CIOMS Guide to Active Vaccine Safety Surveillance

Report of CIOMS Working Group on Vaccine Safety

Council for International Organizations of Medical Sciences (CIOMS)

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Since its inception in 1949 by the World Health Organization and UNESCO, the Council for International Organizations of Medical Sciences (CIOMS) has contribution in various roles by taking up scientific topics benefitting from collaboration across the sectors of the pharmaceutical industry, medicines regulatory or competent authorities, public health agencies, and academia. Over the years CIOMS has evolved into an independent non-governmental, international organization that provides a neutral and objective forum conducive to public-private interaction on issues concerning medical sciences, most recently focused around pharmacovigilance and bioethics.

The previous CIOMS/WHO Working Group on Vaccine Pharmacovigilance was initiated in 2005 with the vision to globally support surveillance of vaccine safety and the evolving need of a harmonized view on terminology and case definitions, published in 2012 *Definitions and Application of Terms for Vaccine Pharmacovigilance: Report of the CIOMS/WHO Working Group*. The new CIOMS Working Group on Vaccine Safety (WG) was created to continue addressing unmet needs in the area of vaccine pharmacovigilance and specifically address Objective #8 of WHO's Global Vaccine Safety Initiative regarding public-private information exchange.[1]

Since the start of this WG in 2013, members have strived to find solutions and harmonized ways of approaching different challenges within this topic with a focus on what would be essential for national immunization programs and national regulatory authorities in resource-limited countries when faced with a launch of a new vaccine or a vaccine that was new to their country. The WG served as an information exchange between industry and other stakeholders, as well as a "think-tank" to develop and propose new approaches in the field. The very comprehensive mix of specialized vaccine manufacturing professionals, immunization practitioners, and medical experts within regulatory authorities that characterized this working group contributed to wide-ranging discussions, clarifications on important issues, and a focus on the truly fundamental needs in vaccine safety.

This CIOMS working group more than any other in recent history has focused on the special needs of the country level organizations responsible for developing strategies and implementing new vaccine programs into resource-limited environments. Through the CIOMS process and dialogue, members listened particularly to the participants based in resource-limited countries (RLCs) and their articulation of the urgent need for practical solutions to the problems facing them when deploying new vaccines into their populations. Sharing ideas and fine-tuning directions, the WG formulated a strategy of creating a guidance document that would be immediately useful (some say long overdue) to those on the frontline of immunization. Taking into consideration resources already in the field (e.g. WHO's Manual on surveillance of adverse events following immunization, 2014) which covers passive vaccine safety surveillance, the WG decided to support decision-makers at country-level with a guide that builds upon this important manual. The WG endeavored to address the challenge of weighing the alternatives when a significant knowledge gap exists with regard to a new vaccine and when passive surveillance is not enough or does not solve the problem – when active vaccine safety surveillance (AVSS) is warranted.

The CIOMS Guide to Active Vaccine Safety Surveillance (Guide) offers a practical step- by-step approach and a graphic algorithm to aid immunization professionals and decision-makers in determining the best course of action when confronting such challenges. The Guide provides a structured process, several case studies for review, and a source list for evaluating the extent of data resources.

The target audience has meant that the WG concepts and approaches were vetted extensively by WHO among their regional and country level colleagues as well as other experts in resource-limited countries, and the input received was incorporated into the materials and final document. The WG

[1] World Health Organization. The Global Vaccine Safety Initiative (GVSI). The eight strategic objectives: #8 Public-private information exchange. http://www.who.int/vaccine_safety/initiative/public_private/.

and the Editorial Board were asked to concentrate on language and formats that would create CIOMS guidance most accessible to professionals at country-level who are often facing significant challenges and demands on their time and resources.

CIOMS gratefully acknowledges the contributions of the members of the WG as well as the generous support from drug and regulatory authorities, industry, academia and other organizations and institutions which, by providing these experts and resources, facilitated the work that resulted in this publication. Each member participated according to their abilities and time demands as actively as they were able in the meetings and discussions, teleconference calls, email exchanges, drafting and redrafting of texts and their review, which enabled the WG to bring the project to a successful conclusion. During the three year process, new members from some organizations were invited, in capacity of their expertise, to cover changes in work assignments, replacing temporarily or more enduringly original or previous members.

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Geneva, Switzerland, January 2017

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ACRONYMS

AE	Adverse event
AEFI	Adverse event following immunization
AESI	Adverse event of special Interest
AVSS	Active vaccine safety surveillance
B-R	Benefit-risk
CIOMS	Council for International Organizations of Medical Sciences
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPI	Expanded Programme on Immunization
EVI	Essential Vaccine Information
GACVS	Global Advisory Committee on Vaccine Safety
HDSS	Health and demographic surveillance sites
HIV	Human immunodeficiency virus
ICD	International Statistical Classification of Diseases
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use[2]
ID	Identity
IPV	Inactivated polio vaccine
IRB	Institutional review board
LMIC	Low- and middle-income country
MA	Marketing authorization
MAH	Marketing authorization holder
MO	Multilateral organization
MOH	Ministry of health
NEC	National expert committee
NGO	Non-governmental organization
NIP	National immunization program
NRA	National regulatory authority
O/E	Observed versus expected
OPV	Oral polio vaccine
PV	Pharmacovigilance
PvC	Pharmacovigilance centre
RLC	Resource-limited country
SCCS	Self-controlled case series
SKG	Significant knowledge gap
UMC	Uppsala Monitoring Centre
USFDA	United States Food and Drug Administration
VSD	Vaccine Safety Data link
WG	Working Group
WHO	World Health Organization

[2] To reflect organizational changes, the ICH changed part of its name to Council from Conference in October 2015.

FOREWORD

In 1949 the Council for International Organizations of Medical Sciences (CIOMS) was established by the WHO and UNESCO as an international, non-governmental, non-profit organization, intended to provide a forum for biomedical research experts drawn from multiple disciplines and regions to address the implications of advances in biomedical sciences upon diverse issues, ranging from health policy to medical education and bioethics. Since that time it has served as a crucible in which stakeholders drawn from government, non-governmental, academia and private sectors, and from the natural and social sciences as well as the humanities, forge new approaches to address emerging issues in the biomedical sciences.

One major set of activities has focused upon the taxonomy used to monitor adverse drug reactions, and more generally to support enhanced medicinal product safety monitoring. These activities have been conducted through working groups representing the relevant major scientific constituencies, including regulatory authorities, the pharmaceutical industry, academia, and international organizations. Early working groups provided guidance for standardized reporting of adverse events using a new form (CIOMS I), development of periodic safety update reports (PSUR, CIOMS II), and the development of core data sheets (CIOMS III).

The initial CIOMS topics addressed pharmacovigilance issues and focused mostly on the post-marketing phase of medicines development. The need for a harmonised approach to evaluate and report the benefit-risk balance of marketed medicines was addressed in CIOMS Working Group IV, whereas CIOMS Working Groups V, VI and VII focused on pragmatic approaches in pharmacovigilance, management of safety information from clinical trials and on harmonisation of the format and content for periodic safety reporting during clinical trials. CIOMS Working Group VIII provided points to consider to pharmaceutical companies, regulatory authorities, and international, national or institutional monitoring centres wishing to better manage the entire 'lifecycle' of a new potential safety concern/signal including signal detection, prioritisation and evaluation.

Vaccines have attributes that set them apart from most drugs: they are typically administered on a population level, provided to healthy populations, often children, to prevent rather than treat disease, and often administered through government programs. Recognizing this different intent and benefit-risk profile for vaccines, it was decided to address the distinct safety issues through CIOMS working group activities. The CIOMS/WHO Working Group on Vaccine Pharmacovigilance was convened in 2005, and charged with: 1) developing standardized vaccine pharmacovigilance (PV) definitions; (2) contributing to the development, review, evaluation and approval of AEFI case definitions developed by the Brighton Collaboration process and to their dissemination; and (3) collaborating with other CIOMS working groups especially that on Standardized MedDRA Queries (SMQs) and CIOMS VIII on signal detection. Recognizing the key role played by WHO in global immunization programs, the CIOMS/WHO Working Group on Vaccine Pharmacovigilance produced the report entitled *Definition and Application of Terms for Vaccine Pharmacovigilance* in 2012.

The subsequent CIOMS Working Group on Vaccine Safety (WG) was convened in 2013 and charged with the task of addressing emerging needs in the context of the new landscape of vaccine introduction. The current publication, CIOMS Guide to Active Vaccine Safety Surveillance (2016), was conceived based on the recognition that the standard spontaneous reporting mechanism for evaluating vaccine safety was not always sufficient to provide timely and accurate vaccine safety assessment during the life cycle of a vaccine. Novel vaccines are on the horizon which are likely to be introduced early and/or exclusively into resource-limited countries (RLCs). In these countries significant prior pharmacovigilance experience could be lacking as they will not have benefited from the years of immunization campaigns which in the past have taken place often first in the high-income countries

whose regulatory groups were affiliated with the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[3]

These novel vaccines may be introduced to address an urgent need (e.g. an epidemic) or because the disease endemicity is primarily in certain RLCs. A challenge in these situations is that RLCs will have limited information on the adverse event profile at the time of licensure of some novel vaccines. In 1974 WHO initiated the Expanded Programme on Immunization (EPI) with the intention of providing all children with basic immunization, to receive protection against six childhood vaccine-preventable diseases. The present era has seen a drastic change of conditions, with earlier introduction of new vaccines in RLCs – such as vaccines against rotavirus and human papillomavirus – as well as vaccines targeting diseases endemic to RLC regions (see http://www.who.int/immunization/diseases/en/ for WHO's list of diseases for which vaccines are in development). These same RLCs often have limited infrastructure to support post-licensure safety assessment using the standard spontaneous report mechanism. For these reasons, one focus of this report is to provide guidance on assessing local RLC needs for vaccine-specific safety assessment, including the use of active safety surveillance strategies to provide timely and efficient evaluation for those responsible for the implementation and oversight of vaccine programs. More generally, the document provides an overview of the role of active vaccine safety surveillance (AVSS) with examples from throughout the world.

The work reflects extensive dialogue and information exchange over this three-year period 2013 – 2016 and is a joint effort representing collaboration between representatives from international organizations, public health organizations, international regulators, pharmaceutical company safety experts from both international firms as well as emerging market manufacturers, and academia. The target audience is focused on the end user in resource-limited countries, such as the immunization programme managers, staff of the national regulatory authority (NRA), public health or non-governmental organizations involved in vaccine safety assessment and policy, and marketing authorization holders.

[3] Countries and regions among the founding and standing regulatory parties of the International Council of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Association include EU (represented by European Commission and European Medicines Agency), USA (represented by US Food and Drug Administration FDA), Japan (represented by the Ministry of Health, Labour and Welfare (MHLW), the Pharmaceuticals and Medical Devices Agency (PMDA)), and Canada (represented by Health Canada). http://www.ich.org/about/membership.html

CHAPTER 1:

KEY BACKGROUND CONCEPTS AND INTRODUCTION

This document provides the reader with tools, resources, and strategies to develop a systematic approach for active vaccine safety surveillance in the context of vaccine safety and pharmacovigilance. The CIOMS Guide to Active Vaccine Safety Surveillance (Guide) will take the stakeholder step-by-step through the process of determining whether active vaccine safety surveillance (AVSS) is necessary, and, if so, choosing the best type of active safety surveillance and the key implementation issues to be considered.

Chapter 1 begins with a number of key definitions that all stakeholders will need to be familiar with in order to appropriately consider AVSS. It will then discuss an important point to be considered for any vaccine pharmacovigilance activity: appropriate collaborations. If complex resource-intensive activities such as AVSS are being considered, it is critical that all stakeholders collaborate effectively. And to that end, this chapter will also focus on the key stakeholders involved in consideration of potential AVSS programs, and discusses their various roles in Figure 1 and Table 1.

Figure 2 provides a schematic algorithm of a six-step process for determining whether ongoing passive surveillance is sufficient – as is usually the case – or whether active vaccine safety surveillance needs to be considered. It will be followed by a more detailed overview of the six-step process that should be followed in considering AVSS. This will give the stakeholder an understanding of the basic approach before going into the details of the following chapters corresponding to each step.

Chapter 2 provides guidance in how to identify any significant knowledge gaps that may exist and choosing the appropriate tools to close them. Chapter 3 describes research methods used to evaluate the safety issue, different types of active safety surveillance available, as well as information on selection of the most appropriate research strategy. Chapter 4 describes practical aspects of active surveillance, including communication between stakeholders and with the general public, ethical considerations, and roles and responsibilities during study implementation. With this information the user may then proceed to work with other sources of information on pharmacoepidemiology, and preferably with subject matter experts and other stakeholders in the design, implementation, and interpretation of active vaccine safety surveillance studies.

1.1 Definitions and key principles

Recent progress in the development and deployment of new vaccines of global importance, as well as novel vaccines targeting diseases specifically endemic to many resource-limited countries (RLCs), carries with it responsibilities for all stakeholders. National regulatory authorities, public health authorities, manufacturers, payers or purchasers of vaccines, international organizations, non-governmental agencies, and health care providers administering vaccines share a common interest in ensuring good pharmacovigilance so that the vaccines used are safe and have a positive

benefit-risk profile. Populations who receive recommended vaccines expect that they will be both safe and effective.

The definition of vaccine pharmacovigilance (PV), also known as vaccine safety, is the "science and activities relating to the detection, assessment, understanding, prevention, and communication of adverse events following immunization, or of any other vaccine- or immunization-related issues."[4]

It is the responsibility of each national regulatory authority (NRA) to assure the safety of vaccines licensed in its country. Safety surveillance is a fundamental pharmacovigilance tool used to assess the safety of licensed vaccines and to promptly identify and address any unexpected safety concerns arising from their use. The cornerstone of vaccine pharmacovigilance is *passive surveillance,*[5] which consists of the spontaneous reporting of adverse events following immunization (AEFI) by immunization service providers, hospitals, and patients to the administrative level appropriate in each country depending on its national surveillance system. From there, reports are sent to the next reporting level(s), ending at the international institutions responsible for global AEFI surveillance."[6] In passive surveillance systems, the primary responsibility for identification and reporting AEFIs falls upon the health care provider, the patient, or the patient's family or carers. The role of those responsible for overseeing the passive surveillance system focuses primarily on assuring the accuracy and completeness of reports that are received, and on analysis of the AEFI reports for necessary action.

In principle, the population followed in passive surveillance systems is typically the entire (i.e. vaccinated) population in the jurisdiction. Reports can then be transmitted from local to higher administrative levels (in some countries the first reporting may be to a national/federal institution), including national-level units and global PV centres. The detection of unknown (i.e. newly reported or emerging) AEFIs, also known as "signals," and the low incremental cost of spontaneous reporting, are the primary strengths of passive surveillance.[7] It is well-suited for identifying AEFIs that occur rarely. Passive surveillance, however, has a number of well-recognized limitations, including:

- underreporting;
- difficulty determining rates of AEFIs; and
- inability to properly characterize strength of association between vaccine exposure and adverse events.[8]

Many countries, particularly in resource-limited settings, lack robust passive vaccine surveillance systems.

In an active public health surveillance system, the health department or other responsible entity (e.g. NRA) initiates and maintains regular contact with health care providers or other relevant reporting sources (e.g. hospitals, laboratories or patients) to identify cases of the health condition(s) of interest. In contrast to passive surveillance or spontaneous reporting systems, in which the responsibility to report is placed on the source of the data (e.g. health care provider or laboratory), in active vaccine

4 CIOMS. Definition and application of terms for vaccine pharmacovigilance. Report of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Geneva: Council for International Organizations of Medical Sciences (CIOMS), 2012.

5 In this document we use the terms spontaneous reporting and passive surveillance interchangeably and we have avoided the use of the term "routine" surveillance because routine can have different meanings in different contexts, e.g. different countries, companies, etc.

6 Adapted for the context of this Guide from World Health Organization. Global manual on surveillance of adverse events following immunization, 2014 (Revised March 2016), §4.2, p.26, http://www.who.int/vaccine_safety/publications/aefi_surveillance/en/.

7 WHO. Global manual AEFI, *op. cit.*

8 WHO. Global manual AEFI, *op. cit.*

safety surveillance the responsible agency regularly solicits reports from various providers.[9, 10] AVSS can take various forms, from active collection as sentinel sites to formally-designed epidemiologic studies. A description of these different forms of AVSS is provided in Chapters 3 and 4.

In general, spontaneous reporting, using a passive surveillance approach, forms the basis of signal detection throughout the world. AVSS can complement a passive surveillance, confirming or discarding the signals detected in the latter. While it is not intended to replace spontaneous reporting systems, AVSS may also be of use to any resource-limited country lacking a sufficient passive system, or requiring vaccine safety information that is otherwise unavailable.

Some relevant situations which could warrant the use of AVSS may include addressing safety concerns in the setting of: 1) introduction of a novel vaccine for which only limited safety data are available from other countries; 2) introduction of a well established (i.e. in widespread use) vaccine into a new country for the first time; and 3) evaluation of special populations or circumstances that could be involved.

The term 'knowledge gap' refers to lack of available or easily accessible information on vaccines in countries which need the respective information in contexts such as: 1) vaccine introduction, 2) new safety issue, 3) change in the nature of the vaccination program, or 4) inadequate passive surveillance system. This lack of information equals a research gap or question on some aspect of vaccine safety that has not been answered sufficiently. If the knowledge gap has the potential to negatively influence the benefit-risk profile of the vaccine to such a degree that it could significantly affect the safety of those receiving vaccinations, it can be described as a "significant knowledge gap" (SKG). An SKG may be specific to a particular country, region, or population subset (e.g. elderly, pregnant women).

Without question, AVSS is a powerful tool; however, it can have significant resource and expertise requirements, which should be considered prior to undertaking an AVSS program. To that end, one goal of this document is to aid stakeholders in identifying settings for which AVSS may be the most suitable method to address a safety concern.

1.2 Collaborating at regional and international levels

Vaccine safety issues may be of interest locally, regionally, and sometimes globally. Adverse events reported from one country may have implications for other countries or places that use the same product or batch of a particular vaccine. Rumours or news about vaccines can spread very quickly locally and likewise globally. Networks of communicators need to be aware of issues and controversies that may influence opinion at home.

Figure 1 identifies some of the major domestic and international vaccine stakeholders, ones that are interested in vaccine safety issues. At the country level, several of these types of organizations may be present; in most countries the national immunization program and regulatory authorities are the main government entities responsible for vaccine safety. Optimal national, intragovernmental and international communication can be enhanced when those national authorities are familiar with international actors that can provide them with information, independent advice or relay their important messages. In Figure 1, four groups of stakeholders are represented around the outer perimeter with the country level entities and experts in the centre.

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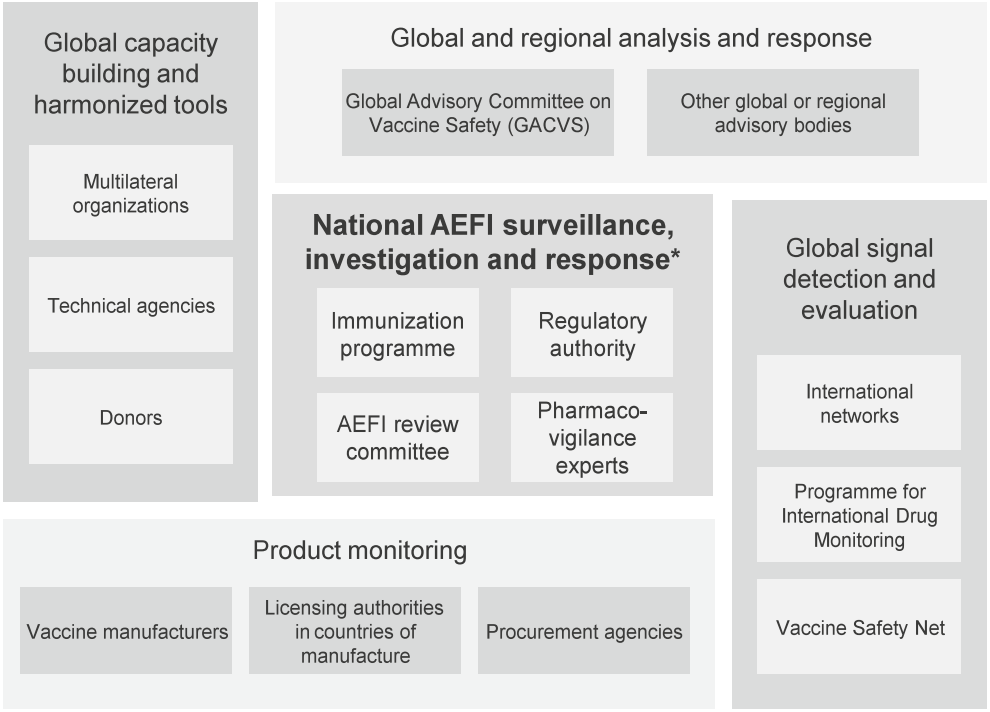
9 Field Epidemiology, Gregg, M ed., Print publication date: 2008, Published to Oxford Scholarship Online: September 2009, DOI: 10.1093/acprof:oso/9780195313802.001.0001.

10 Centers for Disease Control and Prevention (CDC). Manual for the surveillance of vaccine-preventable diseases. Centers for Disease Control and Prevention, Atlanta, GA, 2008, http://www.cdc.gov/vaccines/pubs/surv-manual/.

Figure 1. Stakeholders in global vaccine safety[11]



* Several entities that participate in the national primary health care system usually contribute to vaccine pharmacovigilance.

Once a vaccine safety concern has been identified, several international networks of pharmacoepidemiologists and related scientists are available that have developed expertise for investigation and analysis. If requested, they can offer to support multi-country collaborations. The WHO Programme for International Drug Monitoring maintains a global data base of individual case safety reports that can be accessed in order to verify if concerns/cases have been identified elsewhere with a particular vaccine product. The Vaccine Safety Net (VSN) is a network of websites that was developed to address the variable reliability of information available from the worldwide web. This is particularly important in the area of vaccine safety, for which there are anti-vaccine groups dedicated to instilling distrust of vaccination/immunization by providing unbalanced and misleading information (including the purporting of unfounded rumours). This can lead to undue fears, particularly among the general public, and undermine immunization programs.

The VSN is a network of more than forty reputable governmental, professional associations and academic websites (with an outreach estimated at millions of visits each year) that provide vaccine safety information in numerous languages. Each website has been evaluated by a set of criteria for good information practices recommended by the WHO'S Global Advisory Committee on Vaccine

[11] World Health Organization. Adapted from graphic entitled, "Components of a 21st Century global vaccine safety monitoring, investigation, and response system." Module 5: Vaccine safety institutions and mechanisms Vaccine safety basics learning manual, www.vaccine-safety-training.org.

