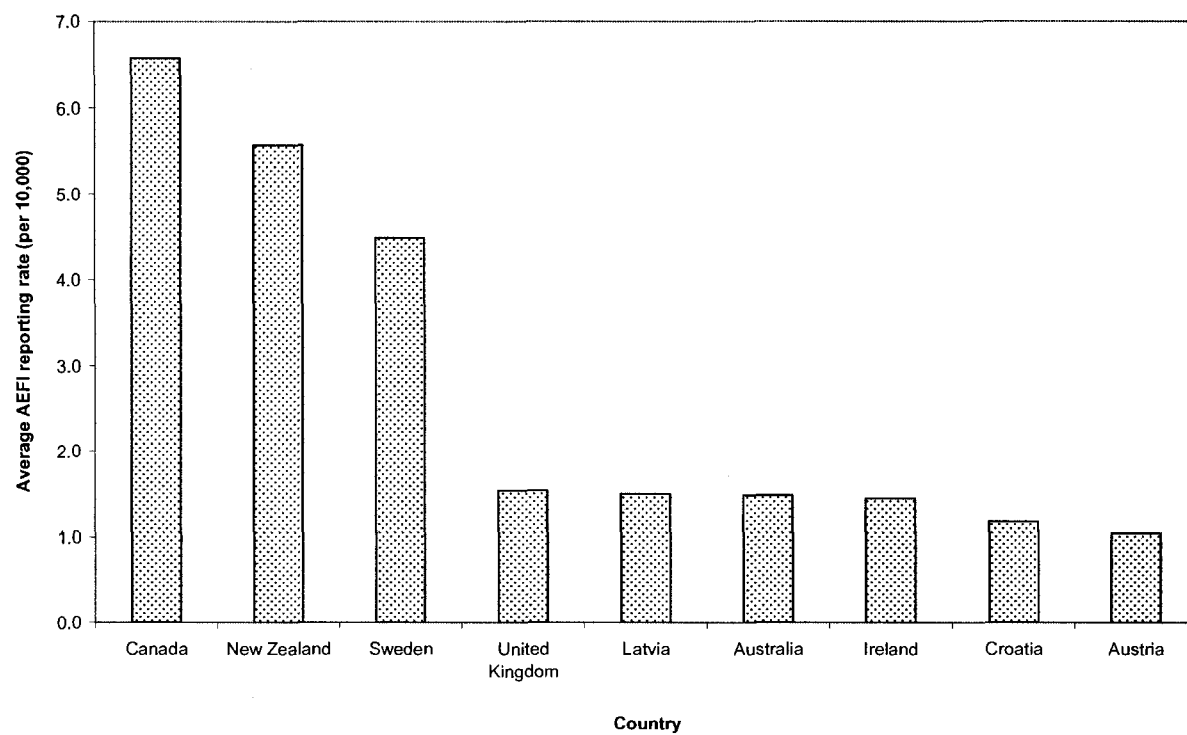


Figure 3. Average yearly AEFI reporting rate, by country, for the population less than 5 years of age, 1996 – 30 May 2005.

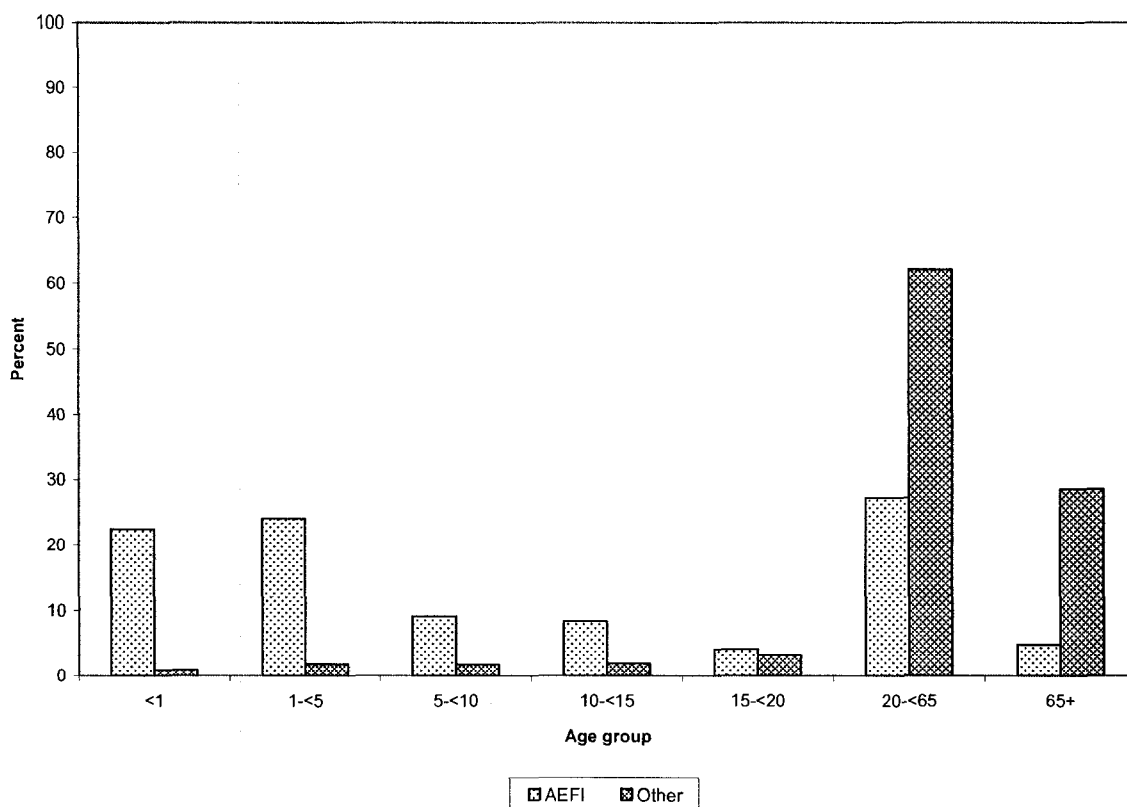


Figure 4. Distribution of reports in the WHO database by age group, for those reports giving the age of the patient, AEFI reports (n=246,877) versus 'Other' reports (n=2,440,241), submitted by 30 May 2005. 'Other' reports refer to all non-vaccine-related reports in the database (e.g., non-vaccine drugs, herbals).

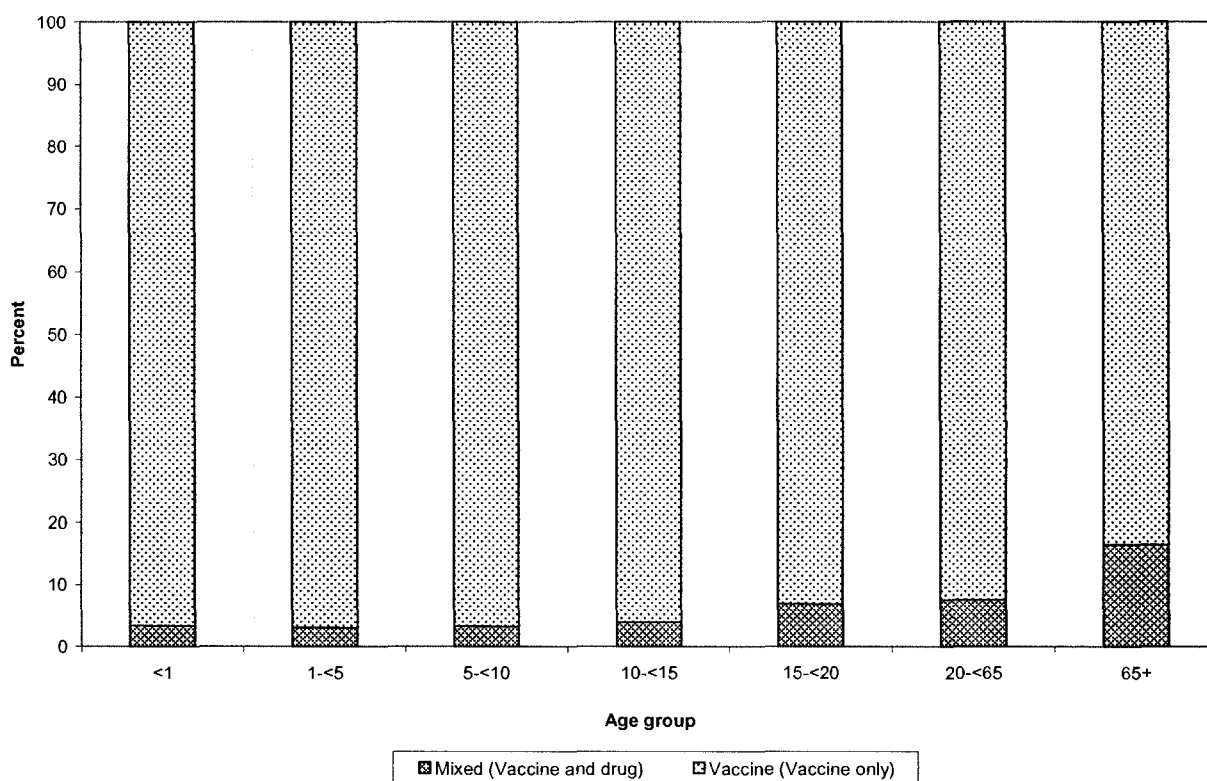


Figure 5. Percentage of ‘Mixed’ reports (n=13,020) and ‘Vaccine’ reports (n=233,857) in the WHO database by age group, submitted by 30 May 2005. ‘Mixed’ reports were AEFI reports concerning individuals who were taking one or medications at the time of immunization. ‘Vaccine’ reports were AEFI reports concerning individuals who were not taking any drugs at the time of immunization.

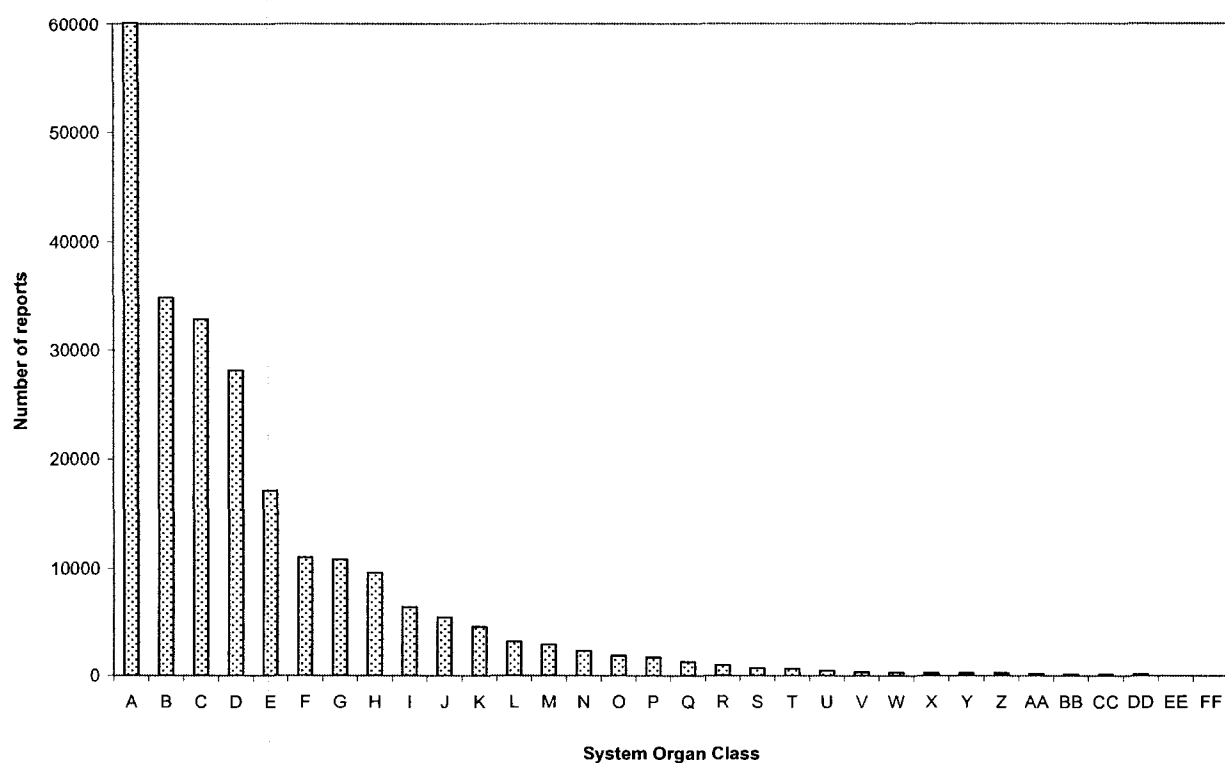


Figure 6. Number of AEFI reports in the WHO database by System Organ Class, 1996 –

