Global Vaccine Safety Blueprint 2.0

(GVSB2.0)

2021–2023

World Health Organization

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ISBN 978-92-4-003696-3 (electronic version)
ISBN 978-92-4-003697-0 (print version)

Suggested citation. Global vaccine safety blueprint 2.0 (GVSB2.0) 2021-2023. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Contents

Acknowledgments

This document was prepared to address the findings from background research published in July 2019 *(1)*, under the leadership of the **WHO Secretariat for the Global Vaccine Safety Initiative** (Patrick Zuber, Christine Guillard, Isabelle Sahinovic, Madhava Ram Balakrishnan), based on a first draft prepared by the **Institute for Vaccine Safety (IVS) at Johns Hopkins Bloomberg School of Public Health** (Daniel A. Salmon, Matthew Z. Dudley, Tina Proveaux). The original draft was revised, based on comments received from two rounds of public consultation in October and November 2019, and from the Global Summit for Vaccine Safety in December 2019.

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Abbreviations and acronyms

AEFI	Adverse events following immunization
AVSS	Active vaccine safety surveillance
CFS	Chronic fatigue syndrome
CIOMS	Council for International Organizations of Medical Sciences
CRPS	Complex regional pain syndrome
DHIS2	District Health Information System 2
GACVS	Global Advisory Committee on Vaccine Safety
GBT	Global Benchmarking Tool
GVSB1.0	Global Vaccine Safety Blueprint, 2012
GVSB2.0	Global Vaccine Safety Blueprint, 2021
GVSI	Global Vaccine Safety Initiative
ISRR	Immunization stress-related response
LLDB	Large linked data bases
LMIC	Low- and middle-income countries
MERS	Middle-East respiratory syndrome
NGO	Non-governmental organizations
NIOH	Norwegian Institute of Public Health
NITAG	National Immunization Technical Advisory Group
NRA	National regulatory authorities
POTS	Postural orthostatic tachycardia syndrome
RITAG	Regional Immunization Technical Advisory Group
SAGE	Strategic Advisory Group of Experts
SARS	Severe acute respiratory syndrome
SF	Substandard and falsified health products
UNICEF	United Nations Children's Fund
VSN	Vaccine Safety Net
WHO	World Health Organization

Prologue

A World Health Organization (WHO) Transformation was launched by the Director-General Dr Tedros Adhanom Ghebreyesus when he took up office in 2017. The goal of Transformation is to make WHO a modern, seamless, impact-focused organization to help Member States achieve the health-related Sustainable Development Goals better, in the context of the United Nations Reform. Through its design and implementation, the Transformation has promoted a new, impact-focused, collaborative, and agile culture. Ultimately, Transformation aims to ensure WHO has a positive impact on people's health by producing the appropriate norms, standards, and technical guidance, and then helping to use these at country level in the policies and programmes of governments and their implementation partners. This requires change in both the way WHO programmes operate across the three levels of WHO and in WHO's presence in country. With the 'three-level' changes introduced to date, and the completion of a substantial number of functional reviews of country office in 2019, further attention is being given to the adjustments needed to ensure predictable, fit-for-purpose WHO capacity at country level.

Applying the Transformation principles to the safety and vigilance work in WHO has meant that the vaccines- and medicines-safety work groups have been brought together to form a new, merged team, the Pharmacovigilance Group (PVG). PVG sits within the Regulation and Safety Unit of the Department of Regulation and Prequalification (RPQ). The rationale for this merger was based on the fact that there are more commonalities than differences in how pharmacovigilance for the vaccines and medicines is carried out. This is why most regulatory authorities do not have separate systems or processes for monitoring the safety of vaccines and medicines. The merger is a step towards supporting an integrated pharmacovigilance system, which will still recognize the necessary differences between vaccines (mostly as preventive therapies) and medicines (mostly as curative treatments).

The relocation of the new PVG team within the Regulation and Safety unit is intended to provide a better regulatory context and framework for the WHO-safety work, and sustain efforts to strengthen PV systems in countries as a regulatory deliverable. The Regulation and Prequalification action plan outlines the strategic priorities and activities which be used to attain this objective *(2)*.

This Global Vaccines Safety Blueprint 2.0 (GVSB2.0) was developed through a step-wise consensus process to define the strategic priorities and objectives in the area of vaccines safety for 2021 to 2023 and beyond. The overall vision, goals and operating principles for a vaccine safety monitoring system described in the GVSB2.0 are equally relevant for medicines and for building product-agnostic pharmacovigilance systems in countries. Where possible, we need to build common systems and approaches that are smart, product-agnostic, address common needs and advance the principles of work-sharing and reliance to take into consideration competing priorities in resource-limited settings. For example, how we collect and manage data (databases) may not be very different between vaccines and medicines; on the other hand, the principles of benefit risk assessment and how risks are communicated requires specialized and perceptive handling for vaccines.