Safety (GACVS), and has been added to the list of reliable websites, accessible on the WHO Global Vaccine Safety website.[12]

In addition, independent global or regional expert advisory bodies[13] provide advice to countries with evidence-based immunization policies that assess the benefits and risks of vaccines. GACVS provides independent, authoritative, scientific advice to WHO on vaccine safety issues of global or regional concerns with the potential to affect in the short or long term national immunization programmes. GACVS's assessments of vaccine safety issues are publicly available and official statements are issued when urgent concerns are identified.

Finally, a broad range of international partners support vaccine safety and are potential relays in addressing and disseminating important information about timely issues. Those include WHO and UNICEF and their country offices, other partner technical agencies engaged in the Global Vaccine Safety Initiative as well as donor agencies. Donors are important parties as they interact with decision-makers, can prioritize resources and provide access to non-state and private sector actors.

1.3 Stakeholders and responsibilities for active vaccine safety surveillance (AVSS)

Stakeholders include all parties responsible for vaccine development and manufacture, licensure, administration and implementation of the vaccine campaign, funding, policy-making and assessment, and communication of the plan and results. Though all parties share a common interest in disease prevention through vaccination, they differ with respect to their responsibilities, their accountability, and their perspectives on who should be consulted, and who should be informed.

As vaccine decision-makers assess the need for additional information, it is useful to engage other stakeholders (see Table 1). Within a country, dialogue among various entities (NRA, national immunization programme (NIP), Ministry of Health (MOH)) may identify mechanisms to efficiently address any significant knowledge gap (SKG). Multilateral organizations (e.g. WHO) may have access to information that would help refine and address the SKG. Similarly, the vaccine manufacturers/ marketing authorization holders (MAHs) may have additional product information or available research data. Academics (e.g. in clinical pharamacology or epidemiology) have expertise in relevant research strategies, including design and conduct of studies. Collectively, discussions among these subject matter experts can help determine or affirm whether an SKG exists and identify early in the process the issues that are important to address, as well as assess the feasibility for utilizing currently available data, resources and tools.

The table below lists the steps and stakeholders involved following the process set forth in the six-step algorithm of Figure 2 for considering AVSS. Table 1 outlines the groups that might be in charge of the decision-making and those that should be consulted or informed, but each country has its own configuration that needs to be understood and engaged in dialogue. The algorithm and explanatory text in the following section provides details on what is entailed in each step.

[12] Vaccine Safety Net. Vaccine safety websites meeting good information practices criteria http://www.who.int/vaccine_safety/initiative/communication/network/approved_vaccine_safety_website.

[13] Such as the Advisory Committee on Immunization Practices (ACIP) https://www.cdc.gov/vaccines/acip/ or national immunization technical advisory groups (NITAGs).

Table 1. Steps and stakeholders for active vaccine safety surveillance

Step #	Steps in determining if there is a gap and how to close it	Responsible and/ or accountable	Consulted and/ or informed of decision
Pre	Is there a reason to consider AVSS?	WHO, NRA/NIP, MAH	PvC, medical communities, appropriate expert advisory and other relevant organizations.
1	Is there a significant knowledge gap?	WHO, NRA/NIP, MAH	PvC, MAH, other NRAs, WHO, NGO, MO, payers, academia
2	Is it confirmed the gap actually exists after further research?	WHO, NRA/NIP, MAH	PvC, MAH, other NRAs, WHO, NGO, MO, payers, academia
3	Can the knowledge gap be closed with existing passive surveillance (including enhanced passive surveillance)?	NRA/NIP, MOH MAH	PvC, MAH, other NRAs, WHO, NGO, MO, academia
4	Confirm: is AVSS the right tool to close the significant knowledge gap?	NRA/NIP, MOH MAH	PvC, MAH, other NRAs, WHO, academia
5	Choose the right type of AVSS.	NRA/NIP, MAH	PvC, MAH, other NRAs, WHO, NGO, MO, academia
6	Consider practical aspects of implementation.	NRA/NIP	NECs, PvC, MAH, other NRAs, WHO, NGO, MO
Post	Who determines action based on results?	NRA/NIP	MAH, donors, PvC, other NRAs, WHO, NGO, MO

MAH=	Marketing authorization holder, usually the pharmaceutical company or manufacturer, if they are the sponsor.
MOH=	Ministry of health
MO=	Multilateral organization (e.g. WHO, UNICEF)
NEC=	National expert committee
NGO=	Nongovernmental organization (typically donors, like Gavi)
NIP=	National immunization programs
NRA=	National regulatory authority
PvC=	Pharmacovigilance Centre – can be part of academia, MOH, or NRA
Other NRA(s) =	Other NRAs having assessed and authorized the vaccine in question.

Table 1 provides a structure to define the steps and possible stakeholder responsibilities and if #4 is positive and AVSS is needed, who might be involved in the design, implementation, analysis, support (infrastructure, funding), as well as actions taken as a result of the AVSS (i.e. dissemination of results, changes to programs). Table 1 was constructed as a general guide. Specific scenarios may result in different stakeholders being involved in different roles.

Benefit-risk considerations are critical to maximize the effectiveness of the new vaccines being introduced. To facilitate decision-making, the data needed to inform the benefit-risk assessment should be agreed upon prior to implementation of the vaccination programs, so that the data needed can be efficiently collected and utilized. Similarly, during the course of a vaccine's use in a country, it is useful to periodically review and refine the benefit-risk assessment. Approaches used to assess benefit-risk should be practical, and may be most useful (interpretable) when aligned with similar strategies used in the country (for other programs) and internationally. Existing information (and any existing studies or active safety surveillance programs) should be leveraged, in order to use resources most effectively (e.g. multiple AVSS programs for the same gaps in knowledge should be avoided). This will likely require a global cooperation between all stakeholders: regulatory authorities, manufacturers, academics, local endusers like the national immunization program or expanded programme on immunization (EPI) and multinational organizations such as WHO.

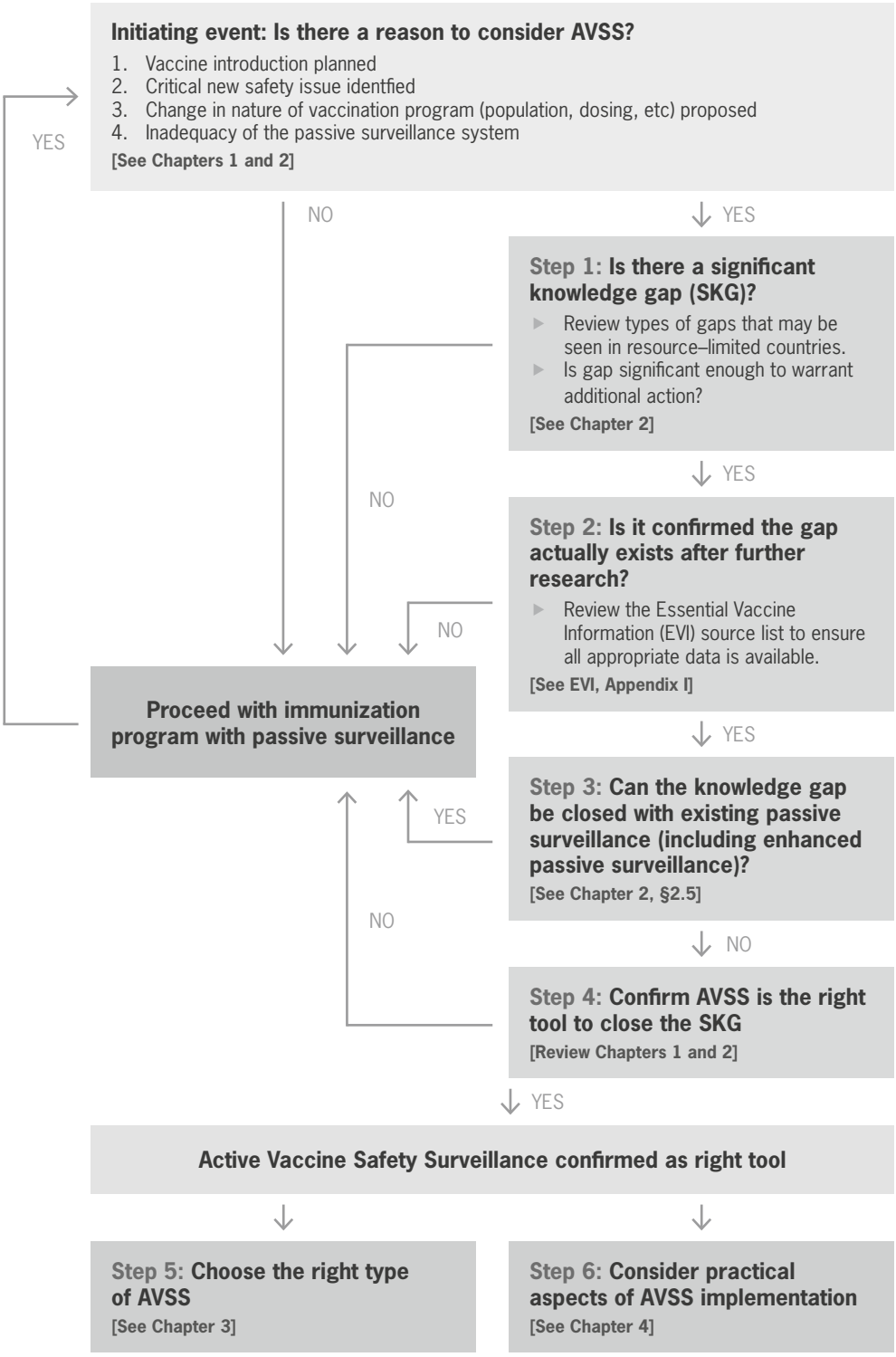
While passive (spontaneous reporting) surveillance approaches are standard and expected to already be functioning within most countries, the implementation of an AVSS study requires additional resources (expertise, laboratory, personnel, infrastructure, financial support). For this reason, careful planning is of particular importance to support efficient resource utilization as well successful implementation. It is recommended to leverage any existing passive surveillance infrastructure where possible, to support AVSS. For example, surveillance infrastructure that may exist for EPI vaccines (e.g. polio, measles) may be of use for an AVSS.

Passive surveillance will be appropriate in the majority of the occasions. However AVSS could be the right tool in situations where a clearly important knowledge gap is identified and results in a question to be answered (e.g. a safety signal that may affect the benefit-risk profile has been identified and needs verification).

1.4 A six-step algorithm for determining the need for AVSS

The remainder of this chapter will focus on an introduction to the systematic approach that should be taken in considering active vaccine safety surveillance. Figure 2 below provides a one page overview of the six-step process or algorithm, and also serves as an overview to the Guide itself. These steps should be followed to identify outstanding informational needs and to formulate an appropriate strategy to obtain them. Following this schematic overview, each of the key steps to follow for determining if, and how, AVSS may be considered and implemented are outlined.

Figure 2. Algorithm: six-step process for considering AVSS



Initiating event

AVSS may be implemented at any time throughout the life-cycle of vaccine use in a country, from vaccine launch until the time when the vaccine is no longer being used. The most common initiating circumstances seen at or prior to vaccine introduction include:

1. AVSS may be indicated in circumstances that include introduction into a country of a vaccine that has been well-characterized elsewhere, but in which local introduction may represent new issues (e.g. new population, new indication, new multivalent form); or
2. A new vaccine without significant prior global experience, such as a novel vaccine aimed primarily at diseases of resource-limited countries or introduced into countries with inadequate passive surveillance systems.

Following vaccine introduction in a country, there may be a need for AVSS because:

1. A concern has arisen on account of a safety signal detected through passive surveillance;
2. A new population or circumstance (e.g. expanded use in an outbreak setting) may benefit from timely impact assessment; or
3. International or local concerns have been raised about the vaccine's safety.

Each of these examples may prompt stakeholders to question whether passive surveillance is sufficient, or if indeed AVSS would be warranted and whether additional data would be needed to inform the benefit-risk assessment for the vaccine's use.

Step 1: Is there a significant knowledge gap (SKG)?

If stakeholders identify a circumstance that may merit attention, the essential question for decision-makers is whether there are specific outstanding data needs that are so substantial that they would be expected to affect the overall benefit-risk assessment for the vaccine, leading to some change in its use. In this setting, the outstanding need for information is referred to as a "significant knowledge gap" (SKG).

Chapter 2 describes in detail why SKGs may exist, including the novelty of the vaccine, factors related to use in a new region (e.g. different health care system, potentially different setting for administration of vaccine, different storage condition options), planned populations for vaccination (e.g. different age groups or pregnant women who may not have been studied previously), and changes to the vaccine schedule, formulation, or dose. The question of how the vaccine will be used (e.g. mass vaccination or reactive vaccination in outbreak setting) as well as any unstudied area of the local disease burden and epidemiology of disease in a specific country or region may also create an SKG. Careful consideration of the existing information is necessary in order to determine if an SKG exists.

Step 2: Is it confirmed that the gap actually exists after further research?

For the purpose of determining what basic safety data is needed and whether a knowledge gap truly exists, the WG developed an instrument, the Essential Vaccine Information (EVI, see Appendix I) source list which lists the types of sources for information that will be most helpful in determining outstanding safety data needs.

The EVI source list in Appendix I provides a set of resources that can be consulted to determine the baseline safety data that may be needed and the names of the documents in which this data would

be presented, depending on the history and circumstances of the vaccine under review. Using the EVI as a reference, decision makers can assemble information to characterize a vaccine, including its known adverse event profile. Through this process the enduser can confirm whether the essential data about the vaccine is available, or instead requires pursuing contacts or seeking out additional source documents.

If a significant knowledge gap appears to exist, steps should be taken to validate it (i.e. confirm that it really does exist). In some cases, an enduser, like the national immunization program or EPI, may not initially have access to all documents that might be available or authorized for its use, if they have not been delivered to them directly. Taking the effort to seek out this data, could aid the decision-making process, saving resources and improving immunization results. Only after all sources of data have been exhausted can a SKG be legitimately confirmed to exist.

The EVI process includes the following steps after determining which vaccine approval scenario applies:

1. Gathering the relevant documents (e.g. data supporting licensure, product label or product insert);
2. Seeing what data is missing;
3. Contacting the relevant stakeholders for more information if available;
4. Refuting or confirming the significant knowledge gap.

If there is no significant knowledge gap, or if additional review of available data determines the gap is already closed, no further action is needed other than continuing the spontaneous/passive reporting system.

Step 3: Can the knowledge gap be closed with existing passive surveillance?

If a significant knowledge gap does exist, in many cases it can be addressed through passive surveillance. Decision makers need to carefully assess whether the SKG can be closed through passive vaccines safety surveillance, using or enhancing existing systems, if there are already adequate ones in place.

One should proceed to consider AVSS only if:

- The knowledge gap is significant enough to warrant additional action.
- The local passive vaccine safety surveillance systems are not in place or may not be adequate to address the issue.

This information gap needs to be reconciled with country needs and resources, in order to determine whether new vaccine safety assessment is most appropriately managed through spontaneous reporting (passive surveillance) mechanisms or whether additional approaches, including AVSS are needed.

If there is a confirmed significant knowledge gap that is determined to merit additional potential data collection that cannot be resolved through passive surveillance, proceed to **Step 4**.

Step 4: Confirm AVSS is the appropriate tool to close the SKG

Chapters 2 and 3 provide an overview of the pharmacovigilance tools (passive surveillance and AVSS, respectively) that might be employed to close a signficant knowledge gap. In many cases, this may be addressed through existing passive safety surveillance, so Chapter 2 should be helpful to consult. Other options may include conducting enhanced passive surveillance, AVSS, other epidemiological research, or in rare cases, clinical studies.

Chapter 3 focuses on the principles and methods of AVSS. Understanding these principles is critical in determining whether AVSS is the appropriate tool. It is critical that stakeholders consider the points raised in this chapter in order to ensure AVSS is the correct tool.

If an SKG cannot be reasonably closed with the various tools reviewed in Chapters 2 and 3, alternative methods for surveillance need to be considered and other sources beyond this document will need to be consulted. Additionally, it is important to note that there may be some unique situations where the gap cannot be closed by any type of study (e.g for practical or ethical reasons).

Only if it is determined that AVSS is the right tool to close an SKG, should decision-makers proceed to **Steps 5 and 6.**

Steps 5 and 6: Moving forward with AVSS: choosing the right type of AVSS and practical implementation issues

At this point in the process, the stakeholder has completed a thorough review of available data, and both identified and confirmed that an SKG exists. They have also reviewed the pharmacovigilance tools at their disposal and determined that indeed active vaccine safety surveillance is the appropriate tool to help close the gap in knowledge. At this point they are ready to move to implementation. The second half of this Guide is designed to help with this process.

Chapter 3 focuses on providing details on the many forms of AVSS that may be used to address significant knowledge gaps. The chapter will provide an overview of each, describing its focus, as well as when it might be selected for use. Examples are provided.

Fundamental technical considerations (design, implementation, and analysis) are introduced in Chapter 4, although advanced information is beyond the scope of this Guide. Chapter 4 also highlights the importance of dialogue and partnership among the vaccine stakeholders listed in Table 1, so that AVSS activities can be successful and informative.

1.5 An example of decision-making regarding AVSS – meningitis vaccine in West Africa

Below is an example that demonstrates how this thought process operated in the real world:

Example 1: Meningitis vaccine in West Africa

An illustrative example is an active vaccine safety surveillance program implemented following the introduction of a new meningitis vaccine into several West African countries at risk for epidemic outbreaks of bacterial meningitis.[14,15] The initial safety profile of the vaccine was similar to other licensed meningitis vaccines and data from clinical trials had not highlighted any specific concerns. Nonetheless, the WHO Global Advisory Committee on Vaccine Safety (GACVS) had concerns about the completeness of ascertainment of AEFI (knowledge gap for identifying rare events in clinical trials). Data had been collected largely through existing passive surveillance systems, and could not be compared to background rates of occurrence of pre-specified adverse events of special interest

[14] Djingarey MH, Barry R, Bonkoungou M, Tiendregeogo S, Sebgo R, Kandolo D et al. Effectively introducing a new meningococcal A conjugate vaccine in Africa: The Burkina Faso experience. Vaccine: 30S (2012) B40– B45.

[15] Ouandaogo CR, Yaméogo TM, Diomandé FV, Sawadogo C, Ouédraogo B, Ouédraogo-Traoré R et al. Adverse events following immunization during mass vaccination campaigns at first introduction of a meningococcal A conjugate vaccine in Burkina Faso, 2010. Vaccine: 30S (2012) B46– B51.

(AESI) in the same populations. This is why GACVS had encouraged the continued collection of data to include a larger population (see GACVS Meeting December 2010).[16] It was recognized that a large scale program of active surveillance would be logistically complicated given the number of health care facilities. A subset of sentinel sites was established for active safety surveillance that collected information on AESI among patients eligible for meningitis vaccination. The focus was on 12 clinically important conditions potentially associated with vaccine administration: local abscess, urticaria, anaphylactic shock, bronchospasm, laryngeal edema, toxidermia, purpura, convulsions, meningitis syndrome, hypotonia, flaccid paralysis, and encephalomyelitis. This program was intended to complement the passive surveillance systems in these countries and focused on these key potential adverse events which would be relevant for assessment of the benefit-risk profile of the vaccine.

Lessons learned: A number of key points are illustrated by the above study. First, active surveillance was used to monitor a limited number of AEFIs in the context of the first widespread introduction of a new vaccine. Second, sentinel sites were used, as cost and complexity made a large scale active surveillance program impractical. Third, the active surveillance can be used to complement other pharmacovigilance tools. In this case, at the national level stimulated passive surveillance was used (attention to AEFI reporting emphasized during campaign preparation) to maximize the amount of information gathered. Finally, this case illustrates that pharmacovigilance is not "one size fits all." Each situation must be thoroughly analysed to determine which method or methods, will be most effective to achieve the stated goal.

1.6 Conclusion

In summary, the Guide to AVSS provides a systematic approach for vaccine decision-makers to assemble the information required to identify and characterize safety considerations for the use of specific vaccines. Where available safety information is inadequate to characterize a significant knowledge gap that could impact the benefit-risk profile of a proposed vaccine (or even a vaccine already in use), the document offers an approach to identify suitable strategies for collecting the necessary information, utilizing both existing mechanisms (passive surveillance) as well as supplementary ones (such as active vaccine safety surveillance). If it is concluded that AVSS is the most effective approach, the Guide provides a strategy for identifying the type of activity needed, and directs the decision-maker to additional informational sources for design and implementation.

[16] World Health Organization, Global Advisory Committee on Vaccine Safety, December 2010 http://www.who.int/vaccine_safety/committee/reports/Dec_2010/en/.

CHAPTER 2:

IDENTIFICATION OF SIGNIFICANT KNOWLEDGE GAPS AND CHOOSING THE APPROPRIATE TOOLS TO CLOSE THEM

2.1. Introduction

Passive surveillance sytems for pharmacovigilance activities, needed for any vaccine in any geographical context, including resource limited countries (RLCs), are described in a global manual for AEFIs, and published by WHO in 2014.[17]

Active safety surveillance may be applicable to:

A vaccine that is newly approved (either globally, locally or both). This may be a vaccine being introduced simultaneously in RLCs and developed markets, or for vaccines aimed primarily at RLCs and being introduced there primarily.

A vaccine that has been approved for some time in non-resource limited countries, with a well established safety profile in those regions. In such a case, AVSS *might* be appropriate if there some aspect of the vaccine's use in a particular RLC or region that would differ such that a significant knowledge gap (SKG) might exist.

A vaccine that has a well established safety profile (e.g., has been marketed for some time globally or locally), but for which a new significant safety signal emerges.

This chapter will highlight instances that may justify additional safety surveillance beyond passive pharmacovigilance. It will describe the types of knowledge gaps that may exist at the time of vaccine introduction, or during usage, and will provide a list of potential gaps that could be pertinent to RLCs especially. It is not expected that these examples will be exhaustive, and stakeholders may indeed find other situations requiring additional action. However, the types of gaps described will provide an important starting point.

[17] WHO. Global manual, *op. cit.*

2.2. General points to consider

The overall positive benefit-risk (B-R) profile of the vaccine is established when the marketing authorization (MA) is granted by the competent regulatory agency based on the submitted regulatory dossier, according to the regulations in the particular country or region. For vaccines newly deployed, there may be the need to quickly generate data from the local population under conditions of routine use to give an assurance of an acceptable safety profile.

The need for additional study of vaccine safety should only be considered if there is a specific knowledge gap (and thus, a specific question has been identified). The gap must be substantive or significant enough to justify formal additional study, and there must be confidence that the question can be answered by the action chosen. Such significant knowledge gaps (SKG) usually either reflect safety signals identified during clinical development or passive surveillance or theoretical concerns related to any particular novel characteristic of a vaccine product.

It should be emphasized that even if an SKG has been identified, that does not necessarily mean that AVSS is the best available tool. Numerous tools for closing a significant knowledge gap can be considered, and AVSS should only be undertaken if it is determined that this is the appropriate approach.