30 May 2005.

A	Body as a whole - general disorders	Q	Heart rate and rhythm disorders
B	Application site disorders	R	Metabolic and nutritional disorders
C	Skin and appendages disorders	S	Hearing and vestibular disorders
D	Central & peripheral nervous system disorders	T	Liver and biliary system disorders
E	Gastro-intestinal system disorders	U	Endocrine disorders
F	Respiratory system disorders	V	Red blood cell disorders
G	Psychiatric disorders	W	Neonatal and infancy disorders
H	Musculo-skeletal system disorders	X	Collagen disorders
I	Vascular (extracardiac) disorders	Y	Foetal disorders
J	Resistance mechanism disorders	Z	Neoplasms
K	Vision disorders	AA	Special senses other, disorders
L	Urinary system disorders	BB	Myo-, endo-, pericardial & valve disorders
M	White cell and reticuloendothelial system disorders	CC	Reproductive disorders, female
N	Cardiovascular disorders, general	DD	Reproductive disorders, male
O	Secondary terms - events	EE	Autonomic nervous system disorders
P	Platelet, bleeding & clotting disorders	FF	Poison specific terms

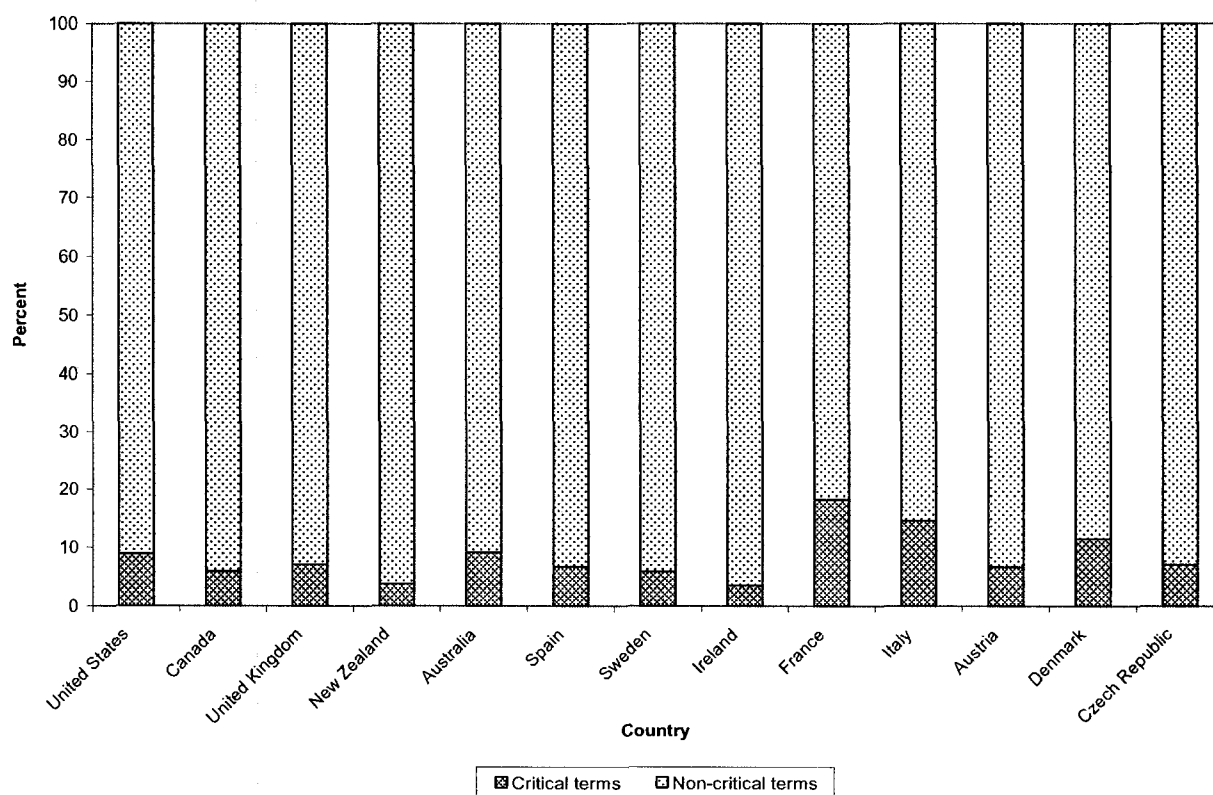


Figure 7. Proportion of critical and non-critical terms in AEFI reports in the WHO database, by country, for those countries that have submitted >1000 AEFI reports, 1996 – 30 May 2005.

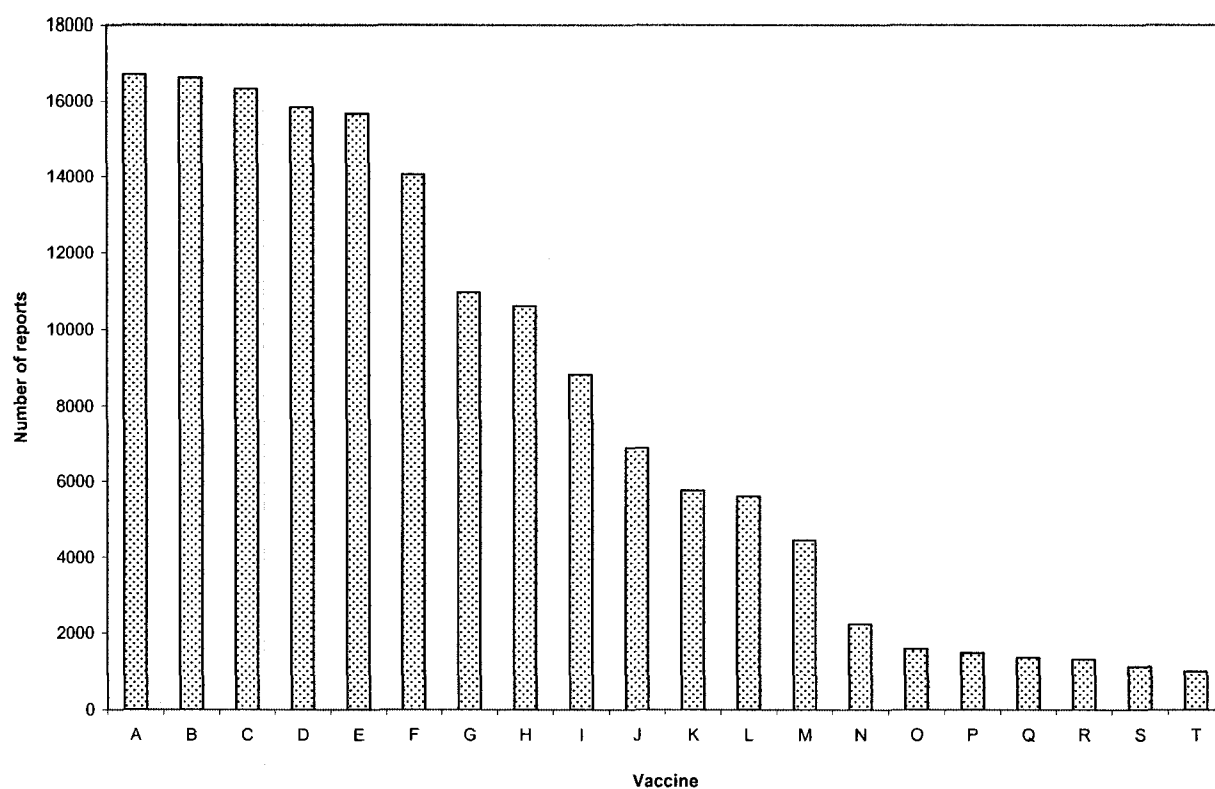


Figure 8. Number of reports by vaccine type for the 20 vaccines most frequently reported, 1996 – 30 May 2005. Vaccine names have been strictly reproduced from the WHO database.

A	Influenza	K	Pneumococcal vaccine
B	HepB	L	DTPHib
C	MMR	M	IPV
D	Hib	N	HepA
E	Meningococcal	O	Anthrax vaccine
F	DTP	P	Tetanus toxoid
G	DT	Q	DTPIPVHib
H	DTPIPV	R	Measles
I	Varicella vaccine	S	Typhoid vaccine
J	OPV	T	Rabies vaccine

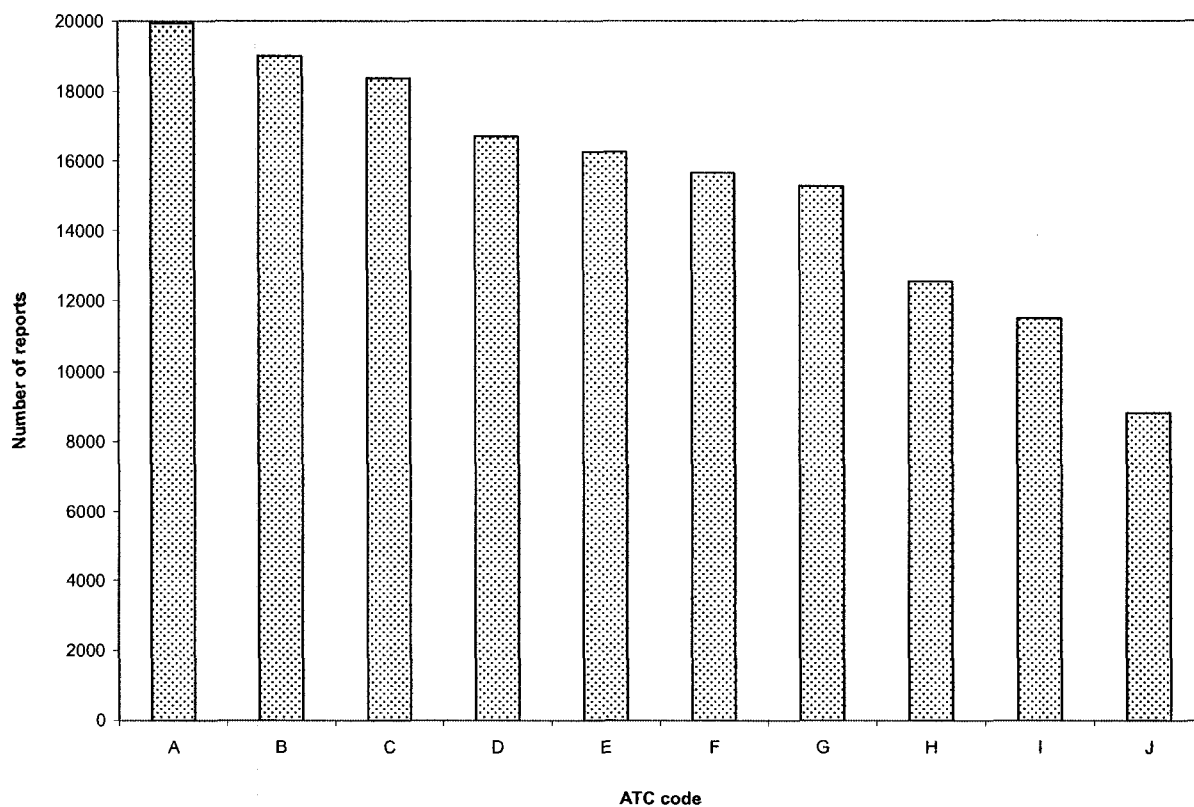


Figure 9. Number of AEFI reports by ATC code for the 10 vaccine-related ATC codes most frequently reported, 1996 – 30 May 2005. ATC code names have been strictly reproduced from the WHO database.

A	Hemophilus Influenzae B
B	Hepatitis
C	Morbilli
D	Influenza
E	Bacterial and Viral, Combined
F	Meningococcal
G	Pertussis
H	Tetanus
I	Poliomyelitis
J	Varicella

CHAPTER FIVE: A SYSTEMATIC REVIEW OF BAYESIAN METHODS USED FOR SIGNALING DRUG AND VACCINE SAFETY CONCERNS

The following is a manuscript prepared for publication, based on a systematic review of Bayesian methods that have been evaluated for their utility in signaling safety concerns in a pharmacovigilance database. The objectives of this manuscript were: 1) to compare Bayesian methods that have been evaluated with respect to their utility in signaling drug and vaccine safety concerns; and 2) to comment on the use of the BCPNN, the signaling method used by the PIDM, and specifically, the use of the BCPNN in identifying vaccine safety concerns. While the previous manuscripts identified many of the strengths and weaknesses of the PIDM and examined the nature of AEFI reports in the WHO database, this manuscript considers the evidence for the use of the BCPNN in identifying potential vaccine signals.