To improve the support of the overall concept of an integrated pharmacovigilance system, the experience gained from the implementation of the GVSB2.0 during 2021–2023 will inform the development of an overarching strategy document providing direction for pharmacovigilance for both vaccines and medicines to the Member States and the WHO. While doing so, the implementation mechanism of the GVSB2.0 called the Global Vaccine Safety Initiative (GVSI) will progressively transition to the newly established WHO network for regulatory systems

strengthening, named 'Coalition of interested parties (CIP)' *(3)*. The purpose of this network is to establish and promote a unified strategic and coordinated approach to strengthening national and regional regulatory systems, to ultimately increase the effectiveness of collective efforts and to achieve the desired impact in countries and regions. The Coalition of interested parties encompasses all regulatory functions, including pharmacovigilance, and will ensure a comprehensive and coordinated approach to capacity building.

INTRODUCTION

Moving from a minimal and enhanced capacity concept to maturity levels

As vaccines and other preventive health interventions have dramatically reduced the incidence and severity of many infectious diseases, tolerance for adverse reactions related to these interventions has decreased in the population. Rare vaccine reactions or individual vulnerability to vaccines can only be detected after vaccines are introduced widely when they can be identified through observational studies. It is therefore critical to monitor and update vaccine safety profiles continuously throughout the product life-cycle as has been demonstrated by the COVID-19 pandemic *(4)*. The Global Vaccine Safety Blueprint (GVSB) provides strategies to establish systems that optimize the monitoring of vaccine safety profiles throughout their life-cycle. The intended audience for the GVSB are all vaccine safety stakeholders: vaccine recipients, those who administer vaccines, regulators, manufacturers and all experts and organizations involved with vaccine administration.

The main goals of vaccine safety systems are universal, regardless of the country or region. These include to:

- fully characterize the safety profile of vaccines in use, to support risk-benefit assessments that inform public health policies;
- detect adverse reactions when they occur;
- manage and treat adverse reactions that occur;
- determine the biological mechanism for adverse reactions;
- prevent adverse reactions, when possible;
- determine when adverse events following immunization (AEFIs) are not caused by vaccines; and
- communicate all the above in an accurate, credible, and timely manner to the media, healthcare providers, policy-makers and the public.

The vision of the first Global Vaccine Safety Blueprint published in 2012 (GVSB1.0) was `everyone everywhere is protected by safe and effective vaccines'. It described the goals of vaccine safety systems in two parts: **minimal capacity** and **enhanced capacity** (see Annex 1).

Although the **minimal capacity** elements are critical for any vaccine safety system, their reliance on surveillance systems based on spontaneous reporting alone leave them unable to perform rapid assessments of causality. It also limits timely detection of vaccine safety signals and early post marketing monitoring of novel products. Rapid response to vaccine safety signals is required to identify rare, but real, adverse reactions when they occur, so that their impact can be minimized. Adverse events following immunization (AEFIs) are any untoward medical occurrence that follows immunization, but which does not necessarily have a causal relationship with the vaccine administered. AEFIs include:

- vaccine product-related reactions;
- vaccine quality defect-related reactions;
- immunization error-related reactions;
- immunization anxiety-related actions; and
- coincidental events.

The first four are reactions caused by the vaccine or the process of vaccination whereas coincidental events are temporally but not causally related to the vaccine. In GVSB1.0, it was determined that countries where an increased level of vaccine safety activity was judged to be necessary, such as those where newly developed vaccines were being introduced or those that manufacture and use prequalified vaccines, should strive for **enhanced capacity.**

GVSB1.0 had three strategic goals:

1. to help low- and middle-income countries (LMICs) to implement at least minimal capacity for vaccine safety activities;

2. to enhance capacity for vaccine safety assessment in countries that introduce newly-developed vaccines, that introduce vaccines in settings with novel characteristics, or that both manufactured and used prequalified vaccines; and

3. to establish a global vaccine safety support structure.

These goals remain fully relevant and the GVSB2.0 will maintain them whilst expanding its scope to all World Health Organization (WHO) Member States.

Since the development of GVSB1.0, surveillance of AEFIs has improved significantly at a global level, in part due to the creation of tools and methods to assist with pharmacovigilance. While capacity is improving in LMICs, many of the same challenges identified in GVSB1.0 remain. These challenges include:

- effective collaboration with clear roles and responsibilities;
- timely provision of safety data on vaccine quality to national regulatory authorities (NRAs) and immunization programmes including surveillance units and healthcare workers;
- more capacity to exchange information across countries and with industry; and
- more effective use of strategic communication.