A rigorous review of all available data should be conducted prior to considering active vaccine safety surveillance. It is possible that the initially identified knowledge gap has already been addressed by another source (e.g. reports generated during clinical trials or published – or even unpublished – data on studies conducted in another country). Within the context of this Guide, an Essential Vaccine Information (EVI) source list has been developed as an aid to guide the stakeholder in vaccine introduction (see Appendix I). The EVI creates a framework to find and organize available data, using source documents. The specific documents may vary depending on how the vaccine has been authorized in a particular country or region. By using the EVI, the stakeholder can determine whether information relevant to introduction in their country is known or if a gap is confirmed to exist.

The gaps to be considered should be relevant to the country/region where the vaccine product is being introduced. However, it should be considered whether this gap might be seen across countries or regions. Before undertaking any additional activities, the stakeholders should consider whether other countries or regions might have similar concerns and whether joint studies could be considered. It is possible that the identified gap has already been closed by a study in another country/region. If not, stakeholders should work together to close the remaining gap in the most efficient and robust manner possible. Thus, information sharing and cooperation between RLCs and other countries should be developed. Countries might also consider data from ongoing studies in neighbouring countries that might become available sooner than the results of their own planned studies.

If no gap with relevance for the specific country is identified, passive vaccine safety surveillance would suffice provided an adequate PV system is in place in the country.[18] However, if a relevant gap is identified, and if this gap could be important for the B-R profile of the vaccine, then actions and tools for active safety surveillance should be considered.

[18] WHO. Global manual, *op. cit.*

2.3. Specific types of gaps: examples of potential gaps related to the vaccine or usage in an RLC

Whether a vaccine is being used for the first time in an RLC after extensive usage/experience globally, or is being used for the first time anywhere in the world, it is critical to identify those knowledge gaps that may require additional post authorization review. These gaps will be dependent not just upon the vaccine itself, its properties, and available data, but especially upon factors specific to an RLC, and the usage of the vaccine in that country. Thus, specific gaps may arise from a combination of these factors and cannot be predicted for all situations. Careful consideration is required to determine if additional post authorization study is warranted. Due consideration should also be paid to the need for additional data from policy makers and national leaders to fill a gap – whether real or perceived – and attempts should be made to satisfy this need for additional data. This could be provided by existing information from local or global sources or from the published literature without necessarily embarking on an AVSS unless there is a clear and justified scientific and ethical need.

While each potential gap cannot be outlined in this manual, there are a variety of different *types* of gaps, as described below, that might be considered. The following list is by no means comprehensive, and the stakeholders may certainly find gaps outside of these categories.

2.3.1. Related to vaccine itself

2.3.1.1. Novelty of the vaccine

Notable would be a vaccine that has not been used in other countries or is still in development, but is being used in an emergency situation in an RLC. An example of such a vaccine introduction might be the initial use of a new or evolving Ebola virus vaccine. In such a case, the use of the vaccine may be specific to certain RLCs. It will not have had global usage, nor would significant parallel use in a developed country be expected at introduction. In a case such as this, there would of course be limited or no post authorization safety information upon which to rely. In fact, in a crisis situation, even the clinical trial data may be relatively limited. Stakeholders in RLCs should be assured that this situation is no different from what would have occurred in a developed country in the face of rapid deployment of a new vaccine in an epidemic, a classic example being the active surveillance that was associated with the deployment of the H1N1 vaccine in Europe and many other countries in 2009.

In such a case, the expected potential gaps would be much broader, and do in fact include a need to further characterize the safety profile generally because a product could be utilized at large scale after only few clinical trial subjects had received it and with limited duration of follow-up. In these cases, the stakeholders will need to consider the totality of their knowledge of the safety profile of the vaccine, and whether the key areas that are not known would warrant formal additional study.

There are a number of possible scenarios in which a vaccine might be introduced under non-emergent conditions and yet also require further study. The novel vaccine may have a first introduction in an RLC but with limited or no use in other countries (or a limited number of countries). Another scenario would be a global introduction in which many countries are introducing the vaccine at the same time. In the various scenarios, the nature and types of gaps in knowledge might be very similar. However, contextually, they might need to be assessed in a different way. If a number of introductions are going on in similar time frames, the gaps themselves could be answered in a variety of ways. The various countries involved could certainly work together to determine the best way to close the gaps, and could certainly share studies and approaches, limiting duplication of effort and using resources in the most efficient manner. The central convening power of WHO is important in these scenarios to ensure that these studies are well coordinated and data shared in real time in order to avoid duplication and promote collaboration.

The remaining examples of potential gaps are more specific in scope. Generally they pertain to vaccines with more extensive post authorization usage (and thus available safety data). Generally, they represent potential gaps that are specific to situations that might occur in an RLC, and are related to issues specific to the usage or situation in these countries.

2.3.1.2. Changes/differences in the vaccine product

Issues may include a new formulation or vaccine antigen serotype or the use of a new or different adjuvant. For instance, a vaccine may have a long history of use in single dose vials, or pre-filled syringes. However, in order to expand vaccination into a larger population, the vaccine may be reformulated to be provided in multi-dose vials. In this case, not only would the vaccine product be reformulated, but the usage pattern (repeated insertions of a needle into a single vial) would change. After evaluating the clinical data supporting the change in formulation, a stakeholder could determine that further study might be warranted in order to ensure these new usage patterns lead to no new safety concerns.

2.3.2. Related to the population

2.3.2.1. Related to the target population

Underlying conditions that are especially prevalent in the target population may be of importance for safety, e.g. sickle cell disease, G6PD deficiency, human immunodeficiency virus (HIV), tuberculosis (TB), malaria, malnutrition or the vulnerability in the population, (e.g., neonates, adolescents, pregnant women, breast-feeding women, geriatric individuals). This is of particular importance if the majority of safety data has been gathered in regions/populations with lower prevalence of these comorbidities/ vulnerable conditions, or if these populations have not been studied during the clinical development program. Thus, while a vaccine may have been used by millions of patients prior to introduction in an RLC, there may still be a gap to be considered if there are not a large number of previously exposed patients with these conditions.

Also, differences in ethnic makeup in the population being targeted in the RLC could be important to consider. Genetic baseline differences in population vulnerability or response will be important factors to inform the successful introduction of a vaccine and related safety surveillance. Again, it may certainly be the case that even though a vaccine has many years and millions of exposures in other settings, there could still be particular populations that do not have significant history of use. For instance, both measles, mumps, and rubella (MMR) and influenza vaccines have been used extensively in pregnant women in many RLCs. However, there is often little clinical or even post - marketing experience in a controlled setting on such use. The real-world safety of these products in these subpopulations in RLC therefore might remain undocumented.

2.3.2.2. Different age groups being targeted

For various reasons, a vaccine may be introduced into an RLC in which patients receiving vaccines may have slightly different age ranges than previous usage. For instance, the disease may be more common in a wider range age band than where it has been previously used. Therefore, a medical decision may be reached that the vaccine will be given to a larger range of patients than previously exposed. For instance, a vaccine may be administered to children up to age 5, instead of just 0 to 2 year olds, due to high disease rates and lack of herd immunity. Another scenario would be vaccinating children at younger ages compared with the experience in other countries: for example, a measles vaccine usually given at 9 months of age, was given to children from 6 months of age due to outbreak conditions. Again, this could represent an important gap related to possible vaccine reactions at different stages of life.

2.3.3. Related to the target disease, or differences in local serotypes, mutations, or virulence factors

While many of these aspects may have a bigger effect on the potential effectiveness of the vaccine when used in a new setting, there are potential safety issues that could arise if the target disease has significant differences in the country of introduction. And, of course, a change in benefit could affect the overall benefit-risk profile of the product, which could lead to the need to ensure the safety profile is understood in this particular setting.

Also, the vaccine itself may be changed based on local differences in the target vaccine preventable disease (or changes in the disease over time). For instance, influenza strains change on a yearly basis, and along with the strain changes, the vaccine is updated. These changes could warrant the need for some additional postmarketing surveillance, depending upon the nature of the change. Similar changes could occur based on local disease epidemiology. For instance, it is possible that a multi-serotype pneumococcal vaccine could be modified to add a serotype specific to an RLC/region, or have a serotype not found in that region to be removed. Again, such change could warrant consideration of additional pharmacovigilance or other additional study.

2.3.4. Related to the use of the vaccine

2.3.4.1. Change in the use of the vaccine

This could regard the dosing schedule or regimen, or dose of the vaccine to be used. For various reasons, the dosing schedule for a well established vaccine might be altered for introduction in a new country (for instance, to match a general vaccination initiative or national immunization schedules). Or a more abbreviated or accelerated vaccination schedule may be used for the first time. For instance, in the past, many countries have chosen to provide pneumococcal vaccination on a two dose (plus booster) regimen, rather than a three dose (plus booster) regimen. This type of change in vaccination schedule, especially if there is limited experience, *may* warrant the need for additional pharmacovigilance activities, either passive or active.

2.3.4.2. Concomitant vaccine or other medication with the present vaccine

The consideration of other products that are being used by the populations receiving a vaccine at rollout can be very important to consider. For example, some countries give medicines for intermittent prevention of malaria in infants or pregnant women or give zinc and vitamin A to infants as part of the Expanded Programme on Immunization (EPI). These can impact the reactogenicity of a new vaccine being introduced. Often, the types of vaccines (and pharmaceuticals) used in RLCs may differ from the countries where the greatest experience in use of a particular vaccine exists. This may be related to disease patterns requiring different vaccinations or different schedules, leading to different vaccines being given concomitantly. It may also be due to delivery systems that may cause vaccines that may not otherwise be given together in developed settings, to be given together as part of a mass campaign.

For instance, stakeholders may be considering the use of a live, attenuated rotavirus vaccine in their country, which also administers oral poliovirus vaccine. When they explore this concern, they could come to realize that the vast majority of countries using the rotavirus vaccine also use inactivated polio vaccine. This lack of experience with concomitant administration could require additional pharmacovigilance if no data are available.

2.3.4.3. Related to the health care setting

If the vaccine is being given in a setting that differs significantly from the previous settings upon which the safety profile is based, additional surveillance may be considered. For example, the majority of

administrations of a vaccine may have been given by physicians in a medical office. This may allow for specific monitoring, and availability of medical facilities in the event of adverse events, including expected events (such as syncope with HPV vaccine). If the same vaccine were to be given to lower level health care workers in community settings, there would be an obvious need for additional monitoring to ensure safety of vaccinees.

In the context of vaccines introduction in many RLCs, the vaccine providers could differ significantly. The vaccine may not be given by a fully-trained health care professional (HCP) or may be given by lower level health care workers trained to administer vaccines. Usually, such workers are given extensive training. However, even with appropriate training, the vaccine provider may usually provide vaccination in a setting outside of a health care facility. While this may require additional training/resource availability, it could certainly require additional pharmacovigilance to understand the potential implications.

2.3.4.4. Is the vaccination initiative part of a mass vaccination campaign?

If the vaccine is being introduced for the first time in an RLC, and is being done so through a mass vaccination program, this could increase the need to consider either passive or active surveillance. If there are open questions or knowledge gaps, the provision of vaccination within a mass campaign can magnify the issues. If there is a realistic possibility of a safety issue arising, the large number of exposures during a mass vaccination campaign could increase the potential impact. In such a setting, it would be particularly important to consider systems to rapidly identify any emerging issues and concerns, and this could include AVSS, especially if the passive surveillance system is limited. At the same time, a formal mass vaccine campaign may actually allow for effective active surveillance since good quality data can be collected quickly and efficiently.

2.3.5 Examples of significant knowledge gaps: conclusion

The above examples of the types of gaps/issues that could lead an RLC to consider additional surveillance, whether passive or active, are by no means exhaustive. They are meant to illustrate some of the more common types of gaps that have been previously encountered, or that are important theoretical concerns and issues. Sometimes, the gaps could simply be community concerns based on rumours or single cases in which proper communication and advocacy may be more powerful and useful tools than AVSS. Before proceeding, stakeholders should both confirm that the SKG exists, and carefully consider which tools will most effectively meet their needs.

2.4 Confirm that the significant knowledge gap exists

Once a potential SKG is identified, it is very important that the gap is confirmed. That is, all available data must be reviewed to confirm that there is insufficient information available to answer the concern. The first step is to review all available data for the vaccine in a systematic manner. In order to assist the stakeholder in ensuring they have reviewed the key data generally available, the WG has developed a new tool, the Essential Vaccine Information (EVI) source list. This tool is described in detail in Appendix I. It will guide the reviewer to systematically review existing data to evaluate whether or not information is already available to answer their open questions.

Even after the EVI process has been completed, it may be necessary to pursue other sources of information to confirm the existence of an important SKG. These may include:

1. reaching out to relevant experts in the field who may have insight into the issue;

2. checking with other RLCs to confirm whether they have faced a similar gap, how it was closed, and even if they have initiated AVSS or other pharmacovigilance tools;
3. discussing with the vaccine manufacturer/MAH to confirm that they are not aware of any additional data that may be relevant to the potential gap; and/or
4. searching thoroughly through the literature for relevant published data.

Once the stakeholder is confident that they have performed their due diligence and a true significant knowledge gap exists, they should proceed to determine which pharmacovigilance tool is most appropriate to close the SKG.

2.5 Can the significant knowledge gap be closed with passive surveillance?

2.5.1 Approaches for performing post-marketing pharmacovigilance

Addressing vaccine safety concerns requires considering the nature of a health event, best way to monitor it, and capability of stakeholders to evaluate a new safety concern. Depending on the stage at which a vaccine product and new safety concerns have been defined, different tools should be considered. The table below includes various methods of post-marketing surveillance, including passive and active safety surveillance methods.

Table 2. Approaches for performing post-marketing pharmacovigilance

	I. Passive safety surveillance	II. Active safety surveillance (non-interventional) Guide to AVSS	III. Active safety surveillance (interventional)
Setting/ approach	Spontaneous reporting Stimulated reporting/ enhanced passive surveillance (e.g. by online reporting, systematic stimulation, additional training.) Sentinel sites for passive surveillance	Active case finding Registries Large linked databases Vaccine/prescription event monitoring	Interventional study
Key design or analysis points	Various forms of AEFI analysis, including: ▶ Case series reviews ▶ Causality assessment ▶ Disproportionality analysis ▶ Data mining	Comparative observational study: ▶ Cross sectional ▶ Cohort ▶ Case-control ▶ Case only study	May be: ▶ Controlled or uncontrolled ▶ Blinded or unblinded ▶ Randomized or non-randomized

The table provides a general categorization of the setting/approach and design points for three types of safety surveillance. The Guide to AVSS is focused on Column II concerning active but non-interventional vaccine safety surveillance. Please note that in real-life situations some surveillance programs could be a hybrid (e.g. see Case study 1).

Column I gives examples of passive pharmacovigilance activities that could be needed for a particular vaccine in a particular geographical context, including resource-limited countries. Passive surveillance approaches are described in a global manual for safety surveillance of vaccines published by WHO in 2014.[19] Detailed information on vaccine pharmacovigilance methods may also be obtained from the Vaccine Pharmacovigilance Toolkit (www.vaccinepvtoolkit.org). However, a short overview of the types of passive surveillance tools available and how they might be most appropriate, is included in this chapter. Please note that passive safety surveillance is considered part of the public health system and not considered "research" – whereas active safety surveillance is considered research involving humans for the purposes of ethics committee approvals (see discussion in Chapter 4).

Column II of Table 2 displays various possible approaches to active vaccine safety surveillance when non-interventional in nature. The remainder of the Guide to AVSS (Chapters 3 and 4) focuses on methods and implementation considerations.

Column III of Table 2 covers approaches and design points for active safety surveillance when it is interventional in nature or an experimental study, which is not detailed in this report (also see section §2.5.3 below concerning this).

2.5.2 A brief overview of passive surveillance and its usefulness for closing a SKG

This section will review several types of passive safety surveillance and the type of information each can generate. It is important to select the appropriate type of surveillance to address areas of missing information. While active vaccine safety surveillance is the subject of this manual and a very powerful tool, it is not always most appropriate. In general, the least resource-intensive approach which can address the information gap is likely the most appropriate. Passive safety surveillance is sufficient to address most gaps and is employed far more often than active surveillance.

Passive safety surveillance implies that no active measures are taken to search for adverse effects other than voluntary, spontaneous reports on safety concerns from health professionals and others. Passive safety surveillance is the standard and often sole resource for pharmacovigilance in many countries.

2.5.2.1. Spontaneous reporting

Pharmacovigilance using a spontaneous reporting system is a first line system designed to detect AEFIs, particularly those that are serious or were not previously observed in pre-licensure or clinical studies. The purpose is to detect signals that may generate hypotheses for possibly causally related AEFIs that need to be assessed or investigated further.

The systems rely on health professionals or the general public reporting any suspected AEFIs in connection with vaccine exposure. This system is simple, relatively inexpensive, and does not limit the population from which reports are accepted. Because of the broad pool of reporters, it offers the potential for detecting rare events. Using a passive surveillance system, a case series can be assembled to detect patterns and possible associations between a vaccine and an adverse event.

[19] WHO. Global manual, *op. cit.*

In some situations, spontaneous reporting may be used to close gaps and may be the only surveillance needed or feasible. This would be particularly true if a vaccine has been used in multiple countries with robust vaccine pharmacovigilance or over a long period of time and has a well-known safety profile with few serious adverse events. For example, injectable polio vaccine has been given in hundreds of millions of doses and typically causes only mild injection site reactions.

Limitations of spontaneous reporting include under-reporting, missing data, and the potential for reporter bias. Despite these issues, spontaneous reporting would likely provide for adequate pharmacovigilance for many vaccines.

2.5.2.2. Stimulated spontaneous reporting

Several approaches have been used to encourage and facilitate reporting in specific situations (e.g. for new products and for limited time periods). Such methods could include publicizing the need to report AEFIs to the public (either generally or specific ally concerning the AEFI of interest) or providing information on what and how to report at the time of vaccination. For example, stimulation via a public information campaign could be used to increase reporting during a mass vaccination campaign. It could also include systematic stimulation of reporting and frequent reminders to vaccine administrators based on a pre-designed case definition for an outcome of interest (e.g. viscerotropic disease after yellow fever vaccine or flaccid paralysis after oral polio vaccine). The stimulation strategy can be tailored to focus on the AEFIs of interest. For example, if reports of small for gestational age infants are of interest, efforts to stimulate reporting could be focused on hospitals and providers who deliver and care for newborns. Although these methods have been shown to improve reporting, they are probably most effective for gathering information during a specific time period (e.g. following the introduction of a new vaccine or a mass vaccination campaign).

2.5.2.3. Sentinel sites

In some instances, it may be useful to limit stimulated passive reporting to a few sites. This could reduce the amount of data gathered and allow a more focused effort to increase reporting in the sentinel sites. An advantage of this approach is that the number of sites can be selected based on available resources and that the focused efforts at increasing reporting may be more effective. It is important to select the sites so that the population of the sentinel sites is representative of the general population to be vaccinated (to reduce the risk of selection bias).

2.5.2.4. Methods to enhance passive surveillance

Any intervention that increases the likelihood that more reports will be submitted via a passive surveillance system could be considered an "enhancement." Thus, stimulated reporting and sentinel sites as described above are forms of "enhanced passive surveillance." The primary method is to sensitize vaccinees or guardians to identify and report AEFIs or any other unusual event at the time of vaccination. There are a variety of specific methods by which reporting can be enhanced. The following section provides some specific examples.

Telephone or online reporting

Submission of AEFI reports via telephone or online reporting can be a convenient way for patients and providers to submit information. This also allows the structuring of the collected information, which should increase the quality and quantity of the collected information. The telephone "hotline" or website can be provided to patients and providers during immunization campaigns as well as advertised in different forms (print, public service announcements on broadcast media). While feasibility of online reporting depends on internet access, the increasing use of smartphones in many countries can make this a practical and inexpensive method.

Online reporting should also facilitate analysis of AEFI data, as large numbers of reports can be compiled and examined for patterns.

Systematic stimulation

It is possible, via publications, email reminders, letters, or personal visits to stimulate reporting over an entire area. The effect on increasing reporting will likely diminish with time, so this method is probably best used for a limited time, such as following the introduction of a new vaccine in a mass vaccination campaign.

One example of systematic stimulation was during the introduction of meningococcal A conjugate vaccine in Burkina Faso.[20] In this case, the ministry of health developed a field guide, case definitions, a case notification form, and an investigation form for serious cases. Additional training, updated AEFI monitoring guidelines, and reminders about AEFI reporting were distributed, all designed to increase the number of reports and quantity of information gathered.

Additional training

Another approach to enhance passive reporting is to provide additional training to health care providers about suspected events and how to report suspected AEFIs. Brazil has used this approach to increase the reporting of viscerotropic disease after yellow fever vaccine. Viscerotropic disease is rare (0.11 – 0.31 cases/100,000 doses) but has a high mortality rate (92.3%). Brazil has stimulated the reporting of this particular event by distributing a manual on AEFIs for health professionals and a guideline for investigation of serious adverse events. At the time of yellow fever vaccination campaigns, a kit is sent to hospitals instructing how to collect and transport patient samples, increasing the likelihood any case of viscerotropic disease will be diagnosed and reported.[21] This approach may result in more reports and reports of better quality, but it is best used for a short period. The effect of any training likely decreases significantly with time.[22]

2.5.3 Confirming the right tool

As stated above, in most cases passive safety surveillance is sufficient to address an SKG. In general, AVSS will be used in those cases where it is not; however, it should be noted that in some rare cases neither passive nor active safety surveillance will be the appropriate tool. In some cases, only targeted clinical trials may be the right tool (see Table 2, right-hand column). While this is rarely necessary, if one determines that passive surveillance is not appropriate, this should be kept in mind while reviewing Chapters 3 and 4. AVSS may not necessarily be the right tool, even when passive surveillance is not adequate.

And finally, one must consider the possibility that no tool (not even active interventional safety surveillance) is capable of closing certain significant knowledge gaps. Some questions are simply not amenable to gathering additional data, and this possibility must also be considered before embarking on an AVSS program.

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20 Ouandaogo CR et al, *op. cit.*

21 Menezes Martins R, Lourdes de S. Maia M, Matos dos Santos E, *et al.* Yellow Fever Vaccine Post-Marketing Surveillance in Brazil. *Procedia in Vaccinology* 2(2010)178-83.

22 Mansouri M, Lockyer J. A meta-analysis of continuing medical education effectiveness. J Contin Educ Health Prof. 2007 Winter; 27(1):6-15.