A summary of the Bayesian methods identified by the systematic review is provided in Appendix D.

This manuscript was co-authored by the student (ML), her co-supervisors, Dr Philippe Duclos and Dr George Wells, and an advisor to the thesis, Dr Wikke Walop. The student is the first author of this paper, having been primarily responsible for data collection, analysis, and writing of the manuscript. Drs Duclos, Wells, and Walop provided valuable feedback throughout the process.

Improving global monitoring of vaccine safety: a systematic review of Bayesian methods
used for signaling drug and vaccine safety concerns

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Abstract

A systematic review of the literature was conducted to identify and compare Bayesian methods that have been evaluated for their utility in signaling drug and vaccine safety concerns. Standard methods to search and select articles and to extract and analyse data were followed. Many studies have evaluated the utility of Bayesian methods for signal detection and have found them effective for signaling drug safety concerns. The Bayesian Confidence Propagation Neural Network (BCPNN), used by the WHO Programme for International Drug Monitoring, is one such method. Very few studies have evaluated a Bayesian method for signal detection using adverse events following immunization (AEFI) reports, and no study has specifically evaluated the BCPNN method for signaling vaccine safety concerns. Recommendations for further study include testing the BCPNN and other Bayesian and non-Bayesian signaling methods with AEFI reports in order to assess the effectiveness of these tools in vaccine safety. The BCPNN may need to be customized for vaccine signal detection.

Keywords

pharmacovigilance, Programme for International Drug Monitoring, vaccine, signaling

Introduction

The World Health Organization (WHO) Programme for International Drug Monitoring (PIDM) is an international adverse event monitoring system developed following the thalidomide disaster of 1961 (1). Administration of the PIDM is the joint responsibility of the WHO Collaborating Centre for International Drug Monitoring, more commonly referred to as the Uppsala Monitoring Centre (UMC), and the WHO Headquarters (WHO/HQ) (2).

Countries participating in the PIDM usually submit adverse drug reaction (ADR) reports, including vaccine-specific adverse event following immunization (AEFI) reports, to the UMC through their National Pharmacovigilance Centre (NPC). Once received by the UMC, reports are stored in the WHO Adverse Reactions Database. Participation in the PIDM has increased significantly since its inception in 1968. The PIDM began with only 10 countries, Canada being one of the founding members. As of March 2006, the PIDM had grown to include 79 member countries and the WHO database contained over 3.5 million reports (3).

The WHO defines a signal as “reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously” (4). Signal detection is the process of identifying previously unknown drug or vaccine safety concerns. When there are a relatively small number of reports, signals can be detected by manually reviewing each case report. However, with the advent of large, computerized databases, automated data mining methods are often the only feasible way of detecting signals. Several automated processing methods for signal

detection have been proposed. In particular, Bayesian methods, such as the Multi-item Gamma Poisson Shrinker (MGPS) and the Bayesian Confidence Propagation Neural Network (BCPNN), have been evaluated with respect to their utility in data mining in pharmacovigilance databases. A 'Bayesian approach' is unique in its use of prior knowledge of an event in predicting the probability of future events. A Bayesian approach is particularly suitable for signal detection in a large database; as new information is added to the database, 'new knowledge' can be used to refine the prediction of the probability of an event. Because the PIDM uses a Bayesian approach to signal detection, this review is limited to the evaluation of Bayesian data mining methods.

A systematic review of the literature was conducted as part of a larger study designed to evaluate the PIDM on how it serves the needs of vaccine safety. The objectives were: 1) to compare Bayesian methods that have been evaluated with respect to their utility in signaling drug and vaccine safety concerns; and 2) to comment on the use of the BCPNN method by the PIDM, and specifically, the use of the BCPNN in identifying vaccine safety concerns.

Methods

A systematic approach to search and select articles and to extract and analyse data was followed.

Search

A search strategy was developed in consultation with an information scientist. The Medline, Embase, HealthStar, and Biosis Previews databases were searched on May 11, 2006.

References matching key words or subject headings related to 'Bayes', 'pharmacovigilance', and 'signal' were retained. Refer to Appendix I for the complete search strategy used.

Selection

References were imported into RefWorks, an online reference management programme.

Duplicate references were removed. Where possible, abstracts were located for the articles and reviewed. Where abstracts could not be found online, two authors (ML and GW) reviewed these articles' titles, and decided whether these articles appeared to meet inclusion criteria (i.e., presented a study that evaluated a Bayesian method and focused on post-marketing surveillance data mining). When the authors were unsure, every effort was made to find the full text article. Studies that evaluated a Bayesian method as a tool for detecting drug or vaccine signals were included in the review. These were studies whose primary purpose was to apply a method in order to be able to investigate the method and its appropriateness as a signaling tool. This included studies that proposed and evaluated a new Bayesian method, studies that evaluated an existing Bayesian method, and studies that compared a Bayesian method against another Bayesian method or against a non-Bayesian method. Not included were articles that presented a theoretical discussion on pharmacovigilance and signaling, and articles whose central purpose was anything other than to evaluate a Bayesian method. This included articles that used a Bayesian method in an example to illustrate a point, but whose purpose was not specifically to evaluate the

method. Conference proceedings, dissertations, editorials, and ‘letters to the editor’ were not included. References cited in included articles were also reviewed following the same procedure as described above.

Extraction

Included studies were reviewed and study details were recorded in an Excel spreadsheet. For each study, the purpose, the Bayesian method(s) evaluated, the conclusions, and any comments made by the author(s) regarding use of the method(s) for vaccine-related signaling, were noted.

Analysis

The information extracted from included studies provided a qualitative description of the methods and some of the advantages and disadvantages of the Bayesian methods evaluated. Only a qualitative analysis of the results could be made because of the nature of the data collected.

Results

Results of the search and selection of articles are presented in Figure 1. The initial search of the databases yielded 184 references. After removing duplicate references, there were 98 references. Abstracts were found for 79 of the 98 references (80.6%), and 13 of the 79 articles (16.4%) met the inclusion criteria. Abstracts were not available for 19 of the 98 references (19.4%). Based on a review of the titles of these 19 articles by two authors, all 19

articles were eliminated from the review. Bibliographies of the 13 included studies were amalgamated yielding 188 references. After duplicate references were removed, there were 134 additional references. Abstracts were found for 85 of the 134 references (63.4%), and 1 of the 85 articles met the inclusion criteria (1.2%). Abstracts were not available for the remaining 49 references (36.6%). Titles of these articles were reviewed by two authors, and all 49 references were determined not to meet the inclusion criteria. In consultation with staff at the UMC, one additional article was found. Bibliographies of the two articles (i.e., one article found by searching the bibliographies of the included studies, and one article identified by UMC staff) were combined, yielding 49 references. After duplicates references were removed, there were 35 additional references. None of these references were found to meet the inclusion criteria. In total, 15 studies met the inclusion criteria and were included in this review.

The two principle categories of Bayesian methods used for signal detection that have been evaluated and reported in the literature are the empirical Bayes methods and the Bayesian Confidence Propagation Neural Network (BCPNN) methods. Three studies that used empirical Bayes methods did not specify which empirical Bayes method was used. Most studies that evaluated an empirical Bayes method evaluated the MGPS, however one study used the prototype for the MGPS, the Gamma Poisson Shrinker (GPS). Three studies that evaluated a BCPNN method specified which BCPNN method was used; two studies used the “feed-forward” BCPNN method and one study used the “recurrent” BCPNN method. Studies that did not specify which BCPNN method was used were assumed to have used the “feed-forward” BCPNN method because this is the method currently used by the UMC.

Included studies either developed and evaluated a Bayesian method or evaluated an existing Bayesian method. A few studies retrospectively scanned a database at a particular point in time, while other studies simply used the database with all case reports present at the time of study. Most assessed a method on an existing database, however one study also evaluated the method on simulated data sets. Some studies examined all combinations that were signaled by a particular method, while others specified specific drugs or adverse events of interest. Most studies identified drug-adverse event signals, however one study evaluated a method on its ability to identify drug group-adverse event signals and one evaluated a method on its ability to identify drug-syndrome signals. A variety of measures for signal thresholds were used (e.g., the Empirical Bayes Geometric Mean (EBGM), the Information Component (IC)). In some cases, different studies using the same threshold measure used different values of the measure to signal an association (e.g., a lower-bound of the 90% confidence interval of the EBGM greater than 2 (i.e., $EB05 > 2$); a lower-bound of the 90% confidence interval of the EBGM greater than or equal to 2 (i.e., $EB05 \geq 2$)). A few studies also compared methods based on sensitivity, specificity, and positive and negative predictive values. A number of studies, particularly those evaluating an empirical Bayes method, incorporated stratification into the analyses. Some studies compared results from a database analysis with signals reported in the literature. Conclusions from these studies are presented in Appendix II.

Results of these studies suggest that, in general, Bayesian methods can effectively signal drug safety concerns in a pharmacovigilance database. Niu et al. (2001) found that the empirical Bayes method could detect an association between a vaccine and an adverse event

(5). Almenoff et al. (2003) found that the MGPS method could be used to investigate drug interactions (6). Bate et al. (1998) demonstrated that the BCPNN is a suitable tool for data mining in a large database (7). Lindquist et al. (2000) found that the BCPNN is a valuable tool for filtering combinations for clinical review and that the BCPNN can find signals early (8). Orre et al. (2000) demonstrated that the BCPNN is an efficient methodology for data mining of large databases in a computationally feasible way, and because it also estimates variances, the BCPNN is a suitable method for data mining on associations with low frequency counts (9). Bate et al. (2002) demonstrated that the BCPNN could identify drug-specific as well as group effects (10). Orre et al. (2005) showed that the recurrent BCPNN could detect syndromes (11). Gould et al. (2003) found that either the empirical Bayes method or the BCPNN could be helpful in finding signals (12).

Banks et al. (2005) (13), van Puijenbroek et al. (2002) (14), and Kubota et al. (2004) (15), each compared data mining methods, and none were able to decisively conclude on a “best” approach to signaling. Banks et al. found that the four compared measures differed in their ranking of combinations and not all known associations were highlighted by the measures. They suggested a need for further analysis in order to determine the best measure. Van Puijenbroek et al. found no difference between the evaluated methods when there were four or more reports per combination, but found that the specificity of the methods as compared with the BCPNN method declined when there were fewer than four reports per combination. Further, no individual approach to signal detection is adequate and therefore the concurrent use of several methods is necessary. Kubota et al. found that the proportion of signals generated differed by method, particularly when there were only one or two reports per

combination. They also found that the agreement between measures was poor between two similar disproportionality measures (i.e., the UK Medicines Control Agency method (MCA), which uses the Proportional Reporting Ratio (PRR) and chi-square, and the method using the 95% confidence interval for the PRR) and excellent between two very different measures (i.e., the MCA method and the BCPNN).

In contrast to the previously cited articles, Hauben (2004a, 2004b) (16, 17) and Hauben et al. (2004, 2005) (18, 19) consistently found that the MGPS method failed to detect a signal, often missing associations already detected by traditional “rule-based” methods (i.e., signals detected using clinical and pharmacologic judgments and threshold reporting frequencies), and reported in the literature. Hauben (2004b) suggested that simple disproportionality measures, such as the PRR, may be more useful. Hauben et al. (2005) suggested that the PRR method may be more sensitive than Bayesian methods, such as the MGPS. Hauben (2004b) conceded, however, that there may be a place for computer assisted algorithms, such as the MGPS, in detecting drug-interactions and syndromes. All four of these studies caution against relying on the MGPS method to signal drug safety concerns, warning that signals may be missed or delayed.

Very few studies comparing Bayesian methods have been performed and reported in the literature. There is no clear “best” method among the evaluated Bayesian methods for signal detection.

Discussion

Because the PIDM uses a Bayesian approach to signal detection, this review was limited to the evaluation of Bayesian data mining methods. It was not in the scope of this study to assess all data mining methodologies, Bayesian (e.g., MGPS and BCPNN) and non-Bayesian (e.g., PRR, Reporting Odds Ratio (ROR)). We therefore cannot conclude whether Bayesian methods are superior to non-Bayesian methods for signaling safety concerns in a pharmacovigilance database. This review highlights, however, the fact that many studies have evaluated the utility of Bayesian methods for signal detection and have found them effective for signaling drug safety concerns. Most studies have found that Bayesian methods can identify signals in a timely manner. There is no “best” Bayesian method at present; further study will be required to compare the relative utility of the Bayesian methods and signal threshold measures.