A landscape analysis to assess the impact and strategic direction of the first Global Vaccine Safety Blueprint (GVSB1.0) was conducted in 2019 for WHO *(1)*. Vaccine safety experts, national regulatory officials, immunization programme managers, global agencies, industry, non-governmental organizations (NGOs), and others were surveyed to collect their initial recommendations for the Global Vaccine Safety Blueprint 2.0 (GVSB2.0). This analysis found that, although many of the issues discovered during the creation of GVSB1.0 remain, new challenges have also emerged. Those new challenges include the relevance of safety concerns to vaccine hesitancy, vaccine safety in fragile states and during emergencies, governance and financing of global vaccine safety systems, and importance of an accountability framework to manage progress and expectations. WHO's General Programme of Work, Sustainable Development Goals, WHO's five-year plan aiming to build effective and efficient regulatory systems and the Immunization Agenda 2030 provide the framework for GVSB2.0 to maximize its impact and utility for the coming years *(5, 6)*.

An important objective of the GVSB2.0 is to provide the best available scientific evidence to increase public understanding of the distinction between AEFIs that are real vaccination reactions and coincidental events. Better vaccine safety infrastructure and data will help to address this challenge, as will improved communication strategies. The recent development of the Vaccine Safety Net (VSN), a global network of websites that provides reliable information on vaccine safety, established by WHO, has demonstrated the value of social networks to share scientific and trusted vaccine safety information to proactively combat the rise of vaccine and vaccination misinformation *(7)*. Another challenge is the increasing number of outbreaks and other emergencies, particularly in fragile states with weak primary healthcare or in situation of conflict. GVSB2.0 provides guidance on monitoring vaccine safety in such settings and managing crisis communications during an outbreak.

To build upon GVSB1.0, rather than repeating this comprehensive approach, GVSB2.0 maintains the same vision of equity with respect to benefiting from safe vaccines. It differs in that it focuses on six key priorities to maximize its impact in the coming years. Several strategic objectives of the GVSB1.0 have been grouped under the AEFI surveillance strategic area (including detection, investigation, tools and training). The regulatory framework and enhanced communication areas are substantially strengthened, and new strategic areas identified by the landscape analysis were added. For each of these key priorities, GVSB2.0 provides objectives, strategies, and an accountability framework, with examples of real vaccine safety issues that demonstrate the application of the strategies.

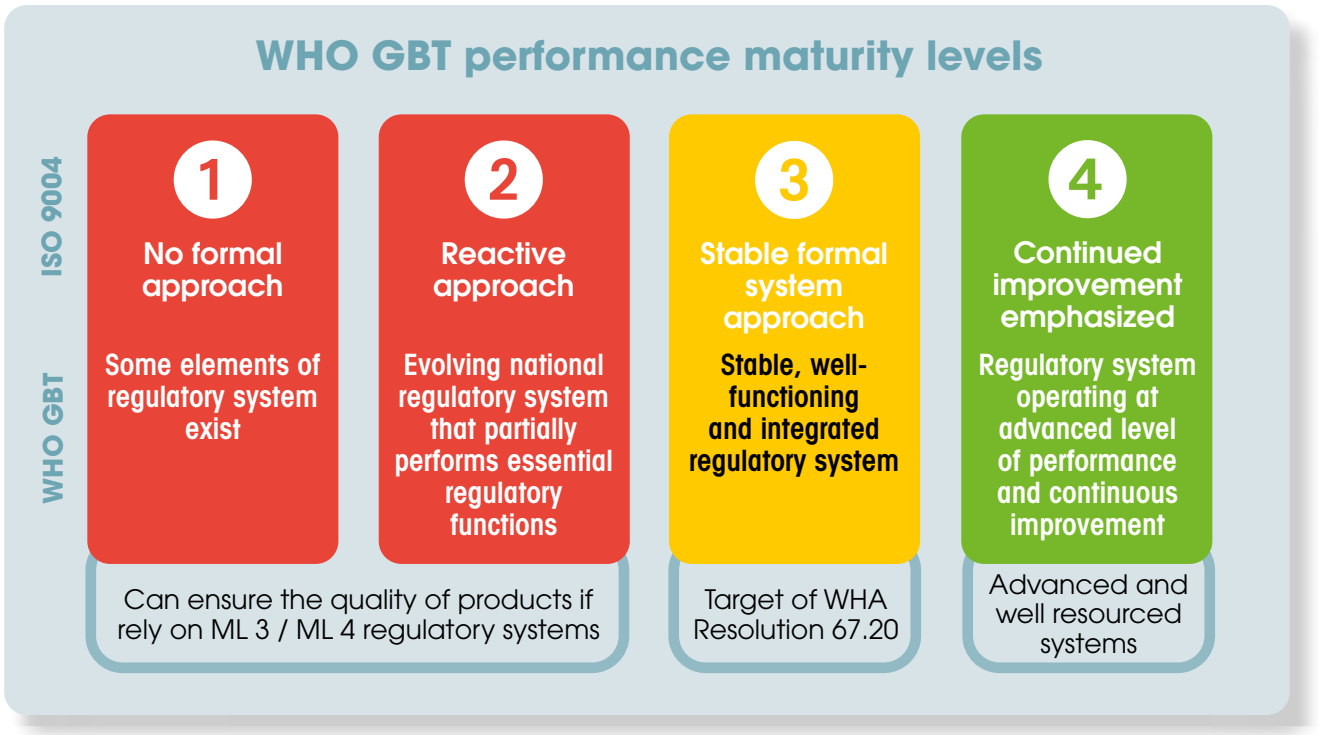
Beyond these strategic focus areas, GVSB2.0 aligns with the Immunization Agenda 2030 core principles *(6)*:

- people-centred,
- country -owned,
- partnership-based, and
- data-driven.

The strategic area on development of governance and systems discusses aspects such as expert advisory structures, resources, and funding (including funding for active surveillance and hypothesis-testing capacities). GVSB2.0 also emphasizes the need for an accountability framework, and its development. This covers the need for a specific monitoring and evaluation framework to analyse progress within each strategic focus area over time, using a stepwise process.

The GVSB2.0 expands upon the dichotomous minimal and enhanced capacity concept by incorporating the concept of maturity levels. The four **maturity levels** enable WHO and regulatory authorities to assess the level of development of monitoring and regulatory systems, using a scale from 1 to 4 (Figure 1; Annex 2).

Fig. 1. Maturity levels concept adapted to the national regulatory functions (including the pharmacovigilance function)



WHO has developed a Global Benchmarking Tool (GBT) to evaluate national regulatory systems using this maturity level concept *(8)*. Countries and WHO can identify the gaps and challenges to drive the improvement of the system, based on the maturity level of the national regulatory system, which can then be used to establish a solid framework for public health interventions.

In GVSB2.0, the pharmacovigilance resources, and managerial elements for each of the four maturity levels have been reorganized, instead of just minimal versus enhanced capacity as in GVSB1.0. This updated organization is summarized in Table 1 and more complete information can be found in Annex 1.

Table 1: Summary of the current WHO Global Benchmarking Tool vigilance sub-indicators per maturity levels (full version in Annex 2)

	MATURITY LEVELS			
INDICATORS	**Level 1 sub-indicators**	**Level 2 sub-indicators**	**Level 3 sub-indicators**	**Level 4 sub-indicators**
VL01 Legal provisions, regulations and guidelines required to define regulatory framework of vigilance	Legal provisions for a national vigilance system exist which: • require the manufacturers to set up a vigilance system for their medical products and periodically report vigilance data to the NRA • allow reliance on vigilance-related decisions from other bodies	Legal provisions allow NRA to require manufacturers to conduct specific safety studies	Legal provisions require manufacturers to designate an individual to be responsible for vigilance Guidelines for planning, conducting, monitoring, and reporting of vigilance activities are available	
VL02 Arrangement for effective organization and good governance		Defined organizational structure with clear roles and responsibilities	Documented procedures to ensure involvement, coordination and communication among all relevant stakeholders	
VL03 Human resources to perform vigilance activities			Sufficient competent staff with adequate job descriptions, implemented and documented training plan	
VL04 Established and implemented procedures to perform vigilance activities	Staff access to relevant information resources is ensured		Procedures for collection and assessment of AEFIs are implemented, and include a risk approach and access to expert committees for review of serious emergent safety concerns	Standard procedures are implemented for the national vigilance system and include regular assessment of the risk-benefit balance and active vigilance activities
VL05 Mechanism in place to monitor regulatory performance and output			Vigilance information used in timely manner to update regulatory decisions	Performance indicators for vigilance activities are implemented
VL06 Transparency, accountability and communication		Vigilance activities appropriately communicated to the public	Mechanism for regular feedback accompanied with a risk communication plan and data shared with relevant partners	

STRATEGIC AREAS

I Governance and systems development
II Coordination of safety systems
III Regulatory framework
IV Surveillance of adverse events following immunization (AEFI)
V Enhanced vaccine safety communication
VI Fragile states and emergencies

STRATEGIC AREA I

Governance and systems development

Introduction

Implementing the GVSB2.0 will require aiming for a close collaboration between global vaccine safety stakeholders. Following endorsement of GVSB1.0 by SAGE in 2012, the Global Vaccine Safety Initiative (GVSI), the implementation mechanism of the blueprint, was established in 2013. *(9, 10)* WHO Members States and partners collaborated to implement the GVSB1.0 strategy, which focused on increasing the capacity in LMICs and enabling them to achieve a minimal standard. In 2009, the Global Advisory Committee on Vaccine Safety (GACVS) identified several organizations that have demonstrated interest and have experience in helping WHO Member States in their vaccine safety activities *(11)*. These include:

- governmental institutions (immunization programmes, pharmacovigilance centres and agencies involved in regulatory activities);
- intergovernmental organizations (including WHO and UNICEF);
- international nongovernmental organizations and academic institutions;
- international industry umbrella organizations; and
- WHO Collaborating Centres.