2.6 Conclusion

A structured approach is essential for a systematic review of available safety data and identification of potential knowledge gaps. In this chapter, a number of potential types of significant knowledge gaps have been introduced to assist the enduser. These examples are not exhaustive; stakeholders will need to review the particular situation of their vaccine introduction to identify key gaps that may exist, paying attention to gaps that have the highest potential to alter the benefit-risk profile, generate substantial public concern for a vaccination programme, and/or relate to vulnerable populations not studied during the vaccine development process (e.g. pregnant or breast feeding women, older vaccine recipients). In order to help confirm a potential gap identified, the Essential Vaccine Information (EVI) source list has been developed (see Appendix I). After using the EVI, and exhausting other sources of data, if an SKG is confirmed to exist, the stakeholder should carefully consider whether passive safety surveillance is sufficient to address the gaps or if another tool might be appropriate. If it is determined that AVSS should be pursued, one should proceed to Chapters 3 and 4 to consider the right type of AVSS, and consider implementation issues.

CHAPTER 3:

ACTIVE VACCINE SAFETY SURVEILLANCE – PRINCIPLES AND METHODS

The purpose of this chapter is to present principles, steps, and approaches to establish AVSS systems, with special reference to RLCs, when passive surveillance is not adequate. When stakeholders in an RLC have decided to launch an AVSS study for a particular vaccine and setting, a design needs to be determined that can achieve the stated objectives. Selection of an appropriate study design is therefore essential.

3.1. Definition and objective of active vaccine safety surveillance

AVSS is a data collection system that seeks to ascertain as completely as possible the number of AEFIs in a given population via a continuous organized process.[23, 24] In active surveillance systems, the surveillance centre (e.g. health department, NRA, or other responsible entity) initiates and maintains regular contact with health care providers or other relevant reporting sources (e.g. hospitals or laboratories) to identify cases of the health condition(s) of interest.

Traditionally, active surveillance systems have been based largely on individual reports solicited from participating clinics, hospitals, or laboratories. With the advent of computerized health records systems, cases of interest can also be ascertained by systematic searches of the computerized databases.

Ideally, AVSS should be population-based, encompassing a known surveillance area with a well-defined population. Unlike passive surveillance, AVSS does not suffer from under-reporting and can be used to accurately estimate rates if the size of the population is known.

In AVSS, information is collected with defined objectives to investigate one or several adverse effects, including predefined events. The hypothesis of a link between a vaccine and an AEFI may have emanated from passive safety surveillance or other well-grounded concerns.

AVSS can also be carried out to complement passive safety surveillance, but with a specific objective. Typically, this is to monitor targeted AEFIs, often denoted as adverse events of special interest (AESIs) for a specified time period. AVSS is generally not designed to identify

[23] Crawford NW, Clothier H, Hodgson K, Selvaraj G, Easton ML, Buttery JP. (2014) Active surveillance for adverse events following immunization, Expert Review of Vaccines, 13:2, 265-276, DOI: 10.1586/14760584.2014.866895. http://dx.doi.org/10.1586/14760584.2014.866895

[24] Davis RL, Kolczak M, Lewis E, Nordin J, Goodman M, Shay DK et al. Active surveillance of vaccine safety: a system to detect early signs of adverse events. Epidemiology. 2005;16(3): 336–341.

unexpected or unknown AEFIs (signal generation) since the number of patients followed up in AVSS may not be sufficient to provide the statistical power needed to identify rare events. For example, an AVSS involving 30,000 patients can only identify events that occur at or more frequently than 1 in 10,000 (know as the "rule of 3").[25]

A primary aim of AVSS systems is to estimate the risk of an AEFI in a population exposed to a vaccine. To evaluate if a vaccine increases the risk of a particular AE requires determination of relative risks. Usually, relative risk estimation involves the comparison with background rates of such events in the underlying population or rates in a comparison cohort, although other methods are available to estimate relative risks, as detailed below.

Estimation of risk, or incidence rates, requires data on the number of exposed individuals in a defined cohort (denominator) and on the subset of these who present an AEFI or condition of interest over a defined time period (numerator). Whilst denominators may come from aggregated population-level data, the numerator requires the ascertainment of all exposed individuals presenting the event of interest through direct follow-up, review of health records, or use of clinical information in databases when available.[26,27] Different AVSS approaches, data requirements and methodologies are described below.

3.2. Type of data needed for establishing active safety surveillance systems

Three main types of data are required for an active surveillance system of vaccine safety:

- Vaccination data for individuals in vaccinated cohorts;
- Health events or outcomes, i.e. adverse events following immunization (AEFIs) or adverse events of special interest (AESIs); and
- Demographic and background information on age, gender, domicile, and on relevant background medical factors, ideally available for both vaccinated and unvaccinated cohorts.

Generally, these data would need to be complete and representative of the studied populations/cohorts. The types and quality of the information collected from the sources will determine what methodological approaches can be employed.

3.2.1. Vaccination data

Specific aspects of vaccines to be considered in pharmacovigilance and pharmacoepidemiology have been highlighted in several documents. The report of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance (2012) emphasizes that characteristics of the vaccine and the vaccinated population, settings and circumstances of vaccine administration, and data analysis are issues worthy of special attention in vaccine safety monitoring.[28]

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25 Hanley JA, Lippman-Hand A . If nothing goes wrong, is everything alright? (For the rule of 3 reference.) JAMA 1983; 259: 1743–1745.

26 London School of Hygiene and Tropical Medicine. The use of epidemiological tools in conflict-affected populations: open–access educational resources for policy-makers (conflict.lshtm.ac.uk).

27 World Health Organization. Global Vaccine Safety Blueprint Geneva, 2012, Glossary, (www.who.int/vaccines-documents).

28 CIOMS. Vaccine Pharmacovigilance, *op. cit.*

Complete, reliable and unbiased data on vaccinations in a defined population is essential for epidemiologic evaluations of associations between specific vaccines and specific AEFIs. Such data is unfortunately often not available in certain RLCs. Global efforts should be made to develop tools to capture such information in all RLCs, preferably in electronic format for easy extraction and use. Thus, an AVSS system would benefit from access to readily-retrievable, documented data on every individual vaccinated concerning:

- Individual identifier
- Place of vaccination
- Vaccine type
- Vaccine presentation, single or multiple dose
- Manufacturer
- Lot number (of vaccine and any dilutents)
- Date of vaccination (and perhaps time)
- Vaccine injection site
- Number of dose

Ideally, vaccination data for exposed individuals should be maintained in a computerized database or registry. Admittedly, this may be difficult in an RLC as there is usually no software or tool for such activities. Even if these tools exist, there may not be adequate numbers of trained personnel to utilize them. However, even simple computer spreadsheets like Microsoft Excel may suffice for smaller data sets and not require a large database and associated software. Stakeholders should however consider the long-term cost effectiveness of encouraging the use of larger databases in RLCs. In the face of new vaccines being deployed, the higher costs associated with these databases and software may be obviated by their ability to yield required information quickly and efficiently without the need for laborious data collection each time a new vaccine is being introduced.

In some predominantly high-income countries, national or regional registries have been used *ad hoc* in connection with vaccination campaigns, for example, for vaccinations during the H1N1 pandemic in Europe (e.g. Sweden, Finland) or are used on a regular basis for vaccination programs (e.g. Sweden). Vaccination data may also be maintained by medical practices, health plans, clinics or hospitals. In the U.S., health plan or health insurance data provide the source of vaccination data for the two main vaccine safety active surveillance systems: 1) The Vaccine Safety Datalink (VSD) is a collaborative project between CDC's Immunization Safety Office and nine health care organizations. The VSD started in 1990 and continues today in order to monitor safety of vaccines and conduct studies about rare and serious adverse events following immunization; and 2) The Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to create an active surveillance system - the Sentinel System - to monitor the safety of FDA-regulated medical products. The work focused specifically on vaccines is known as the Post-licensure Rapid Immunization Safety Monitoring (PRISM) program.[29,30]

[29] Centers for Disease Control and Prevention (CDC). Immunization Safety Office, Vaccine Safety Datalink (VSD), http://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/.

[30] US Food and Drug Administration. Post-licensure Rapid Immunization Safety Monitoring (PRISM) system, http://www.mini-sentinel.org/work_products/PRISM/PRISM_Summary.pdf.

In reality it may not be feasible in some countries to establish and maintain immunization registry resources, whether computerized or paper-based. Alternatives may be considered such as:

- Data on the numbers of distributed vaccine doses could be maintained by the manufacturer, distributors/wholesalers (especially for use in private sector), a non-governmental organization (NGO), or the NRA, and include as much detail as possible, especially lot numbers. Such data could be used in epidemiological approaches using an observed-to-expected (O/E) outcome type of design. The main limitations would be that not all distributed doses are actually administered and also that there will be no data on the characteristics of vaccinated subjects (e.g. age).
- Individual vaccination cards, maintained by the person vaccinated or a parent of a vaccinated child. This approach could be useful for case-based studies (e.g. case-control or self-controlled case series studies). However, problems with lost cards or lack of participation, can be anticipated and can only be controlled if proper vaccination registries are also maintained.
- Immunization coverage surveys could provide data on the proportion of the population that is vaccinated with further coverage estimates in various demographic categories (e.g. sex and age) and different geographic regions. Unless everyone in a specific area is surveyed, sampling methods can be used to extrapolate the proportions into estimated number of people vaccinated. The survey approach could provide data for epidemiological O/E approaches, using background rates or in concurrent analyses of AEFI/AESI rates in vaccinated versus unvaccinated groups. Limitations of this approach include that they are time-consuming, expensive, and not likely to provide timely data unless the surveys are routinely conducted on an ongoing basis. Also, there may be recall bias if the surveys rely on self-reports.
- Self-reports could be used but only as a last resort due to potential problems with erroneous recall by the individual, introducing possible biases. If self-reports are used, efforts should be made to validate the self-reported data (e.g. medical chart review).

3.2.2. Health events/outcomes data

For information on health events or outcomes, the source of data to be used will depend on the type and severity of the health event (AEFI/AESI) of interest. Generally, serious events that require medical care would be better suited for AVSS, since the events have a greater chance of being recorded in medical institutions.

Ideally, the source of event data should contain information on all medical encounters by all individuals, independently of vaccination status. The source should be able to capture data from in-patient care hospital admissions, emergency departments, as well as outpatient/primary care clinics. The data should be readily retrievable (i.e. computerized) and ideally include:

- Patient identifier (to allow for linkage to other data)
- Place of care
- Diagnosis(es) (ideally standardized)
- Date (and time) of onset of first symptom of the event
- Other relevant medical information (e.g. clinical details and treatment outcomes)

In RLC settings, access to medical care may be limited and medical care settings may not provide complete ascertainment of the health event of interest. Even if data sources for the ascertainment of AEFIs/AESIs are deemed to be complete, the possibility for health-care seeking bias should be considered. Individuals being vaccinated could be more or less likely

to seek medical attention in the presence of symptoms. Further, they may have a different propensity to develop the event in question as compared with non-vaccinated individuals, due to pre-existing medical conditions (being healthier or less healthy).

The difficulty in ascertaining AEFI is illustrated by the following example of a project during a yellow fever vaccination campaign in several countries in Africa (See Case study 1). It used a combination of enhanced passive surveillance as well as a form of active vaccine safety surveillance (active case finding). Although extensive efforts were initiated to actively find cases of AEFI in multiple settings, underreporting remained a major limitation (e.g. substantially fewer serious AEFI than expected were recorded). Incomplete AEFI identification and investigation resulted from some cases not being identified, as deaths (for example) were assumed to be attributable to other causes (e.g. malaria) or not associated with vaccination (e.g. traffic accidents). The study also illustrates the importance of understanding local background rates of conditions of interest; they were lacking in this study and AEFI rates had to be compared to US and European rates, which may have been very different considering differences in the populations (e.g. pre-existing yellow fever immunity).

Organizers of immunization campaigns for new vaccines have to adapt to existing medical care infrastructures and availability of medical information. In some circumstances event data may be only available from hospitals, on paper logs or in computerized registries. In other situations there will be a need for individual follow-up through home visits. Focused examinations by trained examiners may be feasible for selected conditions/events. If self-reporting by patients is used, such events would have to be of a fairly general nature.

Other possibilities could be telephone follow-up calls (e.g. cell/smartphones, text messaging) or scheduled clinic follow-up visits. An established health and demographic surveillance sites (HDSS) could serve as a setting for safety surveillance.[31] Followup on individuals vaccinated would be better suited to detect specific AEFIs (a form of AVSS). In considering the important choices of source and approach (passive surveillance/enhanced passive surveillance/active safety surveillance), the costs and efforts should be weighed against the expected yield and quality of information that could be collected in the specific setting.

Case study 1: Enhanced passive surveillance/active case finding for AEFI in multi-country vaccination campaigns in Africa[32]

Issue: To assess the safety of yellow fever vaccine in mass vaccination campaigns in Africa.

Locations: Benin, Burkina Faso, Cameroon, Guinea, Liberia, Mali, Senegal, Sierra Leone, and Togo.

Data sources: Not reported.

Vaccine: Yellow fever vaccine.

Total vaccine doses administered was known.

Outcomes: All eight countries established enhanced passive surveillance/active case finding for AEFI in addition to the existing passive AEFI reporting system integrated into the Expanded Programme on Immunization.

Health workers were trained to identify any adverse events during the vaccination campaign, to complete case report forms, and to send forms weekly to the national level.

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31 Sankoh O, Byass P. The INDEPTH Network: filling vital gaps in global epidemiology. Int J Epidemiol. 2012 Jun;41(3):579-88. doi: 10.1093/ije/dys081. http://www.indepth-network.org/about-us/our-past-present-future.

32 Breugelmans JG, Lewis RF, Agbenu E, Veit O, Jackson D, Domingo C, et al. Adverse events following yellow fever preventive vaccination campaigns in eight African countries from 2007 to 2010. Vaccine 2013;31:1819-1829.

Case study 1: Enhanced passive surveillance/active case finding for AEFI in multi-country vaccination campaigns in Africa (continued)

Dedicated and trained staff identified potential cases in regional and national referral hospitals by means of daily review of hospital registries, medical charts and interviews with emergency room staff.

Population: Reported number of doses administered in each country.

Design: Enhanced passive surveillance/active case finding.

Methods: This project used enhanced passive surveillance/active case finding. All eight countries established enhanced case-finding for AEFI and included standard operating procedures (SOPs) for collection of biological specimens and a customized data entry tool for data management and analysis. A national expert committee (NEC) was created and convened by each ministry of health. Workers were trained to identify and report adverse events during the vaccination campaign, including passive surveillance in regional and national referral hospitals. Data were entered into country-specific databases.

Findings: Rates of AEFI (yellow fever vaccine associated viscerotropic disease and yellow fever vaccine associated neurologic disease) were much lower than in studies of US and European travellers.

Lessons: Initiated extensive efforts to actively find cases of AEFI in multiple settings.

The effort supported development of NECs and raised awareness of AEFIs in countries with limited pharmacovigilance experience.

Underreporting was a limitation (e.g. only 33 deaths within one month of vaccination were identified in the eight countries; however, many more were expected considering the countries mortality rates and the large population under study).

Importance of local background rates – AEFI rates had to be compared to US and European rates which may have very different populations (e.g. pre-existing yellow fever immunity).

Lack of individual data on immunization status – voluntary reporting and incomplete ascertainment of vaccination status of cases contributed to underestimates of AEFI rates.

Incomplete AEFI identification and investigation – in hospitals some cases were not investigated because doctors assumed that they were due to other causes (e.g. malaria) or not associated with vaccination (e.g. traffic accidents).

3.2.3. Population demographic data

Demographic information is important at both a population and individual level.

3.2.3.1. Population level

First, there is a need to define the population under surveillance that is at risk. Usually this population is based on administrative boundaries (i.e country, region, province, district) or the catchment area of a particular health care provider, assuming residents of the catchment area would seek care predominantly at a particular hospital or other local health care service. At a minimum, the total number of people or population in the particular surveillance system should be ascertained. Also, data on other demographic variables, especially gender and age should be obtained.

Sources of population data could emanate from:

- Census and vital statistics, as available, including births and deaths;
- Hospital or clinic patient reference populations (especially primary care), although these could be unrepresentative, particularly if health care utilization is low; and
- Special projects (e.g. health and demographic surveillance sites (HDSS)).

For safety monitoring, aggregate population-level data can be useful in epidemiological approaches using O/E analyses or ecological analyses (see below). Population-level data can also be used to estimate vaccination coverage and background rates.

3.2.3.2. Individual-level demographic and medical information

For more advanced epidemiologic study approaches, such as cohort studies, there is a need for individual-level demographic data. It may, however, be difficult to obtain demographic information on individuals, unless already available in a record system, for example, population registries or hospital or primary care clinic registries.

If available, it is often helpful to have health information on individuals in the population. In epidemiological studies, such as cohort or case-based studies, information on the health status of vaccinated and non-vaccinated individuals can help address possible biases. These biases can be due to selection on account of the indication for vaccination and pre-existing medical conditions. Health information may be available from health care registries in some countries, but in many situations it will have to be collected from the individuals within a particular study.

3.3. What methodological approaches can be used?

Overall, the analytical approaches that can be used depend on the types of data that are available on vaccinations, health events, and population demographic and medical characteristics. It is decisive for the choice of methodological approach whether these data are available on the individual or at a population (aggregate) level. Individual-level data tend to be richer and amenable to more advanced analytical designs, whereas population-level aggregate data are more restricted and subject to a greater degree of biases and confounding.

3.3.1. Individual-level linked data

If vaccination, health events, and demographic data are available for individuals, then a broad spectrum of epidemiologic study approaches is possible, including cohort, case-control, and case-only designs (Table 3). These data are summarized below with reference to how the different data sources apply to the various methodological designs. Many textbooks and tutorials are available on epidemiologic methods. For example, a free online tutorial called ActiveEpi Web is available from Emory University.[33]

[33] Kleinbaum, DG, Department of Epidemiology, Emory University, Atlanta, Ga USA, ActiveEpi Web, online course, 15 chapters, registration required, http://activepi.herokuapp.com.

Table 3. Possible study methods for individual-level data

Data Type			Methods
Vaccine	**Health Event**	**Population/ Demographic***	
Available	Available	Available	Cohort Case-control Self-control
Available	Available	Not available	Self-control
Available	Not available	+/- Available	none
Not available	+/- Available	+/- Available	none

*Available for both vaccinated and unvaccinated individuals

3.3.1.1. Cohort studies

Design features.

In a cohort study, a defined population-at-risk (the cohort) for the disease or event is followed over time for the occurrence of the disease or events of interest (AEFI/AESI). When individual data on vaccine exposed individuals, and data on unexposed subjects, together with their individual follow-up of events, are available, then comparative cohort studies can be performed. The necessary data for cohort studies can be time-consuming and laborious to collect, whether relying on existing health care databases or direct participant follow-up.

Information on vaccine exposure status is ascertained before start of follow-up and thus known throughout the follow-up period for each patient. In a comparative cohort study, a population unexposed to the vaccine is defined and followed in a similar manner. Enrolment of vaccinated subjects could be achieved through ad hoc registration at vaccination centres at one or several sites, or be obtained from vaccination registries in countries that offer such resources. The follow-up of AEFIs/AESIs could likewise be managed through vaccination centres by means of questionnaire or interview-based collection of event data, or when available from health registries.

The number of observed cases of a disease/event of interest (AEFIs/AESIs) is divided by the number of subjects in the populations at risk and time period of observation (person-years) to generate incidence rates as the direct measure of occurrence over a defined study period.

Methodological considerations for cohort studies.

Methodological requirements need to be carefully considered before planning a cohort study, especially in relation to circumstances in RLCs. For a cohort study to be meaningful and effective, that is to be able to detect a change in the risk at a pre-specified level, the cohorts need to have sufficient numbers of subjects enrolled. For rare events, the necessary cohort sample sizes can be substantial and demanding. The follow-up of vaccine exposed and non-exposed subjects need to be as complete as possible for all studied events, and the degree of completeness should be similar in the exposed and non-exposed cohorts. Further, well-conducted cohort studies would need to collect data on other characteristics of the study participants. Data on age, gender and socioeconomic features would be useful for analyses of risk in subgroups of participants in a vaccination programme. These factors and data on medical background factors need to be evaluated in order to address the problems of selection bias and confounding in the risk estimates.

Automated databases

The identification of large numbers of patients for cohort studies could be facilitated if data can be derived from large automated databases. There are several automated databases available for pharmacoepidemiological studies.[34] They contain automated medical records or automated accounting/billing systems. Case study 2 provides an example of a study using a large linked database system for active surveillance in an RLC. The study was aided by an existing infrastructure that included data from a pre-existing census and a well-defined population. Coding and transcription of medical diagnoses had been in place before the study started. The surveillance system provides all necessary data to conduct active surveillance and can serve as an infrastructure to address many immunization safety issues, as well as other issues (e.g. vaccine coverage and effectiveness). Census, coding, and community participation may be costly and time-consuming activities. An active surveillance system that can serve a variety of public health purposes, including vaccine safety monitoring, may be more likely to obtain support from public health agencies and other policy makers.

Case study 2: A large linked database approach for active surveillance in Viet Nam[35]

Issue: To monitor adverse events during a measles mass vaccination campaign. There were concerns that measles immunizations, administered to children across a broad age range of 9 months to 10 years, irrespective of earlier measles immunization status, might trigger adverse events.

Location: Vietnam

Data sources: All vaccinations and vaccine lots used were recorded on an individual vaccination card and in a logbook which were stored at the vaccination centre.

Vaccine: Measles vaccine

Outcomes: All admissions of subjects within the vaccinated age group to polyclinics, district hospitals or the provincial hospital were recorded by the surveillance system.

Population: A dynamic study cohort of children under 15 years of age was assembled based on a census conducted in 2002. Records of births during the study period were collected monthly and used to update the population database. Emigrations and deaths of cohort members were recorded during quarterly visits to the community.

Design: Self-control design for safety assessment (cohort design for vaccine coverage).

Methods: The study was conducted in two provinces in Vietnam. A dynamic relational database was used, containing data on population, vaccination history and medical events. The Commune Health Centre (CHC) system was the primary source of data. Routine vaccinations were usually administered at CHC. The data were linked through a unique identification number assigned to each individual in the study area. An interactive system was designed to enter data collected from health care providers. All medical encounter diagnoses were coded by a trained team of physicians according to ICD-10 guidelines.[36] The project staff visited the vaccination centres every month to record vaccination information (i.e. patient identifiers, vaccine types, vaccination dates and vaccine lots used). Self-controlled case series (SCCS) analysis was performed for the most frequent medical events comparing rates during the 14 days after vaccination with a pre-vaccination period. (In addition to relative rates of AEFIs, vaccine coverage was calculated using a cohort design based on the vaccination and population denominator data.)

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34 Strom, B. L. (2012) Overview of Automated Databases in Pharmacoepidemiology, in Pharmacoepidemiology, Fifth Edition (eds B. L. Strom, S. E. Kimmel and S. Hennessy), Wiley-Blackwell, Oxford, UK.

35 Ali M et al. The use of a computerized database to monitor vaccine safety in Viet Nam. Bulletin of the World Health Organization 2005;83:604-610. http://www.who.int/bulletin/volumes/83/8/604.pdf.