When the number of reports in a database is too large for manual review of individual case reports, such as in the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) database and the WHO database, a data mining methodology offers a good opportunity to signal safety concerns from the database. The MGPS and BCPNN methods should be viewed as tools to assist in narrowing the number of combinations for clinical review. Experts are still needed to manually review the individual case reports that contributed to identifying these associations.

In addition, the UMC has developed a series of triage algorithms that are applied to combinations identified by the BCPNN (20). These algorithms allow the UMC to focus on the most important safety issues, as well as complement the purely quantitative nature of the BCPNN by highlighting potential critical problems in the absence of large numbers of reports.

Much like the post-processing performed by the UMC on combinations identified by the BCPNN, methods for pre-processing reports to improve the effectiveness of a data mining methodology have been proposed. For example, a terminological reasoning tool called “PharmaMiner” has been described in the literature; results from studies that have assessed this tool suggest that “PharmaMiner” can improve the effectiveness of various data mining methods, including the BCPNN (21, 22). Duplicate report detection is another important pre-processing step. The UMC has recently developed a method for identifying duplicate reports; results from initial studies indicate that this method is effective and efficient in identifying duplicate reports in the WHO database (23). Articles describing pre- and post-processing methods were not included in this review because the methods are not, in themselves, Bayesian data mining methodologies.

This review could not assess the quality of the included studies because, to our knowledge, there is no readily available quality assessment tool for assessing these types of articles. Because we could not compare a quantitative value for any particular measure across studies, but rather considered the experiences of the authors who have evaluated Bayesian

methods, the methods employed in each study differed and could not be compared. In the absence of quantitative data, a meta-analysis could not be performed.

Four studies included in our review found negative and discouraging results for the use of Bayesian methods, and specifically the MGPS method, for signaling drug safety concerns in a pharmacovigilance database (16-19). All four of these studies utilized the AERS database and used the EB05 as their signaling measure. Three other studies evaluated the MGPS method and found positive or neutral results (5, 6, 13). The first study used the U.S. FDA and Centers for Disease Control and Prevention (CDC) Vaccine Adverse Event Reporting System (VAERS) database and the EBGM as its signaling measure (5). The second study used the AERS database and the EBGM, EB05, and EB95 measures (6). The third study also used the VAERS database and used the EBGM and EB05 measures (13). While study quality (e.g., choice of the most appropriate method and measures, properly carrying out the chosen method) could not be assessed and cannot be ruled-out as a possible reason for the inconsistency of results, the use of different databases with possibly different quality of reports, and the use of different metrics for signaling associations, may be responsible for the discrepancy.

This study was performed as part of a larger study designed to evaluate the PIDM and the WHO database with respect to vaccine safety. This systematic review was intended to identify available evidence that can be used in assessing how well the BCPNN method can be expected to identify vaccine-related signals in the WHO database. To our knowledge, a systematic review of Bayesian methods used in pharmacovigilance data mining has not been

previously published. Because very few studies have assessed the utility of a Bayesian signal detection method in identifying potential vaccine signals, we felt it was necessary to first consider the evidence for the use of Bayesian methods, including the BCPNN, in pharmacovigilance data mining, in general.

It is important to recognize that vaccines are biological products and differ significantly from chemical drug products. Some of the special characteristics that differentiate those vaccines used for disease prevention from drugs are: vaccines are usually administered to large populations of healthy individuals; most vaccines are administered to infants and children; vaccine administration is often promoted or even made mandatory by governments; a main issue in the safety and efficacy of vaccines is maintaining an adequate 'cold chain' (i.e., a system for keeping vaccines at the appropriate temperature, from the time of the start of manufacture until the time of use, in order to maintain vaccine quality and potency); potential variation between different batches and lots of a vaccine necessitates lot-by-lot surveillance of vaccines at the post-marketing stage; and the public, in general, is less willing to accept the risks associated with vaccines.

The PIDM was initially developed for chemical rather than biological products. Very little has changed since its inception to take into consideration the unique characteristics of vaccines, in particular: the same drug classification system is used to categorize drugs and vaccines; adverse reaction terminologies have not been expanded to include all symptoms of AEFIs; and ADR and AEFI case reports are analysed in the same way. Considering the

differences in characteristics between drugs and vaccines, the ability of the PIDM to meet the needs of vaccine safety is of great international public health importance (24, 25).

As a result of this review, an analysis of the WHO database (Letourneau et al., to be submitted), and a survey of AEFI surveillance authorities of countries participating in the PIDM (Letourneau et al., to be submitted), we have been able to draw several conclusions and make several recommendations with regard to the use of the BCPNN for signaling vaccine safety concerns in the WHO database:

1. The BCPNN appears to be an effective method for identifying drug safety concerns in the WHO database.
2. Very few studies have evaluated a Bayesian method for signal detection using AEFI reports, and no study has specifically evaluated the BCPNN method for signal detection using AEFI reports.
3. Success of the BCPNN is, in large part, dependent on the quality of reports in the database. The quality of AEFI reports may be compromised by the use of reporting forms, adverse event terminologies, and a vaccine classification system, all initially designed for chemical drug products.
4. Many countries participating in the PIDM do not submit AEFI reports. The ability of the BCPNN to signal a vaccine safety concern is compromised by the limited number of countries submitting AEFI reports and often very few reports per country. Effective communication between drug and vaccine safety authorities within a country and recognition of the importance of AEFI surveillance are necessary.

5. The choice of background for vaccine signaling should be carefully considered.

When the whole database is used as the background for signaling, adverse events that have been reported more frequently with drugs than with vaccines are less likely to signal a vaccine-event combination with these adverse events. When AEFI reports are analysed separately from all other reports in the database, the BCPNN is less likely to signal concerns that affect most vaccines in the database (e.g., a programmatic error).

6. The triage algorithms developed by the UMC, that are used to further limit the number of associations identified by the BCPNN for review, were designed with chemical products in mind and may not be effective for identifying vaccine signals. For example, identifying lot-specific safety concerns is important in vaccine safety, however no algorithm is designed to identify a pattern among lot numbers.

Recommendations for further study include further testing the BCPNN and other Bayesian and non-Bayesian signaling methods on AEFI report data in order to assess the effectiveness of these tools in vaccine safety. For the UMC, it will be important to reconsider what information is needed from reporters of AEFIs and how the information can best be used. The BCPNN and algorithms may need to be customized for vaccine signal detection. Adverse event terminologies should be expanded to include all symptoms of AEFIs. Countries participating in the PIDM should be encouraged to adopt standardized AEFI definitions and vaccine safety terminology as they are developed by the Brighton Collaboration (26) and the Council for International Organizations of Medical Sciences (CIOMS)/WHO Working Group on Vaccine Pharmacovigilance (27). As the PIDM

changes to better handle AEFI reports and signal vaccine safety concerns, participating countries may similarly make a greater effort to improve AEFI reporting to the UMC.

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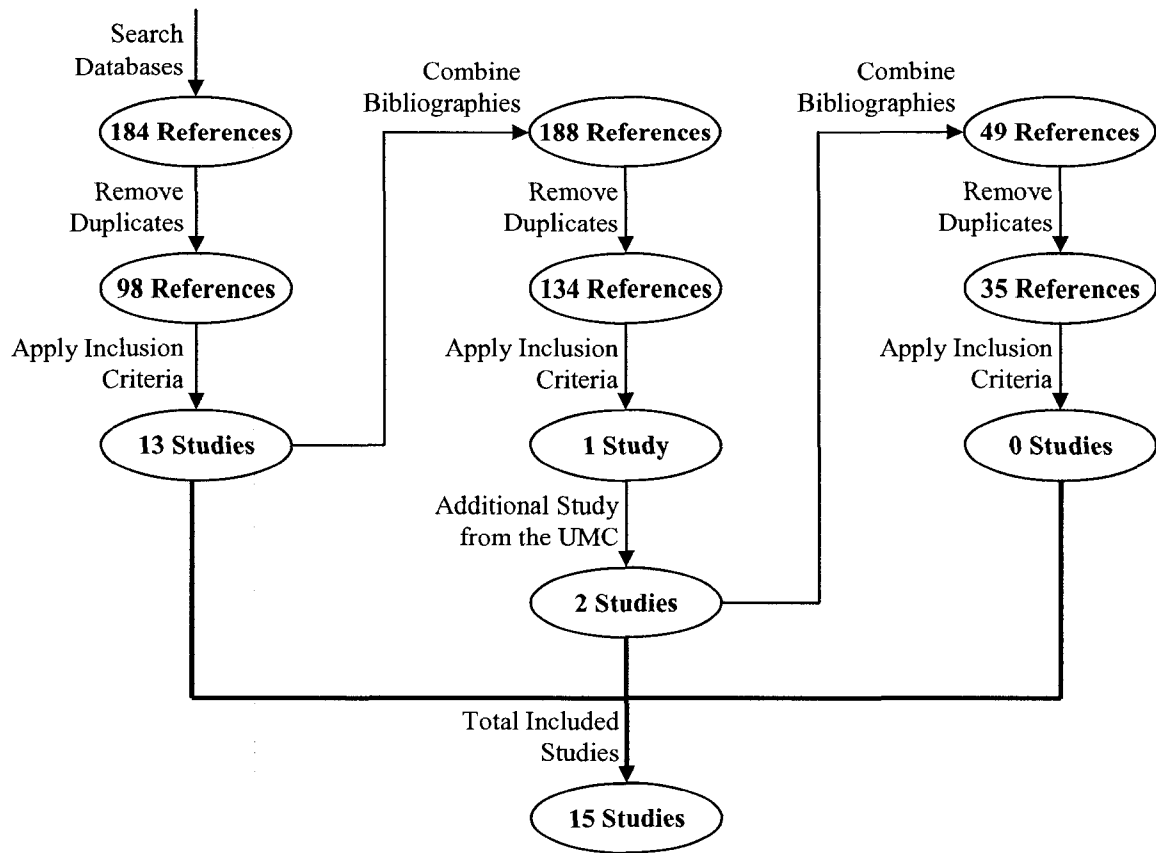


Figure 1. Results of the search and selection of articles for inclusion in the systematic review.

Because UMC staff were aware of this review, one additional article was forwarded to the authors. Because this article met the inclusion criteria, it was included in the review.

Appendix I. Search strategies

Medline (1966-2006, May Week 1) and HealthStar (1966-1998 & 1999-2006, April)

1. bayes theorem/
2. (Bayes\$ or Bayes\$ theorem or Bayes\$ analys\$ or Bayes\$ statistic\$ or Bayes\$ method\$ or Bayes\$ prediction\$ or Bayes\$ forecast\$ or Bayes\$ decision\$ or Bayes\$ decision procedure).tw.
3. exp Product Surveillance, Postmarketing/ or drug monitoring/
4. (pharmacovigilance or ADR surveillance or AEFI surveillance or medicine surveillance or medication surveillance or drug monitoring or vaccine monitoring or medicine monitoring or medication monitoring or drug monitoring program\$ or vaccine monitoring program\$ or medicine monitoring program\$ or medication monitoring program\$ or adverse drug reaction reporting or adverse drug reaction surveillance or adverse event\$ following immunization\$ reporting or adverse event\$ following immunization\$ surveillance or adverse drug reaction reporting system\$ or adverse drug reaction surveillance system\$ or adverse event\$ following immunization\$ reporting system\$ or adverse event\$ following immunization\$ surveillance system\$ or postmarketing surveillance or postmarketing ADR surveillance or postmarketing AEFI surveillance or post-marketing surveillance or post-marketing ADR surveillance or post-marketing AEFI surveillance or drug safety or vaccine safety or medicine safety or medication safety or phase 4 clinical trial\$ or phase 4).tw.
5. data interpretation, statistical/ or automatic data processing/mt or pattern recognition, automated/ or neural networks, computer/ or artificial intelligence/ or probability/ or algorithms/ or triage/ or biometry/

6. (signal\$ or signal detection or signal generation or data mining or data-mining or automat\$ data processing or pattern recognition or knowledge discovery or disproportionality analys\$ or neural network\$ or artificial intelligence or probability or algorithm\$ or triage or biometr\$).tw.