They are involved with capacity building and development of tools, signal detection and evaluation, analysis and response and monitoring individual products. Those organizations are active internationally, either for a group of countries or at the global level. Optimizing the work of a broad and diverse group of partners requires an agile coordination mechanism for governance and funding.

Governance

Rationale

GVSI that implemented GVSB1.0, is not a legal entity; it is a WHO mechanism for enhancing vaccine safety by providing a framework for WHO to bring together its Member States and partners to implement the key strategies in the GVSB.

Over time, the GVSI actions have evolved from attempts to develop and implement work plans, to periodic calls with a planning group, that later became a strategic priority group, with the initiation of various information mechanisms. The GVSI has held seven general meetings and its terms of reference are available *(10)*. There is a need to improve the GVSI structure, to demonstrate the transparency of vaccine pharmacovigilance and to improve the monitoring of its progress. For this reason, the GVSB2.0 also includes a section on the accountability framework and proposes to establish a GVSI Observatory to develop indicators of vaccine safety surveillance, to provide continual progress monitoring, and to link to vaccine safety resources for GVSI members.

Objective: provide the structure for effective decision-making in support of vaccine safety

The main objective of governance and systems development is to provide the structure for effective decision-making in support of vaccine safety. This includes the framework and foundation for development of capacities and feedback that allows the system to function and mature at national, regional, and global levels.

Strategies for objective

A. *Strengthen* the GVSI by providing dedicated secretarial resource and an enhanced structure.
B. *Report* on the accountability framework at each GVSI general meeting *and disseminate* the assessments.

System funding and financing

Rationale

Vaccine safety systems serve both to minimize risks from vaccination by identifying and preventing serious vaccine adverse reactions and maintaining public confidence in immunization systems by addressing concerns about the safety of vaccines. In both cases, adequate funding of vaccine safety systems helps avoid costly negative outcomes, such as the cost of medical care for individuals who experience serious vaccine adverse reactions and the medical and social costs of individuals who suffer from vaccine preventable diseases due to declining immunization rates following a loss of public confidence in an immunization programme. Given the important roles of vaccine safety systems in immunization programmes, adequate dedicated resources need to be provided that do not compete with other health and non-health resource needs.

Immunization programmes should have a dual mission of preventing infectious diseases through vaccination and preventing vaccine adverse reactions. Many vaccine safety activities can be potentially integrated with other immunization programme activities, ensuring efficient performance of those activities. However, it is important that this integration does not have a negative impact on objective AEFI detection, reporting, and response. For example, the same public and private sector healthcare workers who identify, treat, and report cases of vaccine preventable diseases can also identify, treat, and report AEFIs. Field epidemiologists who investigate cases of infectious diseases can also conduct initial AEFI investigations. Risk communication systems that can provide information about epidemics of vaccine preventable diseases can also provide information about vaccine safety. Responses to vaccine and vaccination safety issues can be funded either by industry, for responses involving the vaccine or the vaccination device, or by governments and partner agencies, such as Gavi the Alliance, UNICEF, etc., for responses involving the vaccination programme. However, some response activities are specific to vaccine safety and these require dedicated resources, including:

- development of vaccine safety guidelines and training materials on the identification, treatment, and reporting of AEFIs;
- causality assessment committee functioning, including in-depth examinations of potential causes of serious AEFIs and deaths; and
- responses to newly identified vaccine safety risks, such as the recall of suspect vaccine lots.

In countries that choose to operate them, vaccine injury compensation programmes also require resources *(12, 13)*.

Although vaccine safety surveillance with spontaneous reporting is needed in all countries, funding is also needed for sentinel and active surveillance sites conducting detailed post marketing surveillance for AEFIs. A few such sites may generate sufficient data for entire regions or, in some cases, the entire world, so not all countries need to maintain active surveillance. For new vaccines, active surveillance is often most valuable when conducted in the first countries that introduce the vaccine. Applying the principles of reliance and work sharing, other countries may then learn from the experiences in these countries and may not need to conduct active surveillance themselves. Similar considerations apply for active surveillance to determine background rates of potential adverse events. Given the resources needed for the high-quality data generated by active surveillance and the small number of active surveillance sites usually needed for assessing a given new vaccine, it could be possible to have different funding sources and implementing groups for the different surveillance systems.