36 International Statistical Classification of Diseases and Related Health Problems 10th Revision World Health Organization. II.ICD-10. Fifth edition, 2016. ISBN 978 92 4 154916 5 http://apps.who.int/classifications/icd10/browse/2010/en.

Case study 2: A large linked database approach for active surveillance in Viet Nam (continued)

Findings: No increased risk was found for any of the medical events evaluated.

Lessons learned: This study demonstrates the feasibility of establishing a large linked database system for active surveillance in an RLC setting. The surveillance system provides all necessary data to conduct active surveillance and can serve as an infrastructure to address many immunization safety issues, as well as other issues (e.g. vaccine coverage and effectiveness). An active surveillance system that can serve a variety of public health purposes, including vaccine safety monitoring, affords considerable efficiencies and can leverage public health resources and support. The study was aided by an existing infrastructure that included data from a pre-existing census and a well-defined population. Coding and transcription of medical diagnoses had been in place before the study started. Census, coding and community participation may be costly and time-consuming activities which could complicate the establishment of surveillance networks in other areas.

Sentinel sites

Active safety surveillance can be achieved by using medical records or interview data on patients collected through specially established surveillance areas or centres, so-called sentinel sites. As a strength, such sentinel sites could be organized to ensure complete and accurate data on reported AEFIs/AESIs, from specific patient subgroups. Further, information on the use of a drug/vaccine can be targeted. Where the sentinel site is part of the routine district health system, it is possible to have detailed longitudinal data on patients so as to undertake various types of studies and perform different analyses (as is the case for some INDEPTH Network sites).[37] Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs. AVSS through sentinel sites could be efficient for vaccines since they are prescribed and administered in special settings, such as vaccination centres where an infrastructure for dedicated reporting can be created.

In RLC settings, established health and demographic surveillance sites (HDSS) sites may be considered to serve as regional sentinel sites, particularly in areas that lack administrative data on the population.[38] An example of conducting cohort-based active surveillance in an HDSS setting is provided by a study in Ethiopia (see Case study 3). The study illustrates the use of data on immunization history linked to data on health events ascertained from home visits, clinic visits, hospital admissions and demographic observations of mortality using a common individual ID number assigned to all HDSS residents. As may be often required for active monitoring or follow-up of individuals, informed consent was obtained (see Chapter 4 for more information). Utilization of health care was limited, requiring ascertainment of health events of interest through structured interviews by trained study personnel at home visits. The study utilized verbal autopsies to determine general causes of death.[39] HDSSs exist in several RLC countries, particularly in Africa and Asia, and provide a potential existing infrastructure to serve as sentinel sites for conducting active surveillance of AEFIs. HDSSs are most suitable for locations that lack reliable population-based data; however, establishing and maintaining an HDSS is resource and labour intensive. The population size of an HDSS also may not be large enough to study rare conditions. Ethical or equity issues may also be raised, particularly if an

[37] Sankoh, INDEPTH, *op. cit.*

[38] Pronyk PM, Kahn K, Tollman SM. Using health and demographic surveillance to understand the burden of disease in populations: the case of tuberculosis in rural South Africa. Scand J Public Health Suppl. 2007 Aug;69:45-51.

[39] Mpimbaza A, Filler S, Katureebe A, et al. Verbal Autopsy: Evaluation of Methods to Certify Causes of Death in Uganda. PLoS One 2015Jun18;10(6):e0128801.

HDSS site has access to special health care and other services that are not available to the population in general. Consideration should be given to having adequate capacity or adequate referral procedures to higher level health care facilities to treat AEFI/AESI.

Case study 3: A cohort study utilizing health and demographic surveillance sites (HDSS) in Ethiopia[40]

Issue: To monitor AEFI comparing the rate of injection-site abscess following pneumococcal conjugate vaccine (PCV-10) and the pentavalent vaccine (DTP-HepB-Hib).

Location: Ethiopia

Datasources: Vaccination cards that specified type of vaccine and site of injection plus vaccine registration books maintained at vaccination centres.

Vaccine: Pneumococcal conjugate vaccine (PCV-10) and the pentavalent vaccine (DTP-HepB-Hib).

Outcomes: Household-based surveillance – at 48 hours and 7 days after vaccination by trained interviewers using uniform follow up visit form. Hospital-based surveillance – study personnel visited health care facilities weekly.

Population: House-to-house survey in all the study sites enumerated eligible study population. Photo ID with unique identification number was issued to mothers of eligible infants.

Design: Cohort study

Methods: The study was conducted in existing HDSSs in Ethiopia. Household population records are updated annually. Data on vaccines received and AEFI were collected systematically and prospectively at vaccination centres, households, and clinics/hospitals. Verbal autopsies were conducted for any deaths identified. Unique identification number allowed linkage between data sources. Informed consent was obtained.

Findings: No significant differences were observed.

Lessons: The study illustrates the use of data on immunization history linked to data on health events ascertained from home visits, clinic visits, hospital admissions, and demographic observations of mortality using the common individual ID number assigned to all HDSS residents.

Overall considerations

In summary, cohort studies are robust methods for AVSS of vaccines. They allow generating actual incidence rates of vaccine adverse events, in addition to absolute risk (AR) and relative risk estimates (RR). Further, multiple AEFIs/AESIs can be investigated using the same cohorts. However, cohort studies are demanding in terms of logistics and may require large sample sizes, especially for rare/serious events. In these cases, it may be difficult to enrol sufficient numbers of vaccine exposed patients. Countries and regions should therefore consider joint studies with identical designs so as to pool the data for increased statistical power. This will ensure timely completion of the project and promote cooperation and efficiency.

40 Berhane Y, Worku A, Demissie M, Tesfaye N, Asefa N, Aniemaw W, et al. Children who received pcv-10 vaccine from a two-dose vial without preservative are not more likely to develop injection site abscess compared with those who received pentavalent (DPT-HepB-Hib) vaccine: A longitudinal multi-site study. PLOS ONE 2014;9(6): e97376. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0097376.

3.3.1.2. Case-control studies

Design

Detailed description of the case-control methodology can be found in various guidance documents.[41] In a case-control study, cases with a disease or experienced event (AEFIs/AESIs) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio (OR), which is an estimate of the relative risk (RR) of disease in the two groups (if the disease is not common).

Methodological considerations

Depending on the condition of interest, identifying a sufficient and representative number of case subjects and collecting needed data from medical records or by interviewing can be laborious and time-consuming. The availability of large population-based databases is especially useful to provide efficient means for identifying a sufficient number of cases and determining their vaccine exposure and medical outcome data in a relatively short period of time.

Case-control studies are particularly valuable when investigating whether there is an association between a drug/vaccine and *one* specific rare and serious disease/adverse event, as well as to identify a number of other risk factors in addition to the vaccine. Data on both vaccine exposure and presence of risk factors need to be collected from cases and controls retrospectively, implying that accurate personal recall is necessary when interview data are used. Risk factors important to include concern other predisposing or triggering factors relevant for the outcome under study.

Selection bias, in addition to recall bias, and confounding due to underlying differences in health profiles and risk factors of case and control subjects, need to be addressed in the design (by matching) or the analyses (by statistical adjustment).

The major drawback of the case-control design is that only one AEFI/AESI can be examined for a particular vaccine, rendering this design less practical for AVSS. An example of a case-control study for AEFI monitoring, is a study conducted in Mexico and Brazil to evaluate the risk of intussusception following monovalent rotavirus vaccine (RV1) vaccination (see Case study 4). Although from relatively more advanced settings, the study illustrates the basic principles of conducting a case-control study. Use of hospital-based surveillance would be applicable only in settings where the particular AEFI (intussusception) would have come to medical attention. Matching controls to cases based on area of residence is a useful strategy which could be applied in settings without a well-enumerated population database or register from which to select controls. This type of study, however, is resource-intensive, requiring trained study personnel to conduct periodic monitoring and review of records at several hospitals.

Case study 4: A case-control study of a rare AEFI in Mexico and Brazil[42]

Issue: To assess the association of a newly introduced monovalent rotavirus vaccine (RV1) with intussusception.

Locations: Mexico and Brazil.

[41] Coggon D, Rose G, and Barker D. Epidemiology for the Uninitiated, Chapter 8: Case-control and cross sectional studies, 4th ed. http://www.bmj.com/about-bmj/resources-readers/publications/epidemiology-uninitiated.

[42] Patel MM, López-Collada VR, Bulhões MM, Oliveira LH, Márquez AB, et al. Intussusception Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil. N Engl J Med 2011;364:2283-92

Case study 4: A case-control study of a rare AEFI in Mexico and Brazil (continued)

Datasources: Review of vaccination cards and provider records plus parent interviews.

Vaccine: Monovalent rotavirus vaccine.

Outcomes: Hospital-based surveillance with review of clinical records by trained study personnel.

Population: The study was conducted in 53 hospitals in 7 states in Brazil and 16 hospitals in 10 states in Mexico.

Design: Case-control study (in addition to self-control case series).

Methods: Cases of intussusception were identified independently of their vaccination status through prospective enrolment at the participating hospitals. Informed consent was obtained. Controls were identified from the same population as the cases by matching on neighbourhood of residence. In addition to the case-control analysis, a self-controlled case series analysis was also performed.

Findings: A small increased risk of intussusception was found.

Lessons: Although not strictly from RLC settings, the study illustrates the basic principles of conducting a case-control study. Use of hospital-based surveillance would be applicable only in settings where the particular AEFI (intussusception in this case) would have come to medical attention. Matching controls to cases based on neighbourhood of residence is a useful strategy which could be applied in settings without a well-enumerated population database or register from which to select controls. This type of study could be relatively expensive as trained study personnel were employed to conduct periodic monitoring and review of records at several hospitals

Overall considerations

In summary, the case-control epidemiological design has a major disadvantage in that only one AEFI/AESI can be examined at a time. It is therefore not used much as a first line approach for AVSS. It should be considered to formally test the hypothesis of an association between the vaccination and a specific AEFI following detection of a strong and/or serious signal that has been generated through passive safety surveillance or some other surveillance process.

3.3.1.3. Self-control designs

In recent years, the development and adoption of self-control designs have expanded the capabilities of epidemiologic research on vaccine safety.[43, 44] Variations on self-control designs exist, but probably the best known is the self-controlled case-series (SCCS).[45]

Design, methodology

These types of designs use a person as their own control by comparing the risk of a health event during a time period shortly following vaccination with other time windows before and/or after vaccination in the same individual. Thus, the self-control design implicitly adjusts for all factors that do not vary with time (e.g. sex, ethnicity, and genetics) even if they have not been measured in the study. Also, these designs allow for analyses in highly vaccinated populations

43 Farrington CP Relative Incidence Estimation from Case Series for Vaccine Safety Evaluation. Biometrics 51, 228-235. March, 1995.

44 Andrews N. Epidemiological designs for vaccine safety assessment: Methods and pitfalls. Volume 40, Issue 5, September 2012, Pages 389–392. doi:10.1016/j.biologicals.2011.08.010.

45 Weldeselassie YG, Whitaker HJ, Farrington CP. Use of the self-controlled case-series method in vaccine safety studies: Review and recommendations for best practice. Epidemiology and Infection. 2011 139:12 (1805-1817).

since time periods shortly after vaccination are being compared with other time periods, rather than relying on comparing risks in groups of vaccinated individuals with unvaccinated individuals (which may be few in some populations). Since these designs can be conducted using only vaccinated cases, they are efficient and feasible in settings in which data are not available on unvaccinated individuals. The design requires ascertainment of all (or a representative sample of) vaccinated cases during the study period.

Methodological considerations

The main limitation of self-controlled designs is they are methodologically appropriate only for relatively acute events (AEFIs/AESIs). For events that have a long and variable latency period for development, follow-up may be difficult and specification of an appropriate risk interval may not be possible. Another concern is the appropriateness of including pre-vaccination time periods within the comparison interval, especially if occurrence of the outcome of interest may affect likelihood of future vaccination (and bias the association between the vaccine and the event). Nevertheless, the SCCS method has been successfully used to assess several vaccine adverse effects.

An example of the self-control methodology applied in an RLC setting is provided by a study in Guatemala (See Case study 5). The use of a self-control methodology meant that data was only needed on vaccinated infants and an unvaccinated comparison group was not needed. The feasibility of ascertaining all AEFI through multi-source active follow up was demonstrated. Although the study recruited only parents with access to telephones, 95% of the population of Guatemala City owns a mobile phone and the methodology may be applicable in other RLC settings with relatively high mobile phone coverage.

Case study 5: Active vaccine safety surveillance using a self-control analysis in Guatemala[46]

Issue: To study the safety of DTwP-HepB-Hib combination vaccine.

Location: Guatemala

Datasource: Documented at study enrolment at two paediatric clinics.

Vaccine: DTwP-HepB-Hib combination vaccine.

Outcomes: Parents reported possible AEFIs.

Routine telephone contact with parents.

Reviewed medical records of any health care encounters.

Active daily monitoring of database of paediatric emergency room and hospital.

Population: Healthy infants who received study vaccine at well-child care visits at two paediatric clinics in Guatemala City. Parents accessible by telephone.

Design: Self-control case series.

46 Asturias EJ, Contreras-Roldan IL, Ram M, Garcia-Melgar JA, Morales-Oquendo B, Hartman K, et al. Post-authorization safety surveillance of a liquid pentavalent vaccine in Guatemalan children. Vaccine 2013; 31:5909-5914.

Case study 5: Active vaccine safety surveillance using a self-control analysis in Guatemala (continued)

Methods: Only vaccinated infants were studied to determine relative risk of AEFI occurring within 30 days of vaccination compared with days 31-60. Informed consent was obtained. Parents/guardians were asked to report any possibly serious symptoms to study physician or nurse. They were contacted by telephone at regular intervals to inquire about symptoms and health care visits. The research nurse completed AEFI form and reviewed medical records of health care visits. AEFIs were also captured through active daily monitoring at the paediatric emergency room and hospital using an electronic database (matched using unique identification number). Post-neonatal mortality rate was compared with the rate for the department of Guatemala (which is the jurisdiction in which the capital, Guatemala City is located), in 2008-2009.

Findings: The liquid pentavalent vaccine was not associated with increases in serious adverse events or hospitalizations.

Lessons: This was a comprehensive active surveillance system in an RLC country that could serve as a model for other countries. The use of a self-control methodology meant that data was only needed on vaccinated infants and an unvaccinated comparison group was not needed. The feasibility of ascertaining all AEFI through multi-source active follow up was demonstrated. Although the study recruited only parents with access to telephones, 95% of population of Guatemala City owns a mobile phone and the methodology may be applicable in other RLC settings with relatively high mobile phone coverage.

Overall considerations

In summary, a self-controlled case-based design provides a mechanism to monitor defined AEFIs and to evaluate in a timely and cost-effective way a vaccine safety signal. Since exposure and outcome data are only required on the vaccinated population, the self-controlled design could be considered for AVSS of acute AEFIs in the RLC setting in which unexposed population data would be difficult to obtain.

3.3.2. Aggregate data without individual-level linkage.

In the absence of individual-level data, summary or aggregate data on a population or group of patients may still provide useful information in monitoring vaccine safety. Even though aggregate data provide limited information, such data may be suitable for addressing specific information gaps in situations where it is not necessary or not feasible to implement a full AVSS system. Three types of aggregate summary data may be considered: the number of vaccinations, the number of health events, and population characteristics. These data may be available from separate sources. Aggregate data can be used in observed-to-expected (O/E) analyses and ecological analyses and to estimate background rates.

Observed-to-expected (O/E) analyses can be performed to estimate relative risks associated with vaccination. To be most informative, the baseline (or background) rate of the event in the unvaccinated is needed. The O/E ratio is calculated by applying the background rate of the event in the unvaccinated to the number of vaccinated people to obtain the expected number of cases among the vaccinated (E) and this is compared with the observed number of cases among the vaccinated (O). A classic example of an O/E analysis is provided by the initial evaluation of intussusception reports following rotavirus vaccine introduction in the U.S. in 1999.[47] After the first 15 reports were submitted to the

[47] Centers for Disease Control and Prevention (CDC). Intussusception among recipients of rotavirus vaccine–United States, 1998-1999. MMWR Morb Mortal Wkly Rep. 1999 Jul 16;48(27):577-581.

Vaccine Adverse Events Reporting System (VAERS) an O/E analysis was conducted. The expected number was estimated by applying the background rate of intussusception in infants obtained from the literature to the estimated number of infants vaccinated according to manufacturer estimates of number of doses administered. The expected number of cases was estimated to be 14-16. Although the number observed was not greater than expected, given the known under-reporting to VAERS, the O/E results were interpreted as suggestive of a possible increased risk. Two large epidemiologic studies (case-control and cohort) were launched that confirmed the increased risk and led to the withdrawal of the vaccine.

Ecological analyses can also be performed using aggregate data. Ecological analyses attempt to correlate changes in one factor (e.g. vaccinations) in a population with changes in another factor (e.g. health event). Since they involve population-level correlations, ecological analyses are subject to confounding by many other unaccounted for factors that may have also changed in the population. Thus, ecological analyses tend to be most suitable for hypothesis generation and are not considered to be robust enough to demonstrate causal association. Nonetheless, they are often used in studies of immunization programs, including for vaccine safety issues to explore if a particular trend is observed in multiple settings. Probably the best known use of ecological analyses is in demonstrating the effectiveness of immunization programs; for example, graphs that show how the incidence of a vaccine preventable disease decreases as vaccination coverage increases. In vaccine safety, Gangarosa used ecological graphs particularly effectively in illustrating how vaccine scares about pertussis vaccines in the 1970's and 1980's led to decreasing acceptance of pertussis vaccination with consequent increases in pertussis disease.[48] Another example involves analyses that have shown that autism continued to increase in countries after they had eliminated thimerosal-containing vaccines from their vaccination schedules, thus providing persuasive evidence against an association between thimerosal and autism.[49] If aggregate data are available on vaccinations, health events, and population characteristics, ecological analyses can be performed comparing vaccine coverage with disease rates. If vaccination coverage data are not available, sometimes ecological analyses may simply compare disease trends relative to the date when a vaccine was introduced (or discontinued).

Essential for many types of vaccine safety analyses is the availability of background rates of potential AEFIs.[50, 51] Background rates are especially valuable for evaluating reports from spontaneous reporting systems to determine if the number of cases that are reported following vaccination is more than would be expected by chance. Background rates may be available from the literature or from other countries, but having background rates from the local population provides the most valid data for comparisons with AEFI reports in a particular country or area. Calculation of background rates requires data on the total number of health events in the defined population, as well as the size and other demographic characteristics of the population.

A study from Tunisia provides an example of how a hospital-based network was used to establish disease background rates in an RLC setting (see Case study 6). Although not an active vaccine safety surveillance study, this study demonstrates how a sentinel hospital surveillance system can be used to ascertain and provide background rates of cases of specific health conditions. It could be adapted to provide background rates for possible AEFI (e.g. intussusception). The study

48 Gangarosa EJ, Galazka AM, Wolfe CR, Phillips LM, Gangarosa RE, Miller E, Chen RT. Impact of anti-vaccine movements on pertussis control: the untold story. Lancet. 1998 Jan 31;351(9099):356-361.

49 Madsen KM, Lauritsen MB, Pedersen CB, Thorsen P, Plesner AM, Andersen PH, Mortensen PB. Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. Pediatrics. 2003 Sep;112(3 Pt 1):604-606.

50 Clothier HJ, Lee KJ, Sundararajan V, Buttery JP and Crawford NW. Human papillomavirus vaccine in boys: background rates of potential adverse events. Med J Aust 2013; 198 (10): 554-558.doi: 10.5694/mja12.11751.

51 Kompithra RZ1, Sarkar R, Mathew LG, Muliyil J, Kang G. Study of Common Illnesses Before and After Vaccination: A Risk interval Approach. Indian Pediatr. 2015 Nov;52(11):933-8.

highlights the need for complete case ascertainment and estimates of population denominators for determining background rates.

Case study 6: Background rates from active hospital-based surveillance in Tunisia[52]

Issue: To assess the epidemiology, clinical and laboratory features of rotavirus acute gastroenteritis in children less than 5 years of age.

Locations: Tunisia

Datasources: Clinical data and stool samples collected for children admitted for acute gastroenteritis.

Vaccine: Not applicable.

Outcomes: Cases identified in 11 sentinel paediatric departments.

Population: Population data provided by the national institute of statistics.

Design: Multicentre prospective observational study.

Methods: Clinical data and stool samples collected for children admitted for acute gastroenteritis. Stool samples were tested for rotavirus. Incidence rates calculated using estimated population denominators.

Findings: Estimated incidence rate of rotavirus acute GE was 11 cases/100,000 child-years.

Lessons: Although not an AVSS or safety study, this study demonstrates how a sentinel hospital surveillance system can be used to ascertain and provide background rates of cases of specific health conditions. Highlights the need for complete case ascertainment and estimates of population denominators for determining background rates.

3.4 Conclusion

This chapter focused on the methods to conduct active surveillance and the data sources needed for each design. The data needed to conduct AVSS include information on the vaccine, the health event (outcome), and population/demographic data. If this information is available at the individual level, a number of designs can be used, including cohort, case-control, and self-controlled designs. The type of study to be conducted should be dictated by the particular circumstances encountered and the data sources available. In Chapter 4, practical aspects of AVSS, including communication, patient protections, study implementation, analysis, and reporting/communication of results are discussed.

[52] Soltani M, Bouanene I, Trabelsi A, Harbi A, Hachicha M, Amri F, et al. Epidemiology of rotavirus gastroenteritis among children under 5 years of age in Tunisia – Results of sentinel hospital surveillance 2009 to 2011. Revue d'Epidemilogie et de Sante Publique 2012;60:473-80.

CHAPTER 4:

PRACTICAL ASPECTS OF CONDUCTING AVSS STUDIES

In the earliest stages of planning a study, certain key questions must be addressed, including:

- Who will pay for the study?
- Who will be responsible for actively running the study? That is, which person or agency is the "lead" for the study?
- What approvals are needed to conduct the study? What regulatory or legal bodies are involved?

The answer to these questions will determine the role each party or agency will play in the conduct of the study. The answers will likely vary depending on the study and the RLCs involved.

In the early planning stage and throughout the conduct of AVSS, clear communication is essential.

After deciding to conduct an AVSS study, there are many activities and resources to be considered. All these steps will be detailed throughout this chapter, in the respective subchapters referenced (Table 4).