7. Pharmacokinetics/

8. Pharmacokinetic\$.tw.

9. 1 or 2

10. 3 or 4

11. 5 or 6

12. 7 or 8

13. (9 and 10 and 11) not 12

Embase (1980-2006, Week18)

1. bayes theorem/

2. (Bayes\$ or Bayes\$ theorem or Bayes\$ analys\$ or Bayes\$ statistic\$ or Bayes\$ method\$ or Bayes\$ prediction\$ or Bayes\$ forecast\$ or Bayes\$ decision\$ or Bayes\$ decision procedure).tw.

3. exp postmarketing surveillance/ or drug monitoring/ or drug safety/ or phase 4 clinical trial/

4. (pharmacovigilance or ADR surveillance or AEFI surveillance or medicine surveillance or medication surveillance or drug monitoring or vaccine monitoring or medicine monitoring or medication monitoring or drug monitoring program\$ or vaccine monitoring program\$ or medicine monitoring program\$ or medication monitoring program\$ or adverse

drug reaction reporting or adverse drug reaction surveillance or adverse event\$ following immunization\$ reporting or adverse event\$ following immunization\$ surveillance or adverse drug reaction reporting system\$ or adverse drug reaction surveillance system\$ or adverse event\$ following immunization\$ reporting system\$ or adverse event\$ following immunization\$ surveillance system\$ or postmarketing surveillance or postmarketing ADR surveillance or postmarketing AEFI surveillance or post-marketing surveillance or post-marketing ADR surveillance or post-marketing AEFI surveillance or drug safety or vaccine safety or medicine safety or medication safety or phase 4 clinical trial\$ or phase 4).tw.

5. statistical analysis/ or information processing/ or PROBABILITY/ or artificial neural network/ or artificial intelligence/ or algorithm/ or mathematical computing/ or data analysis/ or biometry/

6. (signal\$ or signal detection or signal generation or data mining or data-mining or automat\$ data processing or pattern recognition or knowledge discovery or disproportionality analys\$ or neural network\$ or artificial intelligence or probability or algorithm\$ or triage or biometr\$).tw.

7. pharmacokinetics/

8. pharmacokinetic\$.tw.

9. 1 or 2

10. 3 or 4

11. 5 or 6

12. 7 or 8

13. (9 and 10 and 11) not 12

Biosis Previews (1990-2006, May 5)

1. Bayes* or Bayes* theorem or Bayes* analys* or Bayes* statistic* or Bayes* method* or Bayes* prediction* or Bayes* forecast* or Bayes* decision* or Bayes* decision procedure*
2. pharmacovigilance or ADR surveillance or AEFI surveillance or medicine surveillance or medication surveillance or drug monitoring or vaccine monitoring or medicine monitoring or medication monitoring or drug monitoring program* or vaccine monitoring program* or medicine monitoring program* or medication monitoring program* or adverse drug reaction reporting or adverse drug reaction surveillance or adverse event* following immunization* reporting or adverse event* following immunization* surveillance or adverse drug reaction reporting system* or adverse drug reaction surveillance system* or adverse event* following immunization* reporting system* or adverse event* following immunization* surveillance system* or postmarketing surveillance or postmarketing ADR surveillance or postmarketing AEFI surveillance or post-marketing surveillance or post-marketing ADR surveillance or post-marketing AEFI surveillance or drug safety or vaccine safety or medicine safety or medication safety or phase 4 clinical trial* or phase 4
3. signal* or signal detection or signal generation or data mining or data-mining or automat* data processing or pattern recognition or knowledge discovery or disproportionality analys* or neural network* or artificial intelligence or probability or algorithm* or triage or data interpretation or statistical analys* or information processing or mathematical computing or data analys* or biometr*
4. NOT pharmacokinetic*

(Note: For the search of Biosis Previews, search "1" was run, followed by "2" on the results of "1", followed by "3" on the results of "2", followed by "4" on the results of "3")

Appendix II. Summary of the results of the data extraction, highlighting the conclusions of the studies included in the systematic review

Category of Study	Citation	Purpose of the study (database used, if indicated)	Bayesian method (measure used)	Conclusions of the study
Test of an empirical Bayes method	Niu MT, et al. (2001)	To retrospectively assess whether data mining would have detected the emergence of the rotavirus-intussusception association. (VAERS database)	An empirical Bayes method (EBGM)	The empirical Bayes method was able to detect the association between rotavirus vaccine-intussusception and between rotavirus vaccine-gastro-intestinal haemorrhage after only a small number of cases had been reported to VAERS.
	Almenoff JS, et al. (2003)	To determine whether the MGPS method can be used to test hypotheses about potential interactions between drugs. Specifically, the authors examined the adverse event profile of verapamil (a calcium channel blocker) alone and in combination with several classes of cardiovascular drugs. (AERS database)	MGPS (EBGM, EB05, EB95)	The MGPS method was able to “correctly” detect the interaction between verapamil-beta-blockers and not detect an interaction between either verapamil-angiotensin-converting enzyme inhibitors or between verapamil-angiotensin-2 receptor blockers.
	Hauben M (2004a)	To determine whether the MGPS method would have detected a signal between pancreatitis and selected antipsychotic drugs (i.e., clozapine, olanzapine, risperidone, and haloperidol) before it was added to the product label or published in the literature. (AERS database)	MGPS (EB05)	The MGPS method failed to generate a signal for any of the combinations, despite signaling of these combinations by traditional methods.

Hauben M (2004b)	To determine whether the MGPS method would have detected the thalidomide-adverse event signals identified by the manufacturer's (non-Bayesian) post-marketing surveillance program. (AERS database)	MGPS (EB05)	The MGPS method did not generate a signal for several serious and unexpected adverse events that were identified by the manufacturer's surveillance program.
Hauben M, et al. (2004)	To retrospectively apply the MGPS method and a non-Bayesian method to a data set of drug-adverse event combinations that resulted in drug labelling changes. (AERS database)	MGPS (EB05)	Not all combinations highlighted by the non-Bayesian method were highlighted by the MGPS. The MGPS method identified combinations after the non-Bayesian method. Both methods, however, identified the combinations before drug-labelling changes were made.
Banks D, et al. (2005)	To compare four signal detection measures (EBGM, EB05, and 2 non-Bayesian) to determine whether one measure is most effective for identifying vaccine-adverse event signals. (VAERS database)	An empirical Bayes method (EBGM and EB05)	Each measure has strengths and limitations.
Hauben M, et al. (2005)	To determine whether the MGPS method or a non-Bayesian method would have detected signals between gentamicin and endotoxin-like reactions. (AERS database)	MGPS (EB05)	Neither method identified 10 of 15 known adverse events associated with gentamicin. Data-mining methodologies may not have much to offer.

Test of the feed-forward BCPNN	Bate A, et al. (1998)	To test whether the feed-forward BCPNN method can find signals early and avoid false positive signals. To see whether the method can identify new signals. (WHO database)	BCPNN (IC)	The BCPNN was able to detect an association between captopril-coughing two years before it was first mentioned in the literature. The BCPNN did not generate false-positive signals for digoxin-acne or digoxin-rash. The BCPNN was able to identify potential signals not previously published in the literature.
	Lindquist M, et al. (2000)	To evaluate the ability of the BCPNN method to detect signals and to compare this method with the previous (non-Bayesian) method of signal detection used by the UMC. (WHO database)	BCPNN (IC)	The BCPNN method had a positive predictive value of 44% (i.e., 44% of the signals, which were not mentioned in the literature at the time, were strengthened or confirmed in the literature 7 years later) and a negative predictive value of 84% (i.e., combinations not highlighted for review by the BCPNN, if not already known, are unlikely to become signals). The BCPNN was able to detect new drug-adverse event combinations, and identified all signals that had been detected by the previous signal detection method that had gone on to be frequently reported in the database.

Orre R, et al. (2000)	To test the ability of the feed-forward BCPNN method to detect signals between a drug or a set of drugs and an adverse drug reaction or a set of adverse drug reactions. (WHO database)	BCPNN (IC)	The BCPNN detected the known associations between suprofen-back pain and azapropazone-photosensitivity, and would have detected the latter association 10 years before it was published. The BCPNN can be used to examine the relationship between 3 variables (e.g., digoxin-rash-age). The BCPNN was able to identify the drug-syndrome association between haloperidol-Neuroleptic Malignant Syndrome.
Bate A, et al. (2002)	To test the usefulness of the BCPNN in detecting drug-specific and drug-group effects. (WHO database)	BCPNN (IC)	The BCPNN method can identify drug-specific and drug-group effects. The BCPNN "correctly" signaled for prazosin-peritonitis and not for all beta-blockers-peritonitis; for captopril-coughing and all ACE inhibitors-coughing; for terfenadine-heart rhythm disorders and all antihistamines-heart rhythm disorders; and for clozapine-myocarditis and all antipsychotic-myocarditis.
van Puijenbroek EP, et al. (2002)	To compare the BCPNN with several non-Bayesian measures, and to examine how their concordance may vary with the number of reports per drug-adverse event combination. (dataset of the Netherlands Pharmacovigilance Foundation Lareb)	BCPNN (IC)	There was no difference between the methods when there were four or more reports per combination. When there were less than four reports per combination, specificity with respect to the BCPNN method decreased, indicating that either the non-Bayesian methods signaled an increased number of false-positives or the BCPNN failed to signal some "real" signals that the non-Bayesian methods detected.

Test of the recurrent BCPNN	Orre R, et al. (2005)	To test whether the recurrent BCPNN method can detect known patterns in the database. Specifically, the authors examined whether the method could identify syndromes associated with the antipsychotic drug haloperidol. (WHO database)	Recurrent BCPNN (IC)	The recurrent BCPNN detected patterns of adverse drug reactions, including several well-known syndromes associated with haloperidol. Clinically relevant patterns were detected, which might not be found using pairwise analysis alone. The recurrent BCPNN is robust with large amounts of incomplete data and does not generate many false positives.
Comparison between Bayesian methods	Gould AL (2003)	To compare the BCPNN and empirical Bayes methods on their assumptions and their ability to detect potential signals.	BCPNN (IC) and an empirical Bayes method (EBGM)	Both methods provide similar results for frequently reported adverse events and can highlight potential signals.
	Kubota K, et al. (2004)	To compare two Bayesian and three non-Bayesian signal detection methods. (Japanese spontaneous reporting system)	BCPNN (IC) and GPS (EB05)	The specific combinations detected and the proportion of possible signals detected varied between the five methods, particularly when the number of reports per drug-adverse event combination was only 1 or 2.

Abbreviations:

BCPNN: Bayesian Confidence Propagation Neural Network	EBGM: Empirical Bayes Geometric Mean
EB05: lower-bound of the EBGM 90% confidence interval	EB95: upper-bound of the EBGM 90% confidence interval
GPS: Gamma Poisson Shrinker	IC: Information Component
MGPS: Multi-Gamma Poisson Shrinker	

CHAPTER SIX: DISCUSSION & RECOMMENDATIONS

6.1 Introduction

The purpose of this thesis was to evaluate the WHO Programme for International Drug Monitoring and WHO Adverse Reactions Database with respect to how well they meet the needs of vaccine safety. This final chapter will bring together the results from our survey of AEFI surveillance authorities of countries participating in the PIDM (Chapter 3), quantitative analysis of the WHO database (Chapter 4), and systematic review of the literature for evidence of the utility of Bayesian data mining methods, and particularly the BCPNN, in pharmacovigilance (Chapter 5). In addition, this chapter will draw on discussions with WHO and UMC staff, as well as NPC representatives. The Centers for Disease Control and Prevention (CDC) outline for evaluating a public health surveillance system was used as a guide for this discussion (1).

This project was initially conceived by the Immunization, Vaccines, and Biologicals Department of the WHO in conjunction with the UMC. It is expected that results of this evaluation will be used by the WHO and UMC to guide further research and action to improve international AEFI surveillance.

6.2 Aims of the UMC

The CDC guide to evaluating a surveillance system outlines the various attributes of a system that should be addressed. The most important attributes to consider in an evaluation will vary depending on the aims and objectives of a particular surveillance system.