For vaccine safety systems to maintain the objectivity and public confidence that are essential for successful operations, it is important that their funding sources do not create any real or perceived conflicts of interest. As a result, private individuals and organizations that have a financial interest in the findings of vaccine safety systems should not use voluntary contributions to influence the functioning of vaccine safety systems, and these private individuals and organizations should not control or unduly influence decisions made by public organizations about vaccine safety activities. However, public organizations, such as NRAs, may require manufacturers to conduct or fund specific safety studies as needed, and manufacturers may choose to fund sites to conduct active post marketing surveillance for AEFIs, potentially including determination of background rates of disease. In both cases, a high level of scientific rigour should be used for the methods and conduct of the studies and the ultimate responsibility and authority for making subsequent and specific vaccine safety policy decisions should remain with the public organizations. Funding for public vaccine safety systems should give vaccine safety staff, especially the staff involved with vaccine safety activities described above, substantial autonomy in setting their priorities and selecting the approaches for minimizing serious vaccine adverse reactions and addressing concerns about vaccine safety. At the same time, the vaccine safety staff must use this autonomy with discretion and transparency and not, for example, favour certain manufacturers or groups over others for commercial or political reasons.

Objectives

Objective 1: Encourage provision of adequate resources for the operations undertaken by public vaccine safety systems

Mobilizing adequate resources for the operations of vaccine safety systems can be difficult, given the many competing demands for resources and the need for funding sources to be compatible with maintaining objectivity and public confidence in public vaccine safety systems. However, evidence for the value of strong vaccine safety systems and the potential consequences if they are absent, combined with the persistence of vaccine safety advocates, can facilitate the mobilization of sufficient resources, particularly in countries with growing economies, and increasing government resources and healthcare budgets.

Vaccine safety is sometimes compared with preventive maintenance or an insurance policy, where the direct benefits are only apparent when an incident, such as a vaccine safety crisis, occurs. Documentation of past vaccine safety crises and their effects can help to demonstrate the potential consequences of inadequate vaccine safety resources to budget holding authorities. In the same way, documentation of potential vaccine safety crises averted or contained through the work of effective vaccine safety systems can help to demonstrate the value of providing adequate vaccine safety resources. Such documentation can emphasize that vaccine safety systems provide, not only direct benefits from preventing adverse reactions, but also indirect benefits by helping to avoid the medical and social costs for patients with vaccine preventable diseases due to declining immunization rates following a loss of public confidence in an immunization programme. Events in one country can be very informative for other countries given the global nature of vaccine production and distribution.

Strategies for objective 1:

1A. *Develop* clear vaccine safety system use cases for communications with budget authorities.

1B. *Systematically document* vaccine safety crises and successes and their consequences for use in communications with budget authorities.

Reduction of iatrogenic infections following documentation of the problem and a policy decision to introduce safer technologies

By the 1980s, increasing documentation and awareness of the risks of spreading blood-borne infections such as hepatitis B, hepatitis C, and HIV through reuse of needles and syringes led to international efforts and funding to encourage the development and use of auto-disable syringes in immunization programmes to decrease the likelihood of needles and syringes being reused. Following work by WHO and UNICEF, which was later supported by Gavi, the Vaccine Alliance, the use of auto-disable syringes in immunization programmes has increased dramatically while the price per syringe has declined. This increase in use of auto-disable syringes contributed to a large global decline in the annual number of unsafe injections per person.

This case study highlights Strategy IB i.e., to document vaccine safety problems and successes and their consequences for use in communications with budget authorities.

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Objective 2: Describe public vaccine safety funding options appropriate for the maturity level of the regulatory system in a country

Even within the limits imposed by the need for public vaccine safety system funding sources to be compatible with the maintenance of the objectivity of the system and public confidence in it, there are potentially multiple funding sources, including:

- general government tax revenue;
- taxes on specific goods or services from which revenue are derived for vaccine safety systems, such as excise taxes on vaccines, e.g., a tax on each unit of vaccine purchased;
- donations from multilateral international organizations or foreign governments;
- donations from non-governmental organizations, including private organizations, that do not have a financial interest in the findings of vaccine safety systems.

The relative proportion of funding for vaccine safety systems can vary considerably across countries, depending on how the vaccine safety systems are organized, the scale of their activities, and the government revenues and spending priorities. Guidance for countries on how to choose among these options could help them to access and use funding for vaccine safety most effectively and efficiently.

Strategies for objective 2:

2A. *Establish* a financial task force that will advise WHO on regional and collaborative funding mechanisms for the GVSI and their oversight.

2B. *Develop* guidance for countries on mobilizing funding for vaccine safety work aligned with country maturity level.

Objective 3: Address injuries caused by vaccine reactions or vaccination errors

As countries continue to expand vaccines use and strengthen their safety surveillance with investigative capacity, occasional injuries caused by vaccines or vaccinations will be identified. Although the need for management of vaccine injuries is fundamental, approaches vary substantially between countries depending on factors such as the healthcare and social services systems. Fair and appropriate compensation also requires the capacity to determine which AEFIs are truly caused by vaccines or vaccination.