Table 4. Summary of practical steps, activities and resources to be considered after deciding to conduct an AVSS study

STEPS	REFERENCE	ACTIVITIES	RESOURCES
Planning	4.2 Study protocol 4.2.1 Protocol writing 4.2.2 Ethical conduct, patient and data protection	- Defining objectives and hypotheses to be tested; - Consider ethical aspects, informed consent and confidentiality; - Defining data to be collected; - Identification of relevant available data sources; - Expert advice on study design options; - Roles and responsibilities of stakeholders; - Plans for data analysis and communication of findings.	▶ National Immunization Programme ▶ NRA ▶ Pharmacovigilance centres ▶ Academia ▶ Manufacturers

STEPS	REFERENCE	ACTIVITIES	RESOURCES
Protocol writing	4.2.1 Protocol writing 4.2.3 Protocol review and approval	- Writing of the study protocol (including sample size, study site(s), data to be collected, principal investigator/ study coordinator); - Application for ethical clearance and other study permit, according to the regulation of each country; - Notification to NRA/other RA as applicable.	▶ National Immunization Programme ▶ NRA ▶ Pharmacovigilance centres ▶ Academia ▶ Manufacturers ▶ Study site(s) ▶ Other research centre(s) according to institution involved in the study.
Study preparation	4.3.1 Study preparation	- Identification of personnel with expertise for the study; implementation, analysis and interpretation of the results; - Identification and training of the study team and other partners; - Agreement (together with scientific committee and field investigators) on feasibility and practicalities; - Public communication.	▶ Study site(s) ▶ Other research centre(s) according to institution involved in the study.
Study implementation	4.3.2 Data collection 4.3.3 Study oversight	- Running of the active surveillance study; - Collection of the data according to the protocol; - Entering the data into the analysis program; - Cooperation with stakeholders.	▶ Study site(s) ▶ Monitoring centre ▶ Other research centre(s) according to institution involved in the study.
Data analysis and report	4.4 Data analysis 4.5 Study report	- Strategies for analyses, including statistical analysis plan; - Analysis of the data according to the protocol; - Writing of the report; - Publication.	▶ Study site(s) ▶ Monitoring centre ▶ Other research centre(s) according to institution involved in the study. ▶ NRA ▶ Manufacturers

STEPS	REFERENCE	ACTIVITIES	RESOURCES
Communication of study findings	4.6 Communication of study findings	- Information about the study rationale and robustness of the data; - Information about the safety and benefit-risk balance; - Consideration of a media conference.	▶ Study site(s) ▶ Monitoring centre ▶ Other research centre(s) according to institution involved in the study. ▶ NRA

4.1 Communication for the conduct of AVSS

A major part of conducting a study is communicating with all involved parties and the general public, including the media. Communicating is likewise crucial for those authorising and overseeing the study conduct. It is crucial to communicate with policy makers, including legislators and politicians, to ensure continued support from national authorities for well-designed studies. The communication process should commence early, when designing the study and obtaining ethical and community approval prior to its start. Clarity and common agreement on the study objectives is key in this respect.

Communication requires setting up a network and mechanisms for multi-party interactions and in particular exchange with the concerned communities, as well as maintaining these interactions throughout the study process. Listening is an essential part of communication, a key component which promotes understanding. Listening should address questions or concerns raised by the concerned communities and stakeholders, both proactively in the protocol and during the conduct of the study.

Communication materials, such as informed consent forms, should be adapted to the target audience in their information content, presentation and tone. Experience has shown that objectives, risks and ethical standards of studies can be questioned from inside and outside the concerned communities, even when a study is already ongoing. Without continuous preparedness and responsiveness of the communication system at any point in time, this may lead to a crisis of trust and premature ending of a study to the disadvantage of individual and community health. This may happen when an AEFI occurs or a new risk is identified, but also due to other concerns of the public.

The practical aspects of conducting studies described below mention at which stages communication becomes particularly important. A specific section gives recommendations for communicating study findings. The fundamental guiding principle for communication is honesty about expected benefits, risks and uncertainties. Persons in charge of communication should be well trained and approach these activities in an alert, empathetic and professional manner.

4.2. Study protocol

4.2.1. Protocol writing

All AVSS studies should have a written protocol, which should be amended or updated as necessary throughout the course of the study. Before being implemented, protocols require approval from regulatory bodies and from national or other ethics committees. This applies also to any subsequent

variations from the approved protocol. The study protocol needs to be carefully developed (by individuals with appropriate scientific background and experience), in order to generate valid and useful scientific data. It should have clearly defined objectives, and should be planned according to epidemiological principles and national requirements.

Guiding documents should be consulted to help ensure the protocol completeness, as well as the quality and integrity of the study and the protection of all study participants. The following list contains resources that might be used and adapted when writing a study protocol:

- EU template for study protocol:[53]
  http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133174.pdf
- ENCePP Checklist for study protocols:[54]
  http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml
- Guide on Methodological Standards in Pharmacoepidemiology:[55]
  http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE_Rev4.pdf
- Guidelines for Good Pharmacoepidemiology Practices:[56]
  https://www.pharmacoepi.org/resources/guidelines_08027.cfm
- STROBE study design checklists for observational studies:[57]
  http://www.strobe-statement.org/index.php?id=available-checklists

Considerations during the writing of the protocol include key design aspects such as the study objective, the population to be studied (all vaccine recipients or limited to certain groups based on age, geography, etc.), type of study, the data to be collected, ethical considerations, the statistical analyses plan, and how results will be presented. The study protocol should also include the study timelines (data collection, interim results, final report, etc.). In addition, the party responsible for each aspect of the study needs to be identified. Experts in study design should be consulted early and throughout the writing of the protocol. Any substantial amendment and update after the start of the data collection will have to be justified and specified.

The design of the study is crucial. A poorly designed study will not address the identified knowledge gaps. Active surveillance is complex and the validity of the study can be compromised by design flaws. The study designs should be appropriate to study objectives. The importance of sound protocol design and the need to involve subject matter experts cannot be overemphasized.

As regards estimates on sample size requirements for different designs and circumstances, consultation with statistical literature and appropriate expertise is recommended. If aiming for a cohort study, the desirable cohort size should be determined. Likewise, if performing a case-control or SCCS, special considerations of sample size are needed.

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53 European Medicines Agency, Guidance for the format and content of the protocol of non-interventional post-authroisation safety studies. Patient Health Protection. EMA/623947/2012, June 2015.

54 European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. ENCePP Checklist for Study Protocols (Revision 3). Adopted by the ENCePP Steering Group on 01/07/2016. Doc.Ref. EMA/540136/2009.

55 European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 4). EMA/95098/2010. http://www.encepp.eu/standards_and_guidances.

56 International Society for Pharmacoepidemiology (ISPE). Guidelines for Good Pharmacoepidemiology Practices (GPP); Revision 3; Bethesda, MD, USA, June 2015.

57 University of Bern, Institute of Social and Preventive Medicine, Clinical Epidemiology & Biostatistics. Strengthening the reporting of observational studies in epidemiology (STROBE) Checklists, Version 4, Bern, Switzerland, Oct/Nov 2007, http://www.strobe-statement.org.

When writing a study protocol, it is important to understand local medical practices. Review of study protocols by the involved stakeholders can significantly improve the quality of the study. For example, clinical personnel may have insight into the practical aspects of vaccine administration and data collection. Soliciting input from a variety of stakeholders will help anticipate (and potentially avoid) difficulties in the conduct of the study.

Data collection tool(s) should be described in the protocol. Questionnaires and case report forms could be attached as annexes. The statistical analysis plan should be sufficiently detailed so that it can be followed in the same way by any competent analyst. It is important to stress that serious attention should be paid to data collection, data management and data analysis prior to the start of any study. Quite often, studies collecting large numbers of data are initiated without consideration on how the data would be managed (i.e. electronically or manually using paper-based systems). This leaves both researchers and policy makers frustrated as their efforts seem to have only collected data which have no meaning as it has not been analysed to generate the needed information. The use of dummy data to test any data collection and analysis tool is important as it highlights potential problems that could be addressed before the study starts.

4.2.2. Ethical conduct, patient and data protection

All research involving humans regardless of the study design, should be carried out in accordance with international ethical principles, namely respect for persons, beneficence and justice, should be considered at all times. Investigators and sponsors must also ensure that proposed studies involving humans conform to generally accepted scientific principles; these requirements would be similar in RLCs as in other countries.

The following references provide useful insight in the ethical guidelines for epidemiological research involving human subjects:

- CIOMS International ethical guidelines for health-related research involving humans, 2017.[58]
- Ethical issues in patient safety research, World Health Organization, 2013.[59]

4.2.2.1. Ethical validity

Ethical principles must be applied consistently to all types of research involving human subjects. Although observational research usually does not pose a risk of physical harm to the individual, psychological harm may be present when sensitive questions are asked, for example, around a child's death or serious events). The ethics of collecting data for AVSS after immunization, in particular, has special features since it is a methodology which may, depending on design option, require the collection of detailed personal data and sometimes the storage of these data for indefinite periods. There may often be a need for follow-up at a later date for the further study of any safety concerns identified, at which time there will be a need to conduct investigations such as a more detailed cohort study, nested case–control studies, comparative safety studies, subgroup investigations (e.g. in children) or even a full clinical trial.

It is recommended to submit all proposals to conduct epidemiological research involving human subjects for review of their scientific merit and ethical acceptability. To minimize the risk for conflicts of interest, the scientific and ethical review committee membership should be independent of the

[58] CIOMS. International ethical guidelines for health-related research involving humans. Geneva: Council for International Organizations of Medical Sciences (CIOMS), 2017. http://www.cioms.ch/index.php/12-newsflash/400-cioms-inernational-ethical-guidelines.

[59] World Health Organization. Ethical issues in patient safety research, 2013, ISBN 978 92 4 150547 5. Published by WHO press, 2013. www.who.int/patientsafety/research/ethical_issues/en/.

research team. Full knowledge of and compliance with local laws should be ensured. In some jurisdictions, once a research proposal has been cleared by a scientific committee, a separate ethical review committee will assess whether the proposal is sound, with study objectives responsive to the health needs and priorities of the country, whether the balance of anticipated benefits to risks is reasonable, the process for selecting subjects is equitable and the procedures proposed for obtaining informed consent, when applicable, are satisfactory.

In certain countries, the studies which meet certain criteria may be exempt from this review. Upon the regulations of the local jurisdiction, some observational studies such as those utilizing publicly available or anonymous data may not be subject to prior review and approval by an ethical review committee. In some countries, if the data collected is non-interventional, there might be no need for ethical approval.

Obtaining ethical approval can sometimes take a long time so careful planning is important especially if conduct of the study is meant to be associated with the deployment of a new vaccine since the delay in obtaining ethical approval can delay vaccine deployment. Expedited reviews are possible and the possibility of these should be explored especially during epidemics and outbreaks.

4.2.2.2. Informed consent

The specificities of the informed consent will vary according to various factors (study design, country, etc.), but in all cases sponsors and study investigators have a duty to ensure that this obligation is fulfilled in accordance with local and international standards. Investigators should not initiate epidemiological research involving human subjects without first obtaining each subject's informed consent unless they have received explicit approval to do so from an ethical review committee or the research is authorized by legislation or competent authorities in accord with the ethical principles of the CIOMS International ethical guidelines for health-related research involving humans (2017) which covers both epidemiological and clinical research studies.[60]

The CIOMS ethical guidelines provide guidance on the essential information to be provided to research subjects, and obligations of investigators and sponsors in obtaining informed consent.

The ethical review committee may approve a waiver of the requirement of a signed consent if the research carries no more than minimal risk – that is, risk that is no more likely and not greater than that attached to routine medical examination. Records and specimens taken in the course of clinical care, or for an earlier study, may be used for research without consent of the patients only if an ethical review committee has determined that the research poses minimal risk, that the rights or interests of the patients will not be violated, that their privacy and confidentiality and anonymity are respected, and that the research is designed to answer an important question and would be impracticable if the requirement for informed consent were to be imposed.

When the practice of collecting patients' records for use in research without informed consent has been approved in a particular setting, patients should be notified of this practice, through patient-information brochures, leaflets or posters; and they should have the option to opt-out of use of their medical records for research purposes.

Patients participating in any active surveillance study should provide their informed consent, especially when personal data is collected by the investigator. Factors leading to potential low level of understanding of informed consent (e.g. low literacy) should be taken into consideration and other practical solutions for promoting understanding could be explored (video, audio, etc.).

60 CIOMS, International ethical guidelines, 2017, op. *cit.*

The investigators should abide by the confidentiality and data protection laws in the respective country. The patient personal data should not be included in any publicly-available information/ communication. For additional information, the International Society for Pharmacoepidemiology (ISPE) guidelines on Data privacy, medical record confidentiality, and research in the interest of public health could be consulted.[61]

4.2.2.3. Safeguarding confidentiality

Many countries around the world have enacted comprehensive data protection legislation or privacy laws applying to certain areas. Data protection laws are not the same in all countries that have them. It is therefore important to understand the data protection laws before undertaking any study, especially multi-country studies since data protection laws may vary across countries.

A health care provider should not submit any identifiable data about a patient to an investigator or to a database unless the patient permits such submission of data or it is authorized or mandated by law. An investigator who receives data for research must establish secure safeguards for the confidentiality of the data. There are many strategies for safeguarding the personal information of individuals involved in research. These include coding abstracted data with unique identifiers rather than names and masking features of specific cases, institutions, or settings that may make them recognizable even without names. Passwords and the best available technology, such as encryption, should be used in order to make sure that only authorized persons are able to access electronic data. The use of aggregated data extracted from health registries would also ensure confidentiality.

In general, access to patient information before it is de-identified should be granted to as few individuals as possible. This might be achieved by assigning medical staff, who already have permission and confidentiality commitments to review patient charts, or asking data collectors to sign the same level of confidentiality agreement(s) required of hospital staff. In addition to these safeguards, patients' consent to abstract data from their hospital records, or a waiver of consent from an ethical review committee should be sought.

4.2.3. Protocol review and approval

Any study should adhere to the laws and regulations of the country or countries in which the study will take place. It is likely that the protocol will need to be reviewed and approved by one or more scientific, regulatory bodies and ethical committees. The study should be initiated only after these approvals are obtained. These bodies could also request progress reports on the study and should be informed about any major amendment to the study protocol. These committees may require the reporting of serious adverse events within specified timeframes and these must be adhered to.

4.3 Study implementation

4.3.1. Study preparation

The implementation step has to be well prepared if an AVSS study is to succeed. The principal investigator or study coordinator is responsible for the study content and implementation, quality

[61] International Society for Pharmacoepidemiology (ISPE). Data privacy, medical record confidentiality, and research in the interest of public health, "Members of the Ad Hoc Committee on Data Privacy in the US, Canada, and the European Union." International Society For Pharmacoepidemiology (ISPE), Bethesda, MD, USA, 1 Sep1997, amended 19Aug1998, http://www.pharmacoepi.org/resources/privacy.cfm.

assurance, interpretation of data and preparation and publication of the final report. The principal investigator should identify the study team and the stakeholders. The first action in the process to ensure this, is to appoint a study coordinator. If deemed necessary, a feasibility assessment should be conducted. Feasibility studies should be independent of the main study results.

Coordination and communication within the team and with the stakeholders need to be initiated as early as possible. The investigators and study personnel engaged in the research should have the appropriate expertise (qualified by education and experience to conduct the research) and should be trained regarding the study procedure. The training should include data collection and recording, various forms to be used (diary cards, case report form, etc.), the procedure to evaluate the AEFIs, etc. A record of all persons involved, with their roles and responsibilities should be maintained and updated throughout the study.

Appropriate study sites that have adequate resources to perform the study should be selected. These resources might include medical staff sufficiently specialized to diagnose and report cases of interest and the research teams which will collect and collate data. During the preparation, all logistics needed for the study should be distributed to the sites prior to study initiation.

The organizations and individuals sponsoring and conducting the study take full responsibility for the research. The roles and responsibilities of all stakeholders and individuals involved should be clearly described, and the timelines (intermediate and for study completion) should be clearly agreed upon in advance. When more collaborating institutions are involved, contractual arrangements between them should be made.

During the planning phases and communication with potential AEFI reporters (patients, health care professionals, health workers and public health staff), it is important to promote willingness for collaboration, and to remove any potential barriers, in order for everybody to share the same vision with regard to the study objective. The information about the study objective and initiation should also be made public, via means specific for each country. Sometimes, the possibility to involve the public including local religious leaders could be considered.

4.3.2. Data collection

Data collection should be aligned with the study design and objective. The data should be collected as per the protocol, in a standard way, and the investigator should ensure its accuracy and completeness. The quality control is very important, as errors that could be made during data collection are difficult to correct. An optimal quality of the primary data needs to be the primary goal. Measures for careful data cleaning are of special importance (see Section 4.4).

Original data will usually be collected by questionnaires or face-to-face/telephone interviews. It is of the utmost importance that confidentiality is ensured at all times. Often it may be not feasible to collect primary data for the study purpose due to limited resources or because of the specific research question. In these cases, existing databases could be explored. Using data that was not specifically collected to answer the study questions can be sometimes challenging (i.e. in terms of quality, standardization, potential biases).

There are two main approaches for data collection. Primary data collection is the collection of data specifically for a study (e.g. prospective studies, registries). In registries, data is entered according to the registry type (disease registry or exposure registry), and they could sometimes be requested by regulators at the time of authorization of a medicinal product. Secondary data collection refers to collection of data already gathered in databases for another purpose (e.g. electronic medical records, record linkage of administrative health records). Many databases are registered in the

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Inventory of Databases (http://www.encepp.eu/encepp/resourcesDatabase.jsp), which is fully searchable. A combination of approaches can also be used.

The following sources provide general guidance on data collection:

- For prospective studies: the ISPE Good pharmacoepidemiology practices (GPP) (http://www.pharmacoepi.org/resources/guidelines_08027.cfm);[62]
- For registries: Registries for evaluating patient outcomes: a user's guide (http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1897);[63]
- For databases: Guidelines for good database selection and use in pharmacoepidemiology research (http://www.pharmacoepi.org/pub/1c2a306e-2354-d714-5127-9fd12e69fa66).[64]

People processing the data must be adequately trained, supervised, and provided with adequate tools. It would be useful to assign a person responsible for the integrity and security of the data. Restricted access to the data should be considered, and a list of individuals who are authorized to make data changes should be maintained.

All study information and documents should be handled and stored as to allow for potential future use or verification. Appropriate database software should be chosen for data storage. It is very important that this system does not crash and that continuous data back-up procedures are put in place. Measures should be taken to prevent accidental or premature destruction of the storage means and documents. It is important that essential documents are retained for a period of time after the study finalization (e.g. in case they need to be made available to regulatory authorities). Materials to be archived should not only include the raw data and files for analyses, but also the study protocol, computer programs, documentation, data processing, measurement protocols, and the final report.

Also, electronically stored documents need to be protected from unauthorized persons accessing the data and hacking. The principal investigator should be aware of the potential for corruption or manipulation internally and should use multiple means to ensure protection of the database in addition to regular backups. In all cases, experts in data management should be consulted to ensure that only the best practice and procedures are being used.

4.3.3. Study oversight

The study oversight will involve various stakeholders, depending on the type of study and RLCs involved. Cooperation and communication within the team and with the stakeholders need to be maintained throughout the study.

Since AVSS is likely to play an increasing role in RLCs, new models for study oversight may need to be created. Given the multiple stakeholders that might participate in AVSS in a RLC, a shared "ownership" or "sponsorship" might be preferred, rather than the traditional well-defined and separate roles typically followed in trials. Creation of a cross-stakeholder oversight committee might best

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62 International Society For Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP), Revision 3: June 2015. Bethesda, Maryland, USA.

63 Gliklich R, Dreyer N, Leavy M, eds. Registries for Evaluating Patient Outcomes: A User's Guide. Third edition. Two volumes. (Prepared by the Outcome DEcIDE Center [Outcome Sciences, Inc., a Quintiles company] under Contract No. 290 2005 00351 TO7.) AHRQ Publication No. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality. April 2014. http://www.effectivehealthcare.ahrq.gov/registries-guide-3.cfm.

64 Hall GC1, Sauer B, Bourke A, Brown JS, Reynolds MW, LoCasale R. Guidelines for good database selection and use in pharmacoepidemiology research. Pharmacoepidemiol Drug Saf. 2012 Jan;21(1):1-10.

serve these types of studies. The membership, role, and authority for such a committee would need to be determined before the start of the study. It seems likely that various models could work and that different models might be used in different situations.

4.4. Data analysis

The analysis plan needs to be agreed upon at the time of the protocol development and before commencement of the study and data collection. The study should be planned and carried out in such a way that its statistical analysis is able to answer the research questions. In the conduct of studies for AVSS there is need for special expertise (e.g. epidemiology, biostatistics).

At the level of the study centre, all the data should be first checked and validated, assessing the clinical details in the reports and determining the appropriate event terms, assessing the duration to onset of each event, the severity and seriousness, and further recording the outcome of each event.

After collecting the data, the process of data cleaning starts. This process has as scope determining whether the data is free of errors, biased or modified in any way, whether there are differences between study sites, whether any inconsistencies can be identified. This process may involve recoding some data and it is, therefore, important that this process is transparent. Data cleaning should involve as little recoding as possible, the recoding rules should be stated in the protocol, and raw data, without any manipulations, should always be stored together with the cleaned data.

Data quality implies quality planning, assurance, control and improvement. The standards to be followed in order to achieve and maintain the quality requirements and the measures applied for quality enhancement should be described. This is particularly important in studies which involve collection of an extensive amount of data, from different sites, over a long period of time, with quality depending on a variety of factors (e.g. study personnel, equipment). Quality control should be applied to each stage of data handling, to ensure that data is reliable and has been processed correctly.

After the data is validated and completed, the study centre may present it to a group of experts (Expert Committee), for review and analysis. A clinical review of all reported and observed cases is necessary. It would be ideal if all serious adverse events (SAE) would be reviewed by the national expert committee (NEC). These SAEs should also be reported to the NRA/NEC and to the national pharmacovigilance centre.

Several documents are relevant to the analysis of AEFIs:

- WHO Causality Assessment of AEFI: http://www.who.int/vaccine_safety/publications/aevi_manual.pdf;[65]
- WHO Global Manual on Surveillance of Adverse Events Following Immunization: http://www.who.int/vaccine_safety/publications/Global_Manual_on_Surveillance_of_AEFI.pdf;[66]
- Adverse effects of vaccines: Evidence and causality. Washington, DC: The National Academies Press. IOM (Institute of Medicine). 2012. (https://www.nap.edu/read/13164/chapter/1).[67]

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65 World Health Organization. Causality assessment of an adverse event following immunization (AEFI), User manual for the revised WHO Classification, WHO/HIS/EMP/QSS. March 2013.

66 WHO. Global manual AEFI, *op. cit.*

67 Institute of Medicine (IOM). 2012. Adverse effects of vaccines: Evidence and causality. Washington, DC: The National Academies Press.

Epidemiologic studies, including those from AVSS, provide measures of risk on a population level, but they do not provide evidence that a particular vaccine caused an adverse event in a particular individual. The main objective of vaccine safety monitoring and assessment activities is to determine if particular AEFIs are caused by a vaccine. Causality assessment may be performed at the individual or population level. It is often not possible to infer causality in individual cases of AEFI, except in certain special situations as described in the WHO manual on causality assessment. More generally, causality assessments rely on weighing different pieces of evidence using criteria such as strength of association (e.g. relative risk), consistency of findings, temporal relationships, potential biases, and possible biological mechanisms.