The aims of the UMC are to (2):

- “ensure that effective, timely international collective effort will never miss a signal of a potential hazard
- ensure that all stakeholders evaluate and learn from decisions and actions through positive impact-assessment, follow-up and debate
- encourage the growth of pharmacovigilance activities around the world, in particular the establishment of new [NPCs]
- encourage existing [NPCs] and other stakeholders in the field
 - to contribute actively to the global vision of the [PIDM]
 - to use and share available information openly and transparently
 - to sponsor and support others in their pharmacovigilance activities
 - to exploit fully the resources of the UMC
- stimulate the development of coherent, harmonized systems worldwide for pharmacovigilance, through education, training, promoting and participating in international forums, the promotion of best practice and the publication of guidelines
- maintain and develop useful products, services and tools in pursuit of the vision and goals of the [PIDM] and the UMC.”

6.3 System Attributes

The CDC guidelines propose evaluating a surveillance system with respect to 10 attributes: simplicity, flexibility, data quality, acceptability, sensitivity, positive predictive value, representativeness, timeliness, stability, and overall usefulness. Many attributes are inter-related, and as a consequence, many of the same issues are important to discuss under several of the attributes.

6.3.1 Simplicity

The PIDM is a complex system. There are currently 79 countries participating in the programme. Reporting adverse events to the UMC involves multiple levels of reporting, usually beginning with HCPs at the local level in each country. Reports are forwarded from the local level to the regional level, on to the national level, and finally to the UMC. Reports that are incomplete may require follow-up, either before or after they are sent to the UMC.

Reporting by national surveillance authorities to the UMC is fairly simple. Countries can submit reports in a variety of formats, including paper, diskette or CD, by email, or using *Vigibase Online*. Twenty of 30 survey respondents indicated that AEFI reporting instructions are clear, and 21 of 30 indicated that instructions are adequate. Respondents also indicated, however, that they would like to see AEFI-specific reporting instructions, with guidance on how to handle certain vaccine-specific concerns, such as programmatic errors. No respondent made any comment alluding to the complexity of the system being a concern.

The UMC employs a relatively small staff, divided into the various focus areas of the organization. Following signal detection, possible signals are forwarded to volunteer consultants, who review identified associations and decide whether or not these associations are true signals. Surveillance and signaling therefore involve a tremendous number of people at every stage and around the globe.

6.3.2 Flexibility

From a vaccine perspective, the PIDM is not flexible. If a country wishes to join the PIDM it must meet several criteria, including the ability to report adverse events in a format acceptable to the UMC. The UMC can generally only maintain contact with one national surveillance programme in a country and this is typically the NPC of the country. In countries with two separate surveillance authorities, the NPC is usually responsible for ADR surveillance. If the AEFI surveillance authority must rely on the ADR surveillance authority to relay information to the UMC and the drug and vaccine authorities do not communicate well, AEFI reporting to the UMC may be compromised.

WHO-ART, the principle adverse event terminology used by the UMC, and MedDRA do not adequately describe symptoms of AEFIs.

The UMC has not sufficiently investigated the appropriateness of using the BCPNN for signaling vaccine safety concerns, and in particular, the appropriateness of using the whole database, versus AEFI reports only, as the background on which to judge the frequency of a specific vaccine-event combination.

In spite of the fact that the UMC employs three staff to specifically address adverse event reports pertaining to herbal products, they do not have a staff person dedicated to AEFI reports.

It should be noted, however, that the UMC has made an effort to adapt some aspects of the PIDM to accommodate changing needs over time. For example, although WHO-ART remains the main adverse event terminology, the UMC has accommodated the use of MedDRA terms. The UMC allows reporting countries to submit new adverse event terms for WHO-ART as needed and has accommodated a growing number of products. The UMC welcomes the addition of new participating countries to the programme.

6.3.3 Data Quality

Data quality of AEFI reports, like data quality of drug reports, is relatively low. For signal generation purposes, reports should be complete, correct, and timely. While studies (i.e., Bate A, et al. (1998) (3), Lindquist M, et al. (2000) (4), Orre R, et al. (2000) (5), and Bate A, et al. (2002) (6)) have shown that the BCPNN is an effective method for detecting drug safety concerns, we cannot say what sort of improvements in drug signaling would be seen if ADR reporting frequency and quality were improved. No similar studies have evaluated the effectiveness of the BCPNN in detecting vaccine signals. We do not know how many vaccine signals are missed or delayed because of the use of inadequate vaccine terminology, lack of use of standardized AEFI definitions, use of an inappropriate ATC classification system for vaccines, or use of an inappropriate background for signaling.

Our analysis of the database revealed that a number of reports lack information that may be useful for signal detection. For example, approximately 10% of AEFI reports in our data listing did not include the age of the patient. We were therefore not able to include these reports in our analysis of AEFI versus ‘Other’ reports by age, or our analysis of AEFI reports by age and ‘Vaccine’ versus ‘Mixed’ status. This latter analysis also revealed that a substantial portion of reports of AEFIs occurring in older patients (i.e., 65+ years) may be incomplete, in particular, lacking information on the drugs that these patients are taking.

Timeliness of AEFI reporting is, on average, quite poor. The mean time from the date of onset of an AEFI to the date the report was entered in the WHO database was 2.4 years.

Because of the number of participating countries and the diversity between countries participating in the PIDM, the quality of report data can vary considerably between countries and even within countries. A country may, for example, be a very good reporter of ADRs but, because of poor communication with the Expanded Programme on Immunization or other AEFI surveillance authority in the country or because of economic constraints, may be a poor reporter of AEFIs.

6.3.4 Acceptability

Acceptability of the PIDM can vary by country and within a country. It is clear that countries want to participate in the PIDM; countries would not seek membership in the programme otherwise. However, a country’s decision to participate in the programme may reflect only acceptance of the programme by the ADR surveillance authority if the NPC

(who is usually responsible for ADR surveillance) is not also responsible for AEFI surveillance.

The time and resources needed to fully participate in the programme may be viewed differently between countries and between surveillance authorities within a country. Most developed countries find reporting to the UMC quite manageable; in general, these countries report fairly regularly and reasonably frequently. Smaller, developing countries may lack the same resources that facilitate reporting within the country and to the UMC, and therefore may find it difficult to report regularly to the UMC. AEFI surveillance authorities in countries where AEFIs are either not perceived to be as important as ADRs or where there are insufficient funds to support both ADR and AEFI surveillance programmes, may similarly find it difficult to maintain an AEFI surveillance programme and report regularly to the UMC.

The UMC has developed several internet-based services (i.e., *Vigimed*, *Vigisearch*, and *Vigibase Online*) to assist member countries in pharmacovigilance activities, including reporting to the UMC, and hopefully encourage greater acceptance of the programme. The UMC also regularly reports signals that have been identified in its publication *SIGNAL*. This publication helps to keep NPCs informed of the outcome and value of the reports that they submit to the UMC, further encouraging reporting and acceptance of the programme. Unfortunately, for countries where the AEFI surveillance authority does not have access to these services, because of, for example, poor communication between drug and vaccine authorities in the country, the vaccine authority may not form as favourable an impression of

the PIDM as the drug authority whose work has been made easier through the use of these services.

The considerable discrepancy between the number of AEFIs sent to the UMC and the number of AEFIs reported on the JRF between 2001-2003 indicates that vaccine authorities may not be very accepting of the PIDM; however, the lack of reports to the UMC may simply reflect a lack of communication between ADR and AEFI surveillance authorities within a country.

Survey respondents' impressions of the PIDM and WHO database ranged from "sufficient" to "excellent". Most respondents indicated that they were generally satisfied with the database, however many indicated that they would like to see improvements made to the programme and database. For example, respondents suggested creating specific AEFI reporting instructions, creating an archiving system in Vigimed to consolidate associated responses, and organizing a training programme on how to use *Vigisearch*.

6.3.5 Sensitivity

Sensitivity of the PIDM, and specifically of AEFI reports, cannot be directly assessed in this study because a passive surveillance system does not collect denominator data. We do not know the true frequency of adverse events in the population, which varies by country and by the type of vaccine.

That being said, for some vaccines, we may expect certain AEFIs to occur and therefore be reported. If these expected AEFIs are not reported, we know that the sensitivity of the system is low, even if not fully quantified.

Because passive surveillance systems rely on voluntary reports, only a percentage of cases that occur are reported. Adverse event reports are often not reported by patients to HCPs, and HCPs do not always forward reports to regional or national surveillance authorities. Even when reports are collected at the national level, they are not always sent to the UMC. Survey respondents indicated that AEFI reports may not be submitted to the UMC because: they are considered ‘non-cases’, are unlikely associations, or are not deemed ‘certain’, ‘probable’, or ‘possible’ following causality assessment; they are duplicate reports; they are not well investigated or the minimum amount of information on the case is unavailable; or they were not forwarded by the Expanded Programme on Immunization. Poor communication between drug and vaccine authorities may limit, or all-together prevent, AEFI reporting to the UMC.

The primary purpose of collecting AEFI surveillance data is to signal vaccine safety concerns. Several studies (i.e., Bate A, et al. (1998) (3), Lindquist M, et al. (2000) (4), Orre R, et al. (2000) (5), and Bate A, et al. (2002) (6)) have evaluated the ability of the BCPNN to detect drug signals in the WHO database and have found it effective and timely.

Unfortunately, no similar studies have been conducted to assess the ability of the BCPNN to detect vaccine signals. We do not know if the BCPNN is appropriate for signaling vaccine

safety concerns, if the whole database or only AEFI reports should form the background of the BCPNN, or if the data collected in AEFI reports is adequate.

While the sensitivity of the system should be improved by increasing the number of AEFI reports forwarded to the UMC, these reports must be of high quality and be timely. We cannot say how much of an improvement in signal detection would be seen if reporting practices were improved. The advent of large linked population databases that link immunization and adverse event data may help to assess the sensitivity of surveillance systems.

6.3.6 Positive Predictive Value

The positive predictive value (PPV) of the PIDM, and specifically of AEFI reports, is not measurable within the context of this study. One study (Lindquist et al., 2000) (4) included in our systematic review found that the BCPNN had a PPV of 44% (i.e., 44% of signals detected by the BCPNN, which were not mentioned in the literature at the time the BCPNN signaled the associations, were later strengthened or confirmed in the literature).

Most AEFI reports forwarded to the UMC have not undergone a causality assessment. Assessments of causality on individual reports are not very informative from an international pharmacovigilance perspective. Because there is no standardized method of assessing causality on individual reports and each reporting country performs its own causality assessments, the meaning of a causal designation, such as “probable” or

“possible”, is ambiguous. Whether or not a vaccine causes an AEFI usually cannot be determined from surveillance data alone.

It would be valuable to investigate the PPV and sensitivity of the PIDM with respect to vaccine signaling in a future study of the BCPNN.

6.3.7 Representativeness

Representativeness of the PIDM, and specifically of AEFI reports in the database, is difficult to assess. Representativeness can be considered from two points of view. First, whether AEFI reports in the database are representative of the AEFIs occurring in those countries participating in the PIDM. Second, since this is an *international* surveillance system, whether AEFI reports in the database are representative of the *international* ‘AEFI experience’ (i.e., representative of all AEFIs occurring around the globe).

It is possible for an international AEFI surveillance system to be representative of the AEFI experience of its member countries. Even though most, if not all, countries do not submit *all* AEFI reports (i.e., even if sensitivity is low), the database can still be representative of the AEFIs occurring in participating countries if there is no systematic reporting bias.

Our survey of vaccine authorities indicated that some countries exclude AEFI reports from certain population groups. If a country were to exclude, for example, the military sector, and the vaccines administered to the military differed from the vaccines administered to the public, and in turn, the AEFIs experienced by the military differed from the AEFIs experienced by the public, then that country’s AEFI reporting to the UMC would not be

representative of the country's AEFI experience, and in turn, the representativeness of the database would be compromised. If, however, a country were to exclude, for example, the private sector, and the vaccines administered to this sector did not differ from those administered from the public sector, the country's AEFI reporting would still be representative of its AEFI experience, and would not compromise the representativeness of the database.

It would be virtually impossible to create an international surveillance system that is representative of the AEFI experience of every country in the world. Different countries often administer different vaccines, in different ways, to people with different cultural backgrounds and different customs, including the use of different drugs and traditional medicines.

The PIDM data is not perfect. AEFI rates cannot be calculated. Signals generated by the UMC will not necessarily be generalizable or important to all participating countries. Signals generated by the PIDM are intended to alert participating countries to potential safety concerns and countries are strongly encouraged to investigate the issues for themselves and to decide the best course of action for their individual country. The UMC does not mandate a particular response to signals generated by the programme.