Progress with vaccine safety surveillance will increase demands for proper handling of vaccine or vaccination adverse reactions and examination of the relevance of injury compensation schemes. Such programmes will have to take into consideration the diversity of countries with regards to economic capacity, performance of immunization programmes, and availability of social welfare programmes.

Vaccine injury compensation is no longer limited to the wealthiest countries *(14)*. Vaccine injury compensation programmes are no-fault schemes established to compensate individuals who may have experienced a known vaccine adverse reaction. These programmes waive the need for accessing compensation of vaccine-related injuries through litigation and recognizes the unforeseen risk to individuals with special but often unknown susceptibilities to vaccine adverse reactions. To date, only a few WHO Member States have implemented such programmes *(15, 16)*.

Strategies for objective 3:

3A. *Encourage* appropriate analysis and handling of injuries caused by vaccines or vaccination
3B. *Develop* guidance on addressing injuries from vaccine adverse reactions based on available evidence and national circumstances

Developing sustainable vaccine safety systems using public concerns as an opportunity

In the late 1970s and early 1980s, public concerns arose about the safety of whole-cell pertussis vaccines, particularly about potential vaccine-related neurological damage. Subsequent research indicated that there was no association, but several countries suspended pertussis vaccination or had substantially reduced immunization coverage, leading to large pertussis outbreaks until acellular pertussis vaccines became available. The United States of America (USA) responded by developing a vaccine injury compensation programme, funded by an excise tax on vaccines, which provided liability protection to vaccine manufacturers to stabilize the vaccine market, as well as an improved vaccine safety infrastructure. This allowed the USA to continue pertussis vaccination without interruption and avoid pertussis outbreaks. It also has proved critical for detecting and addressing subsequent vaccine safety signals and public vaccine safety concerns related to a range of vaccines.

This case study highlights Strategy 3A i.e., for appropriate handling of injuries caused by vaccines or vaccination.

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STRATEGIC AREA II

Coordination of safety systems

Introduction

There are multiple stakeholders within a vaccine safety system and each of the stakeholders contribute significantly to the operation of the system. In addition to national regulatory authorities and industry, other key players should be involved in the vaccine safety system, including the private sector, immunization advisory bodies, the scientific community, the populations that benefit from immunization and the media that inform them.

The GVSB1.0 focused on adequate coordination and transparency between the public and private sectors, however, better collaborative mechanisms remain to be developed to optimize resources. In addition, coordination mechanisms with the other stakeholders are needed.

Rationale

The importance of close collaboration between regulators and industry is well recognized in vaccine safety activities. Depending on the setting, each stakeholder may obtain limited, and different information about AEFIs, hence the need for improved information exchange and communication mechanisms.

The safety of vaccines is critical to all immunization stakeholders. The GVSB2.0 aims to ensure harmonized, standardized approaches to generating and communicating vaccine safety data for all stakeholders. In this strategic area, information exchange is, therefore, considered in terms of five main objectives.

Objectives

Objective 1: Coordination for exchange of information between vaccine manufacturers (or marketing authorization holders) and national regulatory authorities at local, regional and global levels

Vaccine manufacturers and marketing authorization holders are the first stakeholders that are accountable for the safety, quality and efficacy during the entire product life-cycle for products that receive marketing authorization. NRAs are responsible for the safety, quality and effectiveness monitoring of all authorized vaccines on their territory, and the continuous monitoring in the post marketing phase. Close collaboration and exchange of information between regulatory agencies, health authorities, particularly the immunization programmes, vaccine manufacturers and WHO is therefore key for efficient vaccine safety activities, to keep the vaccine safety profiles updated and to act on any safety concerns identified.

Strategies for objective 1:

1A. *Develop and implement* mechanisms and guidance for systematic and timely exchange of vaccine safety related information (individual case reports, safety signals, findings from post marketing studies and any changes in the risk-benefit profile of the vaccine) between vaccine manufacturers (or marketing authorization holders) and public health authorities at local, regional and global levels, to ensure that the safety profile of each product reflects the most recent information at all levels.

Objective 2: Coordination and information exchange between health authorities and other stakeholders at each level

Effective vaccine safety systems require broad collaboration between national, regional and global health systems. At the national level there should be close, clear communication, with information sharing between regulatory agencies, immunization programmes, disease surveillance activities and healthcare workers. At the most basic level the system should consist of the immunization and clinical service providers (public and private) who submit reports on AEFIs to the local health authority. Other than health service providers at local levels, all other staff and structures are co-responsible and potential participants in the report, management, investigation, and actions for AEFI reports and the ultimate feedback to governmental decision bodies and the public. Depending on the administrative structure for healthcare in a country, there can often be one or more intermediate levels between the immunization service providers and the national immunization safety surveillance organization, therefore the roles and responsibilities of all stakeholders and the mechanism for exchange of information should be clearly defined.