The statistical analysis plan should be sufficiently detailed so that it can be followed in the same way by any competent analyst. Clear and complete templates or explanations for each analysis should be provided. A feature common to most studies is that some not pre-specified analyses will be performed in response to chance observations in the data. These modifications to the analysis strategy should be noted and explained.

The analysis plan should describe the data sources, study population and study design with its strengths and weaknesses. All the definitions used for exposure, outcomes, and other variables should be included. Sample size considerations should be presented (except if the study is performed on data that already exist, and where no additional data can be collected). The effect measures and statistical models used to address each objective and the methods of dealing with confounding should be specified.

Missing data can have a significant influence on the conclusions that can be drawn, and it is desirable to show that the results are not influenced by the handling of the missing values. If assumptions regarding missing data are employed, these must be explicitly stated.

4.5. Study report

The study report will be written by the study team, under the direction of the study coordinator and according to the protocol. Sometimes, interim reports will be also issued. The final study report should present, in detail, the study objectives, methods, results, data analysis, discussion, including strengths and limitations, and conclusions. The final study report should also include an abstract containing the summary of methods and results. The results should answer the study question and objectives. The deviations from the study protocol should be mentioned and described. A final study report should be completed even if the study is discontinued, and the reasons for discontinuation should be thoroughly described.

The following document includes a possible structure for the final study report, which could be adapted according to the active safety surveillance study specificities:

- EMA Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies. 2013, http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2013/01/WC500137939.pdf.[68]

According to the agreed strategy between sponsors and investigators, both interim results and final results could be published. Upon the completion of the study, the final study report should also be submitted to the regulatory bodies that approved the study protocol.

[68] European Medicines Agency (EMA). Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies. London United Kingdom, 30July2013.

4.6. Communication of study findings

The recommendations for communication for active surveillance studies above should be applied for communicating the study findings. The objectives of this part of the communication process are to provide information about the safety and benefit-risk balance, in order to support decision-making for immunization policies and individual informed choice in relation to immunization, and to support the safe and effective use of vaccines. Best communication practices, developed by the health communication sciences, for lingual, numerical and visual expression of the findings should be followed. The public also needs to receive explanations on the study rationale and be enabled to understand the robustness and the credibility of the data and their analysis, including the trustworthiness of those having conducted and overseen the study. This requires an in-depth understanding of the knowledge and sentiments prevalent in the public and pre-testing of information materials for assuring that they meet the communication objectives. A media conference should be considered to present the results and answer questions. The wider dissemination of the study results should reach those who need to know. Contact points for questions from the public should be in place.

4.7. Conclusions

In Chapter 4, practical considerations for undertaking AVSS have been reviewed. Communication is a key element of any surveillance activity. Effective communication, both between stakeholders and in the communication of the rationale of the study and the results generated from it to the public, will be essential for a successful outcome. Careful planning throughout the process, including protocol development, ethical considerations and patient protection, data collection, study oversight, data analysis, and reporting of findings are essential for successful AVSS activity.

This Guide has been designed to aid stakeholders in assessing whether a significant knowledge gap exists, how to confirm a SKG, how a SKG might be most appropriately addressed, and when and how active safety surveillance might be undertaken, with emphasis on an RLC setting. While not intended to be comprehensive, this Guide along with the included EVI source list, can serve as a framework to assess when AVSS might be needed and how it might be conducted, and provides a valuable list of practical aspects requiring consideration before undertaking AVSS. The information provided by the CIOMS Work Group is intended to assist RLCs in selecting the most appropriate tools for vaccine safety surveillance and to increase the likelihood of a well-constructed and informative AVSS when needed.

APPENDIX I:

ESSENTIAL VACCINE INFORMATION (EVI)

As part of the process of identifying a safety surveillance strategy for the launch of a new or new-to-the-country vaccine or immunization program, the end user or decision-maker in a resource-limited country (RLC) is usually the national immunization program (NIP) and/or national regulatory authority (NRA), either of which could be part of the government such as the public health department or ministry of health depending on the country (for further information see Figure 1 in Chapter 1). For the implementation of and communication about a launch, the end user needs data on the vaccine's safety profile. Data availability varies by vaccine and method of introduction. As a general principle, though, there are two major mechanisms or scenarios, through which a new vaccine is authorized to be introduced into a country: either through registration by the local regulatory/competent authority or through the WHO Prequalification (PQ) process. These two scenarios are briefly described below.

Vaccine approval scenario 1 - local registration

In the new global landscape some vaccines may be first licensed directly into RLCs without the benefit of having safety data accumulated over a longer period of time in high income countries with more established vaccine safety surveillance systems – which had been the usual pattern until recently. New vaccines anticipated for introduction in the coming years include dengue, malaria, typhoid, TB, and HIV vaccines and newly-licensed vaccines with expanded coverage recommendations including those to prevent HPV, influenza, Herpes zoster, meningococcal and pneumococcal diseases. These new or expanded products coming into new populations place a higher burden on the RLCs to assess and monitor vaccine safety. Better data tools and additional communication between the various stakeholders are useful in this context.

When countries are able to locally register a new vaccine, the NRAs have access to the full dossier prepared by the manufacturer when submitting for approval, which sometimes arrives with an extensive amount of information (such as in the form of the Common Technical Document) due to the complexity of these new products. However, in some cases, the vaccines may have limited prior usage in countries with well established pharmacovigilance systems and therefore, these vaccines may lack baseline safety data. In either circumstance the local competent authorities may have limited capacity and resources to review and assess the data provided. With those new or new-to-country vaccine launches (e.g. new vaccine combinations, HPV, Ebola, dengue, soon perhaps malaria and Zika), absence of a historical track record in other countries puts pressure on the RLC countries to gather data in a different way.

A WHO procedure for expedited review exists and is called a *"Collaborative procedure between the World Health Organization Prequalification of Medicines Programme and national medicines regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines."* The expedited review of imported prequalified vaccines for use in national immunization programmes relies on the WHO PQ assessment described below

in scenario 2. This procedure allows the NRA to take advantage of the scientific assessment work conducted by the World Health Organization Prequalification Team (WHO/PQT). WHO/PQT shares the assessment reports, inspection reports, and laboratory results via a secured site to designated NRA focal persons (with the agreement of manufacturers). However, each NRA should receive all the data from the applicant. This gives the possibility to the NRA to accelerate the registration process. Each country has the final decision to register or not the product.[69]

The lessons learned in early launches of vaccines in RLCs can be valuable to help each subsequent new country's immunization campaign be more successful. Therefore improving the communication flow among the RLCs that are locally-registering vaccines and experiencing new vaccine launches can provide important information for vaccine safety.

Vaccine approval scenario 2 - WHO prequalification

RLCs frequently accept donated vaccines for immunization programmes under circumstances where the national authorities are not in a position to purchase the vaccines themselves. In such circumstances, the vaccine might not be registered by the local regulatory authorities. WHO PQ was originally intended to give countries themselves, as well as United Nations procurement agencies (such as UNICEF and funding programs like the Gavi Vaccine Alliance), the choice of a range of quality medicines and vaccines prequalified by the WHO process.[70] WHO provides a service to GAVI, UNICEF and other UN agencies that purchase vaccines, to determine the acceptability, in principle, of vaccines from different sources or in new configurations. WHO assures that the vaccines meet the specific medical needs of the programme, reflected by the tender specifications: i.e. potency, thermostability, presentation, labelling, and shipping conditions.

PQ vaccines have to be first registered in the country of their manufacture by that country's NRA which is responsible for regulatory oversight of the product. Details on WHO-prequalified vaccine manufacturers and their respective NRAs, as well as a sample of all product inserts for each vaccine, are available on the WHO PQ website.[71] This provides access to publicly-available information for the NRA or national immunization program. Countries receiving vaccines through UNICEF or GAVI can identify the vaccine manufacturer, by their original packaging and package insert in which they arrive from the manufacturer.

In the case of emergency or epidemic situations, the vaccines may not already be registered, even in a country with established vaccine surveillance systems, but may be permitted to be utilized through the WHO emergency use assessment and listing procedures (EUAL) which propose principles for assessing and listing vaccines, medicines, and diagnostics for use in a public health emergency.[72] EUAL offers a special procedure for vaccines in the case of a public health emergency when the community may be more willing to tolerate less certainty about the efficacy and safety of products, given the morbidity and/or mortality of the disease and the shortfall of treatment and/or prevention options.[73] Provision of emergency vaccine supplies to countries during major outbreaks

69 World Health Organization, Immunization standards, Revised procedure for expedited review of imported prequalified vaccines for use in national immunization programmes, 17 July 2015, www.who.int/immunization_standards/vaccine_quality/expedited_review.

70 World Health Organization, Health Systems and Services: Prequalification of Medicines Programme, http://apps.who.int/prequal/.

71 World Health Organization, Immunization Standards, Vaccine Quality, Prequalified Vaccines http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/.

72 Kieny MP and Rägo L. Regulatory policy for research and development of vaccines for public health emergencies, Expert Review of Vaccines, 2016. http://www.tandfonline.com/doi/abs/10.1080/14760584.2016.1188695.

73 World Health Organization, Emergency Use Assessment and Listing procedure (EUAL) for candidate vaccines for use in the context of a public health emergency. http://www.who.int/medicines/news/EUAL-vaccines_7July2015_MS.pdf.

typically involve WHO-prequalified vaccines coordinated by the international coordinating groups on vaccine provision.[74]

Background on the development of the EVI source list

As a subsection of the CIOMS Working Group on Vaccine Safety (WG), a diverse group of experts from industry, regulatory, public health, and academia, discussed, identified and elaborated on the most important data elements that would be needed by the end user for the launch of a new vaccine in an RLC. The members tested the concept using source documents on three different vaccine products: 1) meningococcal A conjugate vaccine, 2) yellow fever vaccine, 3) 6-in-1 paediatric vaccine approved by central EMA (DTaP-IPV-Hib-HepB vaccine) for primary and booster vaccination of infants from six weeks of age.

The WG explored the idea of creating a user-friendly EVI document on baseline vaccine safety data to be completed and provided for country-level immunization professionals, however, there was no agreement on how to proceed forward without a broader mandate. It did not seem feasible to expect voluntary compliance by manufacturers and vaccine procurement/donors to complete a new document since it would have financial and legal implications. To get this EVI document formalized would require approval or authorization by all the stakeholders. Consideration could be given to using this preliminary work in a future CIOMS working group that would involve discussions and consensus around regulatory authority commitment, approval for such a document, and buy-in from industry and public health officials.

As a practical solution, there was consensus that the EVI source list is an instructive tool to be used by immunization specialists as described below.

The Essential Vaccine Information (EVI) source list

The EVI source list aims to provide a guidepost to end users in the NIPs and NRAs by pointing the immunization specialist in the right direction when there is a need for effective review of a vaccine's safety profile. The EVI source list serves as a resource to identify what information is most important and where this data can be found, depending on which source documents are available. This could be especially useful and timesaving if resources are limited in the regulatory authority or immunization programme.

Coupled with technical assistance from WHO or other experts and hands-on training for the immunization staff, the intention is that the EVI source list will provide a resource to be used as part of the decision-making 6-step algorithm created for this report (see Figure 2) for determining whether or not a significant knowledge gap exists and the need for further information gathering. This systematic approach could aid in the process of determining whether to use passive or active vaccine safety surveillance when a new vaccine is being considered. Greater communication and dialogue among the public health, regulatory, and industry stakeholders needs to be further explored to be able to optimize the information flow.

The source documents, systems or contacts described in Table 5 could be available for finding the essential safety data for a new or new-to-country vaccine, depending on where the vaccine has been

[74] World Health Organization, Emergencies preparedness response, Pandemic and Epidemic Diseases (PED), International Coordinating Groups (ICG) on Vaccine Provision, www.who.int/csr/disease/icg/.

developed, approved, and introduced previously. Scenario 1 shows the possible information sources available to local regulatory authorities if a vaccine is being locally-authorized which may include the confidential information submitted by the manufacturers. Scenario 2 shows data sources for the WHO prequalified vaccines which may include the publicly-available information sources which would be available to the end user (whereas the confidential details were part of the dossier submitted to WHO for prequalification.)

Table 5. Essential vaccine information (EVI) source lists*

Scenario 1: Locally-registered vaccine		
A. Documents by category accessible to national regulatory authorities.		
1. Regulatory submission dossiers		
– Common Technical Document (Module 2, Summary of Clinical Safety, Summary of Clinical Efficacy).[75]		
– Product Summary File (including Chapter 8, Clinical Experience) – submitted by the manufacturer if seeking WHO PQ for expedited review for local-authorization.[76]		
2. Risk management documentation		
– Risk Management Plan (RMP - European).[77]		
3. Periodic Safety Update Reports		
– Periodic Safety Update Report (PSUR)[78] / Periodic Benefit Risk Evaluation Report (PBRER).[79]		
B. Documents by type of information.		
Type of information	**Specific information sought**	**Potential source documents or contacts****
1. Safety information from clinical development	Subject exposure in clinical trials, summary of efficacy and/or immunogenicity, serious adverse events, most frequent adverse events.	▶ EudraVigilance.[80] ▶ Common Technical Document (Module 2, Summary of Clinical Safety, Summary of Clinical Efficacy). ▶ Product Summary File (Chapter 8, Clinical Experience).
2. Product characteristics	List of components, characteristics of immune response, potential interactions, indications, dose, preparation and route of administration, schedule of administration, contra-indications, warnings, storage, manufacturer and contact information.	▶ European Summary of Product Characteristics (SmPC).[81] ▶ Package Insert (PI). ▶ Other Country's local label (may be based on manufacturer's package insert). ▶ Product Summary File.

Table 5. Essential vaccine information (EVI) source lists* (continued)

Type of information	Specific information sought	Potential source documents or contacts**
3. Risks and missing information	Important identified risks, important potential risks, missing information, risk minimization strategies, ongoing or planned safety studies.	▶ Product Summary File. ▶ Risk Management Plan (RMP - European).
4. Post-authorization information	Adverse event reporting, world-wide marketing authorization status, post-marketing exposure (if available).	▶ Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER). ▶ Spontaneous Safety Reporting System. ▶ EudraVigilance & UMC Vigilyze.[82] ▶ VAERS WONDER.[83] ▶ Manufacturer or local distributor.
Scenario 2: WHO-prequalified vaccine		
A. Documents by category accessible to national regulatory authorities.		
1. Manufacturer's product characteristics/package inserts		
– Summary of Product Characteristics (SmPC).		
– Package Insert (PI).		
– Patient Information Leaflet.		
2. Regulatory authority assessments		
– European Public Assessments Report (EPAR).[84]		
– Summary Basis for Regulatory Action (SBRA).		
3. Databases		
– Spontaneous Safety Reporting System in the country.		
– EudraVigilance & UMC Vigilyze.		
– Vaccine Adverse Event Reporting System (VAERS WONDER).		
4. Information requests/direct contact		
– Manufacturer or local distributor.		
B. Documents by type of information.		

Table 5. Essential vaccine information (EVI) source lists* (continued)

Type of information	Specific information sought	Potential source documents or contacts**
1. Safety information from clinical development	Subject exposure in clinical trials, summary of efficacy and/or immunogenicity, serious adverse events, most frequent adverse events.	▶ Manufacturer's Package Insert (available on WHO PQ website).[85] ▶ European Public Assessments Report (EPAR). ▶ Summary Basis for Regulatory Action (SBRA).
2. Product characteristics	List of components, characteristics of immune response, potential interactions, indications, dose, preparation and route of administration, schedule of administration, contra-indications, warnings, storage, manufacturer and contact information.	▶ European Summary of Product Characteristics (SmPC). ▶ Package Insert (PI).
3. Risks and missing information	Important identified risks, important potential risks, missing information, risk minimization strategies, ongoing or planned safety studies.	▶ Package Insert. ▶ Risk Management Plan (RMP - European).
4. Post-authorization information	Adverse event reporting, world-wide marketing authorization status, post-marketing exposure (if available).	▶ Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER). ▶ Spontaneous safety reporting system in the country. ▶ EudraVigilance & UMC Vigilyze. ▶ VAERS WONDER.

* Links to sources are footnoted at first occurrence and are listed at end of Table 5.

** Will vary depending on where vaccine has been registered and approved.

Footnotes for Table 5. Essential vaccine information (EVI) source lists

[75] Common Technical Document – International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Harmonised tripartite guideline. The common technical document for the registration of pharmaceuticals for human use. Efficacy – M4E (R1) Clinical overview and clinical summary of module 2 module 5 : clinical study reports. Current Step 4 version, dated 12 September 2002, www.ich.org.

[76] Product Summary File – World Health Organization, Quality Safety and Standards (QSS) team of the Department of Immunization, Vaccines and Biologicals Ordering code: WHO/IVB/06.16 Printed: December 2006, www.who.int/vaccines-documents/ The WHO document "Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies" (WHO/IVB/05.19) explains the procedure followed by WHO under their mandate to provide an evaluation of the manufacturing and regulatory control of vaccines to UN agencies that wish to purchase these vaccines. The product summary file (PSF) is a brief summary dossier containing current information on the product to be supplied to UN agencies. It presents information on the product composition, manufacturing procedure, testing, stability, labelling, clinical experience, and available post-marketing safety information.

[77] Risk Management Plan – European Medicines Agency. Human regulatory/Post-authorisation/Pharmacovigilance/Risk management http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000360.jsp&mid=WC0b01ac058067a113.

[78] Periodic Safety Update Report – European Medicines Agency. Periodic safety update reports. Human regulatory/Post-authorisation/Pharmacovigilance/ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000361.jsp&mid=WC0b01ac058066f910.

[79] Periodic Benefit Risk Evaluation Report – E2C(R2) (PBRER) Guidance for Industry, U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), July 2016, Revision 1.

[80] EudraVigilance – European Medicines Agency. EudraVigilance data https://eudravigilance.ema.europa.eu/ or http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000674.jsp&mid=WC0b01ac0580a69390.

[81] European Summary of Product Characteristics – European Medicines Agency. Human regulatory/Marketing authorization/Product information /(How to prepare an SmPC. www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000357.jsp&mid=WC0b01ac05806361e1.

[82] UMC Vigilyze – Uppsala Monitoring Centre. Pharmacovigilance/Tools/VigiLyze. http://who-umc.org/DynPage.aspx?id=123391&mn1=7347&mn2=7252&mn3=7254&mn4=7695

[83] AERS WONDER – Centers for Disease Control and Prevention. Vaccine Adverse Event Reporting System (VAERS). Wide-ranging OnLine Data for Epidemiologic Research (WONDER). https://wonder.cdc.gov/wonder/help/faq.html#1.

[84] European Public Assessments Report – European Medicines Agency. European public assessment reports. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125. Note: The product can be identified using one of the tabs: Browse A-Z; Keyword search; Browse by therapeutic area; Browse by type. After the product is identified, the tab 'Product information' should be selected, and in the respective tab the first link 'EPAR – Product Information' corresponds to the SmPC. The same link of the SmPC contains the Labelling and the Product Information.

[85] Manufacturer's Package Insert – World Health Organization, Immunization Standards, Vaccine Quality, Prequalified Vaccines, www.who.int/immunization_standards/vaccine_quality/vq_index.

APPENDIX II:

MEMBERSHIP AND MEETINGS OF THE CIOMS WORKING GROUP ON VACCINE SAFETY

The CIOMS Working Group on Vaccine Safety (WG) was formed in 2013 following the completion of CIOMS/WHO Working Group on Vaccine Pharmacovigilance to continue addressing unmet needs in the area of vaccine pharmacovigilance and specifically address Objective #8 of WHO's Global Vaccine Safety Initiative regarding public-private information exchange. The original composition of the group consisted of experts from regulatory, public health, academia, and industry.[86]

The WG met in a series of eight meetings from May 2013 through March 2016. Some representatives changed during the years according to organizational and professional developments.

The seven members of the Editorial Team were: Steven R. Bailey (Editor-in-Chief), Novilia Bachtiar, Irina Caplanusi, Frank DeStefano, Corinne Jouquelet-Royer, Paulo Santos, and Patrick Zuber. CIOMS staff and advisors who supported this WG include: Lembit Rägo, Gunilla Sjölin-Forsberg, Ulf Bergman, Karin Holm (as the WG's Technical Collaboration Coordinator), Amanda Owden, and Sue le Roux.

The collaboration process involved examining a variety of ways to address the objectives, starting with a set of twelve topic groups and then distilling into a consolidated chosen set of three with associated deliverables. The topic group (TG) leaders were: TG1 on Essential Vaccine Information - Ulrich Heininger (final stage) and David Martin (early stage), TG2 on the Guide to AVSS – Corinne Jouquelet-Royer, Steven Bailey and Mimi Darko (final stage) and Françoise Sillan (first stage), TG3 on Vaccine Safety Communication - Priya Bahri (final stage) and Ken Hartigan-Go (first stage).

The chapter leads were: Steven Bailey (Ch. 1 and 2), Walter Straus (Ch. 1 and Appendix 1 early stage), Frank DeStefano (Ch. 3), Irina Caplanusi and Christine Maure (Ch. 4). Special mention for contributions in writing, researching various parts: Scott Winiecki, Walter Strauss, and Irina Caplanusi and for strategy and support on input from resource-limited countries: Christine Maure. Special advisors for specific sections: Ingemar Persson, Bruce Hugman, Katrine Bach Habersaat, and special reviewers: Madhav Ram Balakrishnan, Ananda Amarasinghe, Mimi Darko, Siti Abdoellah, Dong Duo.

This WG report was reviewed in draft form by participating members in May 2016 and following a review by the editorial team and team members, and external review, was finalized thereafter

[86] Original formation of the CIOMS Working Group on Vaccine Safety included the following main contacts on record: Peter Arlett (EMA), Novilia Sjafri Bachtiar (Bio Farma), Joan Benson (Merck), Jan Bonhoeffer (Brighton), Adrian Dana (Merck), Mimi Darko (Ghana FDA), Frank Destefano (CDC), Alex Dodoo (U Ghana), William Gregory (Pfizer), Katharina Hartmann (Crucell/JNJ), Ulrich Heininger (Uni Basle), Suresh Jadhav (Serum Inst), Brigitte Keller-Stanislawski (PEI), Terhi Kilpi (Finland THL), Xavier Kurz (EMA), Marie Lindquist (UMC), Patricia Mandali (ANVISA), David Martin (FDA), Eliane Matos dos Santos (Bio-Manguinhos), Christine Maure (WHO), Harry Seifert (GSK), Françoise Sillan (Sanofi Pasteur), Gunilla Sjölin-Forsberg (CIOMS), Amina Tebaa (CAPM), Mona Hassan Abu Youssef (Egyvac), Patrick Zuber (WHO).

for publication. CIOMS and the Working Group are grateful for valuable input received from senior experts outside the Group who during their external review made valuable suggestions: Amavi Edinam Agbenu, Fabien Diomande, Houda Langar, Adiela Saldaña, and Akiko Hori and Miki Ohta (experts from the Japanese Pharmaceuticals and Medical Device Agency).