Many participating countries do not report AEFIs to the UMC; this must be improved. Participating countries should also improve the quality and regularity of reporting to the UMC, and, in general, should not exclude AEFI reports from any population subgroup. The

UMC should continue to help countries from all areas of the world establish surveillance programmes and join the PIDM. However, it is still of greater interest to both participating countries and the UMC, that each understand the strengths and limitations of the PIDM and the WHO database, and in turn, the signals generated by the system.

6.3.8 Timeliness

Timeliness of reporting of AEFIs to the UMC is, on average, poor. Reporting timeliness varies from country to country, and may be significantly affected by the relationship between drug and vaccine authorities at the national level and between national and regional surveillance authorities and HCPs. Our analysis of the database revealed a significant discrepancy between the date of onset of AEFIs and the date reports were entered into the WHO database. The average difference was 872.3 days, or 2.4 years.

Reports may be sent to the UMC via a number of methods, including *Vigibase Online*. *Vigibase Online* is expected to facilitate timely and regular reporting. At the time of our survey, five countries had already begun using *Vigibase Online* and six others indicated that they planned to switch to *Vigibase Online* sometime in the future. With so few countries using this method at this time, however, we cannot yet say how helpful this service is for improving reporting timeliness.

The available database data did not allow us to evaluate the regularity of AEFI reporting. Survey respondents, however, were asked whether they report regularly to the UMC. Twenty of 30 respondents indicated that they do. Respondents who indicated that they do

not report regularly to the UMC indicated that a shortage of staff, competing demands, and insufficient financial resources to purchase *Vigibase Online*, were some of the factors impeding regular reporting.

It should be noted that timeliness often refers to the time between the onset of an AEFI and the reporting of that AEFI to a HCP, surveillance authorities, or the UMC; however, timeliness can also refer to the effectiveness of the BCPNN at quickly detecting vaccine signals. At the moment, the BCPNN is used on the entire database on a quarterly basis. The effectiveness of the signaling process at quickly detecting vaccine safety concerns is dependent on a number of factors, including timeliness of reporting within participating countries and reporting to the UMC. Because no studies have been conducted to evaluate the ability of the BCPNN to detect vaccine signals, we cannot say whether the BCPNN is an appropriate method for signal detection of vaccine safety concerns, let alone whether the method can detect signals in a timely manner.

6.3.9 Stability

The PIDM is a reliable, stable programme for drug safety. Its reliability as a vaccine surveillance programme, however, has not been adequately assessed.

The PIDM was set up in Uppsala, Sweden in 1978. The programme currently receives no funding from either the WHO or the Government of Sweden, however it has managed to function consistently to date. The costs associated with running the programme are met through the sale of UMC products (e.g., the WHO-DD to pharmaceutical companies) and

services (e.g., *Vigibase Online* to participating countries). The UMC employs a staff of dedicated people, committed in their work.

The development of tools such as *Vigisearch* and *Vigimed* allow NPCs to perform their own searches and conference with each other, reducing the workload associated with some searching tasks for UMC staff. *Vigibase Online* allows countries who have bought the programme to enter their data directly online, facilitating in-country reporting and easy forwarding of reports to the UMC, and reducing the amount of data entry required by UMC staff. Unfortunately, because of the organization of ATC codes for vaccines, using *Vigisearch* can be a challenge.

We believe that there is a need for a ‘vaccine expert’ to join the UMC team. Someone with an extensive knowledge of vaccines could assess and address concerns relating to AEFI terminology, ATC classification of vaccines, and signaling vaccine safety concerns with the BCPNN.

6.3.10 Usefulness

The usefulness of a surveillance system is largely determined by how well the above attributes of the system are met. Determining which attributes are most important to a particular system should be based on an understanding of the aims of that system. For the PIDM, we must ask ourselves the following: whether the programme encourages vaccine pharmacovigilance activities around the world; whether membership in the PIDM is increasing and whether more countries are submitting AEFI reports; whether the PIDM can

detect vaccine-AEFI associations in a timely manner; and whether the UMC has been able to create products and services that assist participating countries in their own vaccine pharmacovigilance activities, as well as in their AEFI reporting to the UMC. The attributes that are most important to achieving these aims are acceptability, data quality, sensitivity, timeliness, and stability. In general, these attributes are not being adequately addressed for vaccines, which is affecting the usefulness and credibility of the PIDM as an international AEFI surveillance system.

6.4 Conclusions and Recommendations

The PIDM is a unique, international collaboration deserving of recognition as an important member of the global network of people and organizations dedicated to pharmacovigilance.

This project, comprising a survey of AEFI surveillance authorities of countries participating in the PIDM, a quantitative analysis of the WHO database, and a systematic review of the literature to identify evidence for the use of Bayesian methods, and specifically the BCPNN, to signal drug and vaccine safety concerns in a pharmacovigilance database, has allowed us to identify specific areas of concern that should be addressed through further evaluation and action.

In summary, our recommendations are as follows:

1. It is essential that the organizations and individuals involved in pharmacovigilance recognize vaccines as a distinct group of drugs. Vaccines should not be grouped

with all other drugs and they require special consideration in pharmacovigilance.

The annual meeting of NPCs is an excellent opportunity to further this message by inviting both drug and vaccine safety authorities to attend the meetings and allotting a segment of each meeting to discussions around vaccine safety issues. We recognize that this may require considerable effort on the part of the UMC to ensure that invitations are extended to both parties, however, meetings such as this present a unique opportunity to assist countries in improving the relationship between their ADR and AEFI surveillance authorities.

2. A staff person dedicated to AEFI reporting and vaccine signaling would be a valuable addition to the UMC team. The ideal candidate would be able to address concerns relating to deficiencies in the adverse event terminologies used to describe AEFIs, the lack of use of standardized AEFI definitions, the ATC classification of vaccines, and the use of the BCPNN and additional algorithms for vaccine signaling. Improvements to the programme that facilitate AEFI reporting and improve AEFI data quality should help to encourage better AEFI reporting. As the programme is improved and more AEFIs are reported, vaccine signaling capabilities will also be improved.
3. It will be necessary to continue evaluating the PIDM. This thesis is only a first step.

Success of the PIDM with respect to vaccine safety will require finding a balance between meeting the most important attributes identified by the aims of the programme and the costs associated with making these changes. Considering the limitations the UMC faces with respect to funding, we respectfully propose these suggestions and acknowledge that

planning and time will be needed before changes can be made. We are confident, however, that improvements in AEFI surveillance and vaccine signaling will be made over time, and the international community's support for the PIDM and drug safety will be extended, in turn, towards vaccine safety.

6.5 References

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APPENDICES

Appendix A. Letter of approval from the Ottawa Hospital Research Ethics Board



The Ottawa Hospital | L'Hôpital
d'Ottawa

Research Ethics Board
Conseil d'éthique en recherches
798-5555 ext 14146, 14902 or 15072
Fax No. - 761-4311
<http://www.ohri.ca/ohreb/>

Thursday, August 25, 2005

Dr. George Wells
University of Ottawa
Epidemiology and Community Medicine
Roger-Guindon Hall
451 Smyth Road, Room 3227A
Ottawa, Ontario K1H 8M5

Dear Dr. Wells:

**Re: Protocol # 2005487-01H Evaluation of the World Health Organization (WHO) Adverse Drug
Reaction (ADR) Database and How It Serves the Needs of Vaccine Safety**

Protocol approval valid until - Thursday, August 24, 2006

I am pleased to inform you that your study (listed above), the Protocol, the English Cover Letter, the English Reminder Letter, and the English Questionnaire were given expedited review by the Ottawa Hospital Research Ethics Board (OHREB) and are approved. No changes, amendments or addenda may be made in the protocol without the OHREB review and approval.

The validation dated should be indicated on the bottom of all consent forms and information sheets (see copy attached). Approximately two months prior to the expiration date listed above, a single renewal form should be sent to the OHREB office.

The Tri-Council Policy Statement requires a greater involvement of the OHREB in studies over the course of their execution. You must inform the Board of adverse events encountered during the study, here or elsewhere, or of significant new information which becomes available after the Board review, either of which may impinge on the ethics of continuing the study. The OHREB will review the new information to determine if the protocol should be modified, discontinued, or should continue as originally approved.

Yours sincerely,

Frédéric F.-A. Sarazin, Ph.D., C.Psych.
Vice-Chairman
Ottawa Hospital Research Ethics Board

Encl.

/cb

QUESTIONNAIRE

Adverse events following immunization (AEFI) surveillance in countries participating in the WHO Programme for International Drug Monitoring

The purpose of this questionnaire is to gather evidence on the process and product of adverse events following immunization (AEFI) data collection in your country. We are seeking your thoughts on your country's AEFI surveillance programme, particularly as it may pertain to the WHO Programme for International Drug Monitoring.

We thank you for taking the time to complete this questionnaire.

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IF THIS QUESTIONNAIRE HAS BEEN FORWARDED TO YOU BY YOUR COUNTRY'S NATIONAL PHARMACOVIGILANCE CENTRE, PLEASE IDENTIFY YOURSELF ON THE FIRST PAGE AND BEGIN WITH QUESTION # 2.

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1. In your country, what organization is responsible for the surveillance of adverse events following immunization (AEFI)?

If you are *not* an agent of the organization most responsible for AEFI surveillance in your country, please forward this questionnaire and cover letter to the responsible authority. If there are two organizations responsible for AEFI surveillance in your country, please forward the questionnaire to both authorities. Please contact Megan Letourneau (email: mleto028@uottawa.ca) to advise us of the authority (or authorities) responsible for AEFI surveillance and to provide us with the contact information for this (or these) authorities. We appreciate your assistance in this process and thank you for your time.

2. Does your country have separate surveillance systems for the reporting of adverse drug reactions (ADR) and AEFI?
 - ☐ Yes
 - ☐ No

3. Who can submit AEFI reports to your country's AEFI surveillance authority? (please tick all that apply)
- ☐ Physicians
 - ☐ Nurses
 - ☐ Pharmaceutical companies
 - ☐ Pharmacists
 - ☐ Complementary medicine professionals
 - ☐ Patients
 - ☐ Other (please list) _____
4. a) Is data collection and reporting of AEFI by any health care professionals **mandatory** in your country?
- ☐ Yes
 - ☐ No (**please skip forward to question #5**)
- b) For whom is reporting mandatory? (please tick all that apply)
- ☐ Physicians
 - ☐ Nurses
 - ☐ Pharmaceutical companies
 - ☐ Pharmacists
 - ☐ Complementary medicine professionals
 - ☐ Other (please list) _____
- c) From whom are you receiving AEFI reports? (please tick all that apply)
- ☐ Physicians
 - ☐ Nurses
 - ☐ Pharmaceutical companies
 - ☐ Pharmacists
 - ☐ Complementary medicine professionals
 - ☐ Patients
 - ☐ Other (please list) _____
5. a) Are any population subgroups (e.g., recipients of travellers' vaccines, the private sector, the military sector, etc.) systematically excluded from your country's AEFI surveillance system?
- ☐ Yes
 - ☐ No (**please skip forward to question #6**)

b) Which subgroups are excluded? (please tick all that apply)

- ☐ Recipients of travellers' vaccines
- ☐ Private sector
- ☐ Military sector
- ☐ Other (please specify) _____

6. Does your country forward AEFI reports to *the* Uppsala Monitoring Centre?

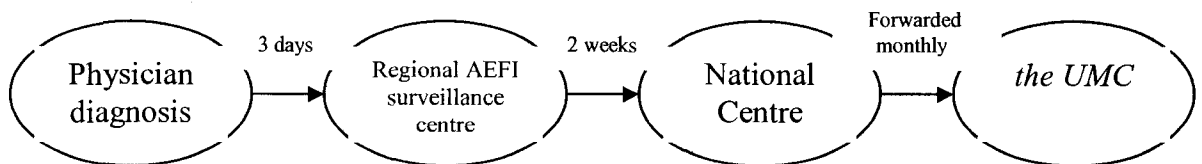
- ☐ Yes
- ☐ No (please explain) _____

7. Are there financial or other considerations that hinder or limit the reporting of AEFI to *the* Uppsala Monitoring Centre?

- ☐ Yes (please explain) _____
- ☐ No

8. Please explain or illustrate the path that AEFI reports follow from the point of AEFI identification to their arrival at *the* Uppsala Monitoring Centre (*the* UMC) (or other final destination point). Please indicate the approximate length of time between steps.

For example:



If your country does not forward AEFI reports to *the* Uppsala Monitoring Centre, please skip forward to question #18.

9. a) Does reporting to *the* Uppsala Monitoring Centre occur at regular intervals?
- ☐ Yes (**please skip forward to question #10**)
 - ☐ No
- b) What is impeding regular reporting of AEFI to *the* Uppsala Monitoring Centre?
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10. Are *the* Uppsala Monitoring Centre's instructions for AEFI reporting ...
- a) ... clear?
- ☐ Yes
 - ☐ No
- b) ... adequate?
- ☐ Yes
 - ☐ No
- c) Can you suggest any improvements to these instructions?
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11. a) Is the workload associated with AEFI reporting to *the* Uppsala Monitoring Centre manageable?
- ☐ Yes
 - ☐ No (Please explain) _____
- b) How much time, in total, would you estimate is spent on transferring, entering, editing, storing, and backing-up your country's AEFI data that is submitted to *the* Uppsala Monitoring Centre?
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12. What AEFI reports are forwarded to *the* Uppsala Monitoring Centre?
- ☐ Serious AEFI reports only
 - ☐ All AEFI reports
 - ☐ Other (please describe) _____

13. Are vaccine programme errors (i.e., “medication errors”) reported to *the* Uppsala Monitoring Centre?
- ☐ Yes
 - ☐ No
14. Are vaccine failures reported to *the* Uppsala Monitoring Centre?
- ☐ Yes
 - ☐ No
15. If *the* Uppsala Monitoring Centre were to request additional information on an AEFI case reported by your country
- a) ... would you be **able** to provide *the* Uppsala Monitoring Centre with follow-up information on the case?
- ☐ Yes
 - ☐ No (please explain) _____
- If you have indicated that you would be unable to provide *the* Uppsala Monitoring Centre with additional information, please skip forward to question #16.**
- b) ... would you be **willing** to provide *the* Uppsala Monitoring Centre with follow-up information on the case?
- ☐ Yes
 - ☐ No (please explain) _____
16. Are individual AEFI reports ever screened, ruled-out as cases, and not submitted to *the* Uppsala Monitoring Centre?
- ☐ Yes (please explain) _____
 - ☐ No
17. a) Does any assessment and classification (e.g., definite, probable, possible) of causality of the relationship between reported AEFI and vaccine administration take place at the **national level** before AEFI reports are forwarded to *the* Uppsala Monitoring Centre?
- ☐ Yes
 - ☐ No (**please skip forward to question #18**)

b) By what method is the causality assessment performed? (please tick all that apply)

- ☐ Committee clinical assessment
- ☐ Individual clinical assessment
- ☐ Causality assessment form (algorithm or other form)
- ☐ Other (please describe) _____

18. a) Which terminology do you use to code AEFI reports sent to *the* Uppsala Monitoring Centre? If reports are not sent to *the* Uppsala Monitoring Centre, please indicate which terminology is used to code reports for your national AEFI surveillance system.

- ☐ WHO-ART
- ☐ MedDRA (**please skip forward to question #19**)
- ☐ Other (please name) _____

b) Are you planning to switch to MedDRA?

- ☐ Yes (please indicate when you will be switching) _____
- ☐ No

19. a) Are there specific terms that cause problems for classifying AEFI? (please feel free to attach an additional page if more space is required)

- ☐ Yes (please list/explain) _____
- ☐ No

b) Are there terms missing from the coding terminology you are using?

- ☐ Yes (please list/explain) _____
- ☐ No

20. a) Have you heard of the Brighton Collaboration?

- ☐ Yes
- ☐ No (**please skip forward to question #21**)

If interested, you may like to review the Brighton Collaboration website at <http://www.brightoncollaboration.org>.

b) Will you be applying the definitions proposed by the Brighton Collaboration to your national AEFI surveillance system?

- ☐ Yes
- ☐ No (please explain) _____

21. a) Have you heard of 'Vigibase Online' (i.e., *the* Uppsala Monitoring Centre's internet-based report management system)?
- ☐ Yes
 - ☐ No (**please skip forward to question #22**)
- b) Are you planning to switch to Vigibase Online?
- ☐ Yes (please indicate when you will be switching) _____
 - ☐ No (please explain) _____
22. a) Have you used 'Vigimed' (i.e., an e-mail conferencing facility for *the* Uppsala Monitoring Centre member countries) for your vaccine-related queries?
- ☐ Yes
 - ☐ No (**please skip forward to question #23**)
- b) Are you satisfied with the number of response you have received to your queries?
- ☐ Yes
 - ☐ No (please explain) _____
- c) Can you suggest any improvements to Vigimed?
- _____
23. a) Have you used 'Vigisearch' (i.e., an online search facility for searching data in the WHO Database) to find vaccine-related data in the WHO Database?
- ☐ Yes
 - ☐ No (**please skip forward to question #24**)
- b) Are you satisfied with the results of your search?
- ☐ Yes
 - ☐ No (please explain) _____
- c) Can you suggest any improvements to Vigisearch?
- _____
24. a) Do you receive *the* Uppsala Monitoring Centre's 'SIGNAL' publication?
- ☐ Yes
 - ☐ No (**please skip forward to question #25**)

b) Is the SIGNAL publication useful?

☐ Yes

☐ No (please explain) _____

25. Have vaccine-related signals generated by *the* Uppsala Monitoring Centre been the impetus for...

a) ... further investigation in your country?

☐ Yes (please explain) _____

☐ No

b) ... policy change in your country?

☐ Yes (please explain) _____

☐ No

26. a) What is your overall impression of the WHO Database as it pertains to AEFI surveillance and vaccine safety?

b) Can you suggest any areas for improvement?

c) Do you have any additional comments?

If possible, please attach a copy of your country's national AEFI reporting form.

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**Thank you for completing this questionnaire.
Your time and cooperation are appreciated.**

Appendix C. Detailed description of data obtained from the Uppsala Monitoring Centre

Data from the WHO database was obtained directly from the UMC. In June 2005, the UMC provided the authors with:

- 1) Excel tables summarizing all case reports in the WHO database as of 30 May 2005.

The first table identified the total number of adverse event reports submitted to the UMC, by country by year. The second table highlighted the total number of adverse event reports submitted to the UMC by age of the patient.

- 2) A complete data listing of all AEFI reports received by the UMC. The variables included in this dataset were: report identification number, reporting country, date of onset of the adverse event(s), date the report was entered into the WHO database, age of the patient, Anatomical Therapeutic Chemical (ATC) classification of the vaccine(s) administered, adverse event(s), System Organ Class (SOC) affected by the adverse event(s), whether the patient was taking any drugs at the time of the immunization, basis of the event (i.e., the reporting country's indication as to whether the administered vaccine is suspect, concomitant, or interacting in the adverse event), and causal designation (e.g., probable, possible).

The first dataset included the ATC classification of the vaccine(s) administered but not the name of the specific vaccine(s). After discovering a number of problems with the ATC classification of vaccines, it was decided that an analysis of the number of AEFI reports by vaccine type would be useful. The UMC therefore prepared a second data listing in October 2005. Unfortunately, the staff person at the UMC who had prepared the initial data listing

was no longer working at the UMC. The task of preparing a second listing was taken on by a second staff person. The variables included in the second dataset were: report ID, date of onset of adverse event, date report was entered into the WHO database, ATC classification of vaccine(s) administered, name of vaccine(s) administered, adverse event(s), and basis of the event.

The second data listing included an additional four months of data. Case reports added to the database after 30 May 2005 (date of the last report included in the first data listing) were removed from the second dataset. While this ensured that all new cases added to the database after the last case that was included in the initial dataset would not be in the second dataset, some cases included in the first dataset were missing from the second dataset.

When changes are made to a report, the UMC assigns the modified report a new identification number and removes the old report from the database. Based on the information provided by the UMC, there was no way to trace the modified reports in the new dataset to their original reports in the first dataset. Unfortunately, this meant that our modified second data listing was somewhat smaller than our initial data listing. Since the number of cases affected was small, and because we were interested in trends rather than actual counts, the discrepancy was disregarded. The modified second dataset was used in the analysis of the number of reports by vaccine type and by ATC code only, since these two analyses were to be compared.

Appendix D. Overview of the empirical Bayes and BCPNN data mining methodologies

Data mining methodologies can be grouped into two categories: simple disproportionality methods and methods that utilize Bayesian inference (1, 2). Simple disproportionality methods utilize point estimate measures of disproportionality, such as the Reporting Odds Ratio (ROR) and the Proportional Reporting Ratio (PRR), along with estimators of the precision of the point estimate, such as the lower-bound of the 95% confidence interval of the point estimate (3). Methods that utilize Bayesian inference most notably include empirical Bayes methods, such as the Gamma Poisson Shrinker (GPS) and the Multi-item Gamma Poisson Shrinker (MGPS), and the Bayesian Confidence Propagation Neural Network (BCPNN), including both the feed-forward and the recurrent methods (2).

While the details of the Bayesian methods differ, both the empirical Bayes and the BCPNN methods use the frequency of drugs and events in the database as an internal control and calculate an observed-to-expected ratio for each drug-event combination based on this internal control (2, 4). The observed-to-expected ratio for each combination is expressed as the information component (IC) (3). The IC for a particular drug-event pair is the logarithm to the base 2 of the observed-to-expected ratio (i.e., $\log_2 n_{ij}/E_{ij}$) (4). (Note that the IC is equivalent to the logarithm to the base 2 of the PRR (i.e., $\log_2 \text{PRR}$) (4)). The Bayesian methods are designed to weigh-down the observed to expected ratio, particularly for those associations of drug-event pairs that are based on small numbers of reports (2).

The empirical Bayes and BCPNN methods differ most significantly in terms of how they determine the contributions of the observed-to-expected ratio (4). The empirical Bayes methods (i.e., GPS and MGPS) assume that the expected number of reports for each drug-event combination is fixed (4) and that the observed number of reports for each combination follows a Poisson distribution (4, 5). The BCPNN methods, on the other hand, express the number of reports for each drug-event combination as a function of the total number of reports in the database, the number of reports for that drug, and the number of reports for that event, all of which are assumed to have independent binomial distributions (4).

The empirical Bayes methods adjust for sampling variability by shrinking the observed-to-expected ratio towards the overall mean when there are few observed events (7, 8). This improved estimate of the ratio is known as the Empirical Bayesian Geometric Mean (EBGM) and it identifies observed counts that are larger than expected counts (8). An EBGM close to 1 indicates that there is no association between a particular drug and event; a large EBGM suggests a possible association (i.e., an association that may or may not be shown to be causal with further investigation) between the drug and event (8). The lower-bound of the 90% confidence interval of the EBGM is known as the EB05 (7). An EB05 $\geq$ 6 is often used as the signal threshold measure (1, 2, 9). If a particular drug-event combination had an EB05 equal to 6, for example, this would mean that reports of this drug-event combination occur in the database 6 times more frequently than would be expected if the drug and event were in fact independently distributed in the database (1, 2, 9). The EB05 measure is conservative and should minimize false-positives (7).

The MGPS was developed by extending the GPS in order to compute the EBGM for pairs and high-order combinations of drugs and adverse events (e.g., two drugs and an event, one drug and three events) (5).

The BCPNN methods use a neural network architecture to identify unexpectedly strong associations within the database (10). A neural network is a type of artificial intelligence, inspired by the functioning of the human brain (6, 11). The organization and weights of processing elements, called neurons, in the neural network determine the output (6, 11). Neural networks are particularly effective for predicting events when they have a large database of prior events to draw on (11), as is the case with the WHO database.

In the BCPNN, every report in the database has a certain probability that a specific event is listed on it (i.e., the prior probability). If a report has a particular drug listed on it, the probability of that specific event also being present may be changed (i.e., the posterior probability). When the posterior probability is higher than the prior probability, then the drug has enhanced the chance of the event being present, and the drug-event combination is present more frequently than expected (6). The BCPNN calculates an IC for each drug-event combination in the database (12) based on the number of reports with drug i , the number of reports with event j , the number of reports with the specific combination of drug i and event j , and the total number of reports in the database (10). A positive IC value indicates that the drug-event combination is reported in the database more frequently than would be expected from reports already in the database, and the higher the value of the IC the more the combination stands out from the database (10). Standard deviations are

calculated for each IC value. The greater the number of reports with drug *i*, the number of reports with event *j*, and the number of reports with the specific combination of drug *i* and event *j*, the narrower the confidence interval will be (10). Associations with an IC value minus 2 standard deviations greater than zero (i.e., $IC-2SD > 0$) are highlighted for review (3). (Note that this is equivalent to saying associations with a lower 95% confidence limit of the IC value above 0 are highlighted for review (10)).

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