During the course of its work, the WG recognized its membership to represent the following broad groups of stakeholders (or interested parties) in risk minimization approaches: regulatory authorities; biopharmaceutical industry; international organizations; and academia. Table 6 provides a cumulative list of senior scientists who have been important contributors to the WG development over its life span organized alphabetically by last name, and each member's associated organizations. These contributors have served as members or alternates in the WG for differing periods of time; some have contributed for the full duration (2013 to 2016), while others have attended at least one meeting and/or contributed to the report. Members were invited to join one or more of what became the three topic groups to contribute to the deliverables and product of the groups' collaboration. In some cases organizations changed representatives over the course of this project or contributors changed affiliations; this is not always reflected in the listing. The list generally includes the affiliation of the contributor when he or she first joined the WG. Members, their institutional affiliations and stakeholder groups (as defined above with some specific variations) as well as a chronological summary of the WG meetings are listed below.

Table 6. Members and affiliations of CIOMS Working Group on Vaccine Safety[87]

	WG Member Name	Organization (Stakeholder group)
1.	Abdoellah, Siti Asfijah	Indonesia National Agency of Drug and Food Control *(Regulatory authority)*
2.	Arellano, Felix	Merck *(Pharma industry)*
3.	Ayoub, Ayman	Pfizer *(Pharma industry)*
4.	Bachtiar, Novilia	Bio Farma Indonesia *(Pharma industry)*
5.	Bahri, Priya	European Medicines Agency (*Regulatory authority)*
6.	Bailey, Steven R.	Pfizer *(Pharma industry)*
7.	Benkirane, Raja	Centre Anti Poison et de Pharmacovigilance du Maroc (CAPM) *(Public health authority and WHO Collaborating Centre)*
8.	Bergman, Ulf	Council for International Organizations of Medical Sciences (Independent organization)
9.	Blum, Michael	MedImmune/Astra Zeneca *(Pharma industry)*
10.	Caplanusi, Irina	European Medicines Agency (*Regulatory authority)*
11.	Ceuppens, Marc	J&J/Crucell *(Pharma industry)*
12.	Chandler, Rebecca	Uppsala Monitoring Centre (*Independent foundation and WHO Collaborating Centre)*
13.	Chua, Peter Glen	Philippines *Food and Drug Administration* (*Regulatory authority)*
14.	Darko, Mimi Delese	Ghana Food and Drug Authority (*Regulatory authority)*
15.	Destefano, Frank	Centers for Disease Control and Prevention *(Public health authority)*

[87] Some associated representatives who were not able to attend meetings or actively participate, but who may have been involved behind the scenes or in a supervisory capacity include: Bahdar Johan Hamid (Indonesia FDA), Bernhard Heiles (Merck), Prasad Kulkarni (Serum Inst.), Dirk Mentzer (PEI), Hanna Nohynek (Finland), Raphaele Roten (JNJ), Sidarta Silva (anvisa), Fernanda Simioni (anvisa), Antonia Utami (Indonesia).

	WG Member Name	Organization (Stakeholder group)
16.	Dodoo, Alex	University of Ghana (*Academia*) and *(WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance)*
17.	Duo, Dong	Center for Drug Reevaluation CFDA, China (*Regulatory authority)*
18.	Gunale, Bhagwat	Serum Institute *(Pharma industry)*
19.	Hartigan-Go, Ken	Philippines Dept of Health *(Public health authority)*, Asian Institute of Management *(Academia)*
20.	Heininger, Ulrich	University Hospital Basel *(Academia)*
21.	Jouquelet-Royer, Corinne	Sanofi Pasteur S.A. *(Pharma industry)*
22.	Kilpi, Terhi	Finland THL (*Regulatory authority)*
23.	Kurz, Xavier	European Medicines Agency (*Regulatory authority)*
24.	Leviano, Fabio	Merck *(Pharma industry)*
25.	Lindquist, Marie	Uppsala Monitoring Centre (*Independent foundation and WHO Collaborating Centre)*
26.	Liu, Dawei	Chinese Center for Disease Control and Prevention *(Public health authority)*
27.	Mandali, Patricia	Anvisa (Brazilian Health Surveillance Agency) (*Regulatory authority)*
28.	Mangrule, Somnath	Serum Institute of India *(Pharma industry)*
29.	Maroko, Robert	Pfizer *(Pharma industry)*
30.	Martin, David	US Food and Drug Administration *(Regulatory authority)*
31.	Maure, Christine	World Health Organization (*U.N. specialized agency for health*)
32.	Menezes, Reinaldo	Bio-Manguinhos / Fiocruz *(Government pharma industry)*
33.	Nishioka, Sergio	Brazilian Ministry of Health *(Public health authority)*
34.	Oberle, Doris	Paul Erlich Institute *(Regulatory authority)*
35.	Olsson, Sten	Uppsala Monitoring Centre (*Independent foundation and WHO Collaborating Centre)*
36.	Patel, Mayur	MedImmune / Astra Zeneca *(Pharma industry)*
37.	Ramkishan, Ajmeer	Central Drug Standard Control India *(Regulatory authority)*
38.	Rauscher, Martina	J&J/Crucell (through 2015), Takeda (from 2015) *(Pharma industry)*
39.	Santos, Paulo	Bio-Manguinhos / Fiocruz *(Government pharma)*
40.	Seifert, Harry	GSK *(Pharma industry)*
41.	Shimabukuro, Tom	Centers for Disease Control and Prevention *(Public health agency)*
42.	Sillan, Françoise	Sanofi Pasteur S.A. *(Pharma industry)*
43.	Sjölin-Forsberg, Gunilla	Council for International Organizations of Medical Sciences *(Independent organization)*
44.	Srivastava, Swati	Central Drug Standard Control India *(Regulatory authority)*
45.	Straus, Walter	Merck *(Pharma industry)*

	WG Member Name	Organization (Stakeholder group)
46.	Tebaa, Amina	Centre Anti Poison et de Pharmacovigilance du Maroc (CAPM) *(Public health authority and WHO Collaborating Centre)*
47.	Vellozzi, Claudia	Centers for Disease Control and Prevention *(Public health authority)*
48.	Winiecki, Scott	US Food and Drug Administration *(Regulatory authority)*
49.	Wivel, Ashley	Merck *(Pharma industry)*
50.	Xia, Wei	WHO China *(Country office of U.N. specialized agency for health)*
51.	Youssef, Mona Hassan	EGYVAC-VACSERA *(Government pharma)*
52.	Zuber, Patrick	World Health Organization (*U.N. specialized agency for health*)

Table 7. Meetings of the CIOMS Working Group on Vaccine Safety*

	Date	Location	Host
1.	May 2013	London, UK	European Medicines Agency
2.	September 2013	Geneva, Switzerland	World Health Organization
3.	February 2014	Atlanta, Georgia, USA	Centers for Disease Control and Prevenetion
4.	May 2014	Uppsala, Sweden	Uppsala Monitoring Centre
5.	September 2014	Rabat, Morocco	Centre Anti Poison et Pharmacovigilance du Maroc
6.	May 2015	Lyon, France	Sanofi Pasteur
7.	September 2015	Collegeville, near Philadelphia, Pennsylvania, USA	Pfizer
8.	March 2016	Accra, Ghana	Ghana Food and Drug Authority

* Costs for travel to face-to-face meetings and accommodation were covered by each WG member's parent organization *or by CIOMS as per rules*, and were not covered by the meeting hosts. Numerous virtual meetings by teleconference were arranged and covered both by CIOMS as well as by member organizations.

GLOSSARY

Absolute risk
Probability that a specified event will occur in a specified population, in contrast to the relative risk of the event.

Source: http://medical-dictionary.thefreedictionary.com/absolute+risk

Active Vaccine Safety Surveillance (AVSS)
AVSS is a data collection system that seeks to ascertain as completely as possible the number of AEFIs in a given population via a continuous organized process.

Source: Proposed by CIOMS Working Group on Vaccine Safety.

Adverse Event Following Immunization (AEFI)
Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

Source: Report of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance, 2012.

Aggregate data
In statistics, aggregate data describes data combined from several measurements.
When data are aggregated, groups of observations are replaced with summary statistics based on those observations.

Source: Aggregation and Restructuring of data (chapter 5.6 from the book "R in Action", Manning Publications)

Background rates
Rate of an event (occurring/reported/measured) *due* to all cases fitting the case definition, which are expected to occur in the community in the absence of the putative vaccine.

Source: http://www.who.int/vaccine_safety/initiative/tools/Guide_Vaccine_rates_information_sheet_.pdf

Common Technical Document
The Common Technical Document (CTD) is a set of specification for application dossier for the registration of medicines to the regulatory authorities in the three regions of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). It is an internationally agreed format for the preparation of applications regarding new medicines intended to be submitted to regulatory authorities in participating countries.

Source: Adapted by CIOMS Working Group on Vaccine Safety from ICH, Wikipedia, and FDA definitions.

Knowledge gap
Refers to lack of available or easily accessible information on vaccines in countries which need the respective information in contexts like vaccine introduction, new safety issue, change in the nature of the vaccination program, or which have an inadequate passive surveillance system. This lack of information equals a research gap or question which has not been answered sufficiently.

Source: Proposed by CIOMS Working Group on Vaccine Safety.

Passive vaccine safety surveillance
The spontaneous reporting of adverse events following immunization (AEFI) by immunization service providers, hospitals, and patients to the administrative level appropriate in each country depending on its national surveillance system. From there, reports are sent to the next reporting level(s), ending at the international institutions responsible for global AEFI surveillance.

Source: Adapted for this context from WHO Global manual on surveillance of adverse events following immunization, 2014.

Vaccine Pharmacovigi-lance
"Vaccine pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding, prevention, and communication of adverse events following immunization, or of any other vaccine- or immunization-related issues."

Source: Report of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance, 2012.

Serious AEFI
AEFI that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Any medical event that requires intervention to prevent one of the outcomes above may also be considered as serious.

Source: WHO Global manual on surveillance of adverse events following immunization, 2014.

Significant knowledge gap
If the knowledge gap has the potential to negatively influence the benefit-risk profile of the vaccine to such a degree that it could significantly affect the safety of those receiving vaccinations, it can be described as a significant knowledge gap (SKG).

Source: Proposed by CIOMS Working Group on Vaccine Safety.

Surveillance
The continuing, systematic collection of data that are analysed and disseminated to enable decision-making and action to protect the health of populations.

Source: WHO Global manual on surveillance of adverse events following immunization, 2014.

Vaccine safety
The process that maintains the highest efficacy of, and lowest adverse reaction to, a vaccine by addressing its production, storage and handling. Vaccine safety is a part of immunization safety.

Source: WHO Global manual on surveillance of adverse events following immunization, 2014.

BIBLIOGRAPHIC REFERENCES

Authored Works Cited:

Ali M et al. The use of a computerized database to monitor vaccine safety in Viet Nam. Bulletin of the World Health Organization 2005;83:604-610. http://www.who.int/bulletin/volumes/83/8/604.pdf.

Andrews N. Epidemiological designs for vaccine safety assessment: Methods and pitfalls. Volume 40, Issue 5, September 2012, Pages 389–392. doi:10.1016/j.biologicals.2011.08.010.

Asturias EJ, Contreras-Roldan IL, Ram M, Garcia-Melgar JA, Morales-Oquendo B, Hartman K, et al. Post-authorization safety surveillance of a liquid pentavalent vaccine in Guatemalan children. Vaccine 2013; 31:5909-5914.

Berhane Y, Worku A, Demissie M, Tesfaye N, Asefa N, Aniemaw W, et al. Children who received pcv-10 vaccine from a two-dose vial without preservative are not more likely to develop injection site abscess compared with those who received pentavalent (DPT-HepB-Hib) vaccine: A longitudinal multi-site study. PLOS ONE 2014;9(6): e97376. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0097376.

Breugelmans JG, Lewis RF, Agbenu E, Veit O, Jackson D, Domingo C, et al. Adverse events following yellow fever preventive vaccination campaigns in eight African countries from 2007 to 2010. Vaccine 2013;31:1819-1829.

Clothier HJ, Lee KJ, Sundararajan V, Buttery JP and Crawford NW. Human papillomavirus vaccine in boys: background rates of potential adverse events. Med J Aust 2013; 198 (10): 554-558.doi: 10.5694/mja12.11751.

Coggon D, Rose G, and Barker D. Epidemiology for the uninitiated, Chapter 8: Case-control and cross sectional studies, 4th ed. http://www.bmj.com/about-bmj/resources-readers/publications/epidemiology-uninitiated.

Crawford NW, Clothier H, Hodgson K, Selvaraj G, Easton ML, Buttery JP. (2014) Active surveillance for adverse events following immunization, Expert Review of Vaccines, 13:2, 265-276, http://dx.doi.org/10.1586/14760584.2014.866895.

Djingarey MH, Barry R, Bonkoungou M, Tiendregeogo S, Sebgo R, Kandolo D et al. Effectively introducing a new meningococcal A conjugate vaccine in Africa: The Burkina Faso experience. Vaccine: 30S (2012) B40– B45.

Farrington CP Relative Incidence Estimation from case series for vaccine safety evaluation. Biometrics 51, 228-235. March, 1995.

Field Epidemiology, Gregg, M ed., Print publication date: 2008, Published to Oxford Scholarship Online: September 2009, DOI: 10.1093/acprof:oso/9780195313802.001.0001.

Gangarosa EJ1, Galazka AM, Wolfe CR, Phillips LM, Gangarosa RE, Miller E, Chen RT. Impact of anti-vaccine movements on pertussis control: the untold story. Lancet. 1998 Jan 31;351(9099):356-361.

Hanley JA, Lippman-Hand A . If nothing goes wrong, is everything alright? (For the rule of 3 reference.) JAMA 1983; 259: 1743–5.

Kieny MP and Rägo L. Regulatory policy for research and development of vaccines for public health emergencies, Expert Review of Vaccines, 2016, http://www.tandfonline.com/doi/abs/10.1080/14760584.2016.1188695.

Kleinbaum, DG. Department of Epidemiology, Emory University, Atlanta, Georgia, USA, ActiveEpi Web, online course, 15 chapters, registration required, http://activepi.herokuapp.com.

Kompithra RZ, Sarkar R, Mathew LG, Muliyil J, Kang G. Study of common illnesses before and after vaccination: A risk interval approach. Indian Pediatr. 2015 Nov; 52(11):933-8.

Madsen KM, Lauritsen MB, Pedersen CB, Thorsen P, Plesner AM, Andersen PH, Mortensen PB. Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. Pediatrics. 2003 Sep; 112(3 Pt 1):604-606.

Mansouri M, Lockyer J. A meta-analysis of continuing medical education effectiveness. J Contin Educ Health Prof. 2007 Winter; 27(1):6-15.

Menezes Martins R, Lourdes de S. Maia M, Matos dos Santos E, et al. Yellow fever vaccine post-marketing surveillance in Brazil. *Procedia in Vaccinology* 2(2010)178-83.

Mpimbaza A, Filler S, Katureebe A, et al. Verbal autopsy: evaluation of methods to certify causes of death in Uganda. PLoS One 2015Jun18;10(6):e0128801.

Ouandaogo CR, Yaméogo TM, Diomandé FV, Sawadogo C, Ouédraogo B, Ouédraogo-Traoré R, et al. Adverse events following immunization during mass vaccination campaigns at first introduction of a meningococcal A conjugate vaccine in Burkina Faso, 2010. Vaccine: 30S (2012) B46– B51.

Patel MM, López-Collada VR, Bulhões MM, Oliveira LH, Márquez AB, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. N Engl J Med 2011;364:2283-92.

Pronyk PM, Kahn K, Tollman SM. Using health and demographic surveillance to understand the burden of disease in populations: the case of tuberculosis in rural South Africa. Scand J Public Health Suppl. 2007 Aug;69:45-51.

Sankoh O, Byass P. The INDEPTH Network: filling vital gaps in global epidemiology. Int J Epidemiol. 2012 Jun;41(3):579-88. doi: 10.1093/ije/dys081. http://www.indepth-network.org/about-us/our-past-present-future.

Soltani M, Bouanene I, Trabelsi A, Harbi A, Hachicha M, Amri F, et al. Epidemiology of rotavirus gastroenteritis among children under 5 years of age in Tunisia – Results of sentinel hospital surveillance 2009 to 2011. Revue d'Epidemiologie et de Sante Publique 2012;60:473-80.

Strom, BL. Overview of automated databases in pharmacoepidemiology, in Pharmacoepidemiology, Fifth Edition (eds B. L. Strom, S. E. Kimmel and S. Hennessy), Wiley-Blackwell, Oxford, UK, 2012.

Weldeselassie YG, Whitaker HJ, Farrington CP. Use of the self-controlled case-series method in vaccine safety studies: Review and recommendations for best practice. Epidemiology and Infection. 2011 139:12 (1805-1817).

Institutional documents cited:

Centers for Disease Control and Prevention (CDC). Immunization Safety Office, Vaccine Safety Datalink (VSD), http://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/.

Centers for Disease Control and Prevention (CDC). Intussusception among recipients of rotavirus vaccine–United States, 1998-1999. MMWR Morb Mortal Wkly Rep. 1999 Jul 16;48(27):577-581.

Centers for Disease Control and Prevention (CDC). Manual for the surveillance of vaccine-preventable diseases. Centers for Disease Control and Prevention, Atlanta, GA, 2008, http://www.cdc.gov/vaccines/pubs/surv-manual/.

CIOMS. Definition and application of terms for vaccine pharmacovigilance. Report of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Geneva: Council for International Organizations of Medical Sciences (CIOMS), 2012, http://www.cioms.ch/index.php/2012-06-10-08-47-53/working-groups/vaccine-pharmacovigilance/definition.

CIOMS. International ethical guidelines for health-related research involving humans. Geneva: Council for International Organizations of Medical Sciences (CIOMS), 2017.

CIOMS. International ethical guidelines on epidemiological studies. Geneva: Council for International Organizations of Medical Sciences (CIOMS), 2009. ISBN: 929036081X, http://www.cioms.ch/index.php/2012-06-10-08-47-53/ethics/cioms-guidelines-working-group.

European Medicines Agency, Guidance for the format and content of the protocol of non-interventional post-authroisation safety studies. 26 Sept 2012. Patient Health Protection. EMA/623947/2012.

European Medicines Agency. Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies. 30July2013. 7 Westferry Circus Canary Wharf London United Kingdom. http://www.ema.europa.eu/docs/en_GB/document_library/ Regulatory_and_procedural_guideline/2013/01/WC500137939.pdf.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on methodological standards in pharmacoepidemiology (Revision 4). EMA/95098/2010. http://www.encepp.eu/standards_and_guidances.

International Society for Pharmacoepidemiology (ISPE). Data privacy, medical record confidentiality, and research in the interest of public health. 1 Sep1997, amended 19Aug1998. “Members of the Ad Hoc Committee on Data Privacy in the US, Canada, and the European Union.” International Society For Pharmacoepidemiology (ISPE) 5272 River Road, Suite 630, Bethesda, MD, USA, http://www.pharmacoepi.org/resources/privacy.cfm.

International Society For Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP); Revision 3; June 2015, Bethesda, MD, USA.

London School of Hygiene and Tropical Medicine. The use of epidemiological tools in conflict-affected populations: open –access educational resources for policy-makers (conflict.lshtm.ac.uk).

University of Bern, Institute of Social and Preventive Medicine, Clinical Epidemiology & Biostatistics. Strengthening the reporting of observational studies in epidemiology (STROBE) Checklists, Version 4, Oct/Nov 2007, Bern, Switzerland, http://www.strobe-statement.org.

US Food and Drug Administration. Post-licensure Rapid Immunization Safety Monitoring (PRISM) system, http://www.mini-sentinel.org/work_products/PRISM/PRISM_Summary.pdf. http://www.mini-sentinel.org.

World Health Organization, Emergencies preparedness response, Pandemic and Epidemic Diseases (PED), International Coordinating Groups (ICG) on Vaccine Provision, www.who.int/csr/disease/icg/.

World Health Organization, Emergency Use Assessment and Listing procedure (EUAL) for candidate vaccines for use in the context of a public health emergency. http://www.who.int/medicines/news/EUAL-vaccines_7July2015_MS.pdf.

World Health Organization, Health Systems and Services: Prequalification of Medicines Programme, http://apps.who.int/prequal/.

World Health Organization, Immunization standards, Revised procedure for expedited review of imported prequalified vaccines for use in national immunization programmes, 17 July 2015, www.who.int/immunization_standards/vaccine_quality/expedited_review.

World Health Organization, Immunization Standards, Vaccine Quality, Prequalified Vaccines, http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/.

World Health Organization, Immunization Standards, Vaccine Quality, Prequalified Vaccines, www.who.int/immunization_standards/vaccine_quality/vq_index.

World Health Organization. Ethical issues in patient safety research, 2013, ISBN 978 92 4 150547 5. Published by WHO press, 2013. www.who.int/patientsafety/research/ethical_issues/.

World Health Organization, Global Advisory Committee on Vaccine Safety, December 2010, http://www.who.int/vaccine_safety/committee/reports/Dec_2010/en/.

World Health Organization. Global manual on surveillance of adverse events following immunization, 2014 (Revised March 2016), http://www.who.int/vaccine_safety/publications/aefi_surveillance/en/.

World Health Organization. Global Vaccine Safety Blueprint Geneva, 2012, v Glossary, (www.who.int/vaccines-documents).

World Health Organization. The Global Vaccine Safety Initiative (GVSI). The eight strategic objectives: #8 public-private information exchange. 15 April 2014, http://www.who.int/vaccine_safety/initiative/public_private/.

World Health Organization. Components of a 21st century global vaccine safety monitoring, investigation, and response system. Module 5: vaccine safety institutions and mechanisms, Vaccine safety basics learning manual, www.vaccine-safety-training.org.

The CIOMS Guide to Active Vaccine Safety Surveillance addresses the situation facing any country in which a new vaccine is being introduced for the first time and vaccine safety needs to be assured. With more vaccine solutions available and opportunities for earlier availability of new vaccine products in resource-limited countries (e.g. such as vaccines against rotavirus, human papillomavirus or pneumococci) as well as new products that address diseases endemic in those countries only (e.g. malaria, dengue among others), generating reliable data about specific safety concerns is becoming a priority for all countries.

The Guide offers a practical step-by-step approach and algorithm to aid immunization professionals and decision-makers in determining the best course of action if additional vaccine safety data is needed. The Guide provides a structured process for evaluating whether significant knowledge gaps exist, whether passive safety surveillance is adequate, and if not, methods for and practical aspects of conducting active vaccine safety surveillance. The Guide also includes an essential vaccine information source list for evaluating the extent of data resources and several case studies for review.

CIOMS Guide to active vaccine safety surveillance: report of CIOMS Working Group on Vaccine Safety. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2017.

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