Strategies for objective 2:

2A. *Develop and implement* guidance for vaccine safety surveillance (harmonized with regional and global standard guidelines), defining the roles and responsibilities of health system stakeholders, including regulatory authorities, immunization programmes, services providers and national and global pharmacovigilance stakeholders involved in vaccine safety

2B. *Define* respectful, innovative and effective mechanisms of collaboration and exchange of information between stakeholders and regulatory authorities and foster partnerships and collaborative networks in support of vaccine safety surveillance at national, regional and global levels

Collaboration between national public health and regulatory agencies in Norway

The Norwegian Institute of Public Health (NIPH) is the national centre for vaccine safety and manages individual case safety reports for vaccines on behalf of the national regulatory authority (NoMA).

Healthcare workers are legally required to report serious adverse events following immunization (AEFI) to NIPH. Vaccine safety experts review all reports and provide the reporter with a causality assessment. They also provide advice for further vaccination and register the data in the Norwegian Adverse Drug Reaction Registry. In addition to collaboration on routine safety monitoring, NoMA and NIPH exchange information on emerging safety concerns, signals and events that might trigger media attention. NIPH also receives information on vaccine injury compensation claims submitted to the Norwegian System of Patient Injury Compensation.

NIPH has e-mail and hotline services for healthcare workers, to provide answers to questions on immunization schedules, safety, availability of vaccines and other vaccine-related topics. This service is important for the identification of safety concerns that healthcare workers or the public might have and the need for information. Summaries and statistics on safety and adverse reactions are published regularly.

This example illustrates Strategies 2A and 2B i.e., with roles and responsibilities for vaccine safety surveillance and collaboration and information exchange between stakeholders.

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Objective 3: Coordination and exchange of information between health authorities and advisory bodies at local, regional and global levels

Independent expert advisory bodies can provide advice on vaccine safety issues and can also guide the development of stronger national and international vaccine safety systems. They can provide expertise in multiple areas relevant to the conduct of vaccine safety surveillance, such as clinical medicine, epidemiology, regulation, pathology, statistics and methodology. The national authorities should inform and propose priority agenda items. Currently, the Global Advisory Committee on Vaccine Safety (GACVS), a WHO vaccine safety technical advisory body that was set up in 1999, and national vaccine safety committees, either standalone or part of the mandate of the national immunization technical advisory group (NITAG) are available in a growing number of countries. Regional relays and collaborative mechanisms across levels should be considered. In addition, global networks of voluntary experts have provided extremely valuable tools for harmonization of vaccine safety surveillance (Brighton Collaboration, CIOMS working groups, etc.) and they have the potential of catalysing new initiatives such as distributed data networks *(17, 18)*.

Strategies for objective 3:

3A. *Develop* independent national and regional advisory bodies for vaccine safety that are functionally aligned with NITAGs, regional immunization technical advisory groups (RITAGs) and other bodies involved in vaccine safety.

3B. *Promote* global alignment of methods and collaboration between national and global advisory bodies and examine the need and relevance of similar regional committees.

3C. *Promote* global expert collaborative networks in support of vaccine safety surveillance.

Objective 4: Collaboration between the scientific community and health authorities

Information on all ongoing and completed post marketing safety studies, should be made publicly available to ensure transparency, avoid duplication of efforts, inform the scientific community, facilitate access to all available evidence and update current vaccine safety profiles. Access to information is also important for equity, in particular, for countries that are not in a position to develop this type of resource.

Strategies for objective 4:

4A. *Establish* registries of vaccine safety studies at appropriate levels, until a suitable global model can be proposed.

4B. *Establish* a periodic review of these study registries by the GACVS to ensure the quality and potential impact of studies.

4C. *Develop* technical cooperation and build capacity to help countries to adapt and implement standards for post marketing safety studies.

Coordination mechanisms of the CIOMS Working Group on Vaccine Safety (WG)

The CIOMS Working Group on Vaccine Safety (WG) was established in 2013 to develop guidance documents on harmonized tools and methods for the conduct of vaccine safety surveillance. Cross-sectorial teams including public health agencies, regulatory authorities, industry and other stakeholders identified critical areas where collaboration with the WG was needed. They also produced consensus guides on active vaccine safety surveillance and vaccine safety communication, particularly useful for responsible parties involved in vaccine safety in resource-limited countries.

This case study highlights Strategy 4C, i.e., to develop technical cooperation to help countries to adapt and implement standards for post marketing safety studies.

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Objective 5: Communication between health authorities and the populations they serve

The NRA, immunization programme and other authorities should establish mechanisms of communication on vaccine safety issues directly and through the media with the public. Sources of validated information on vaccines safety should be provided to the public. Education of young children about the value and safety of vaccines should be considered as an investment for the future. People and media should be informed about the importance and complexities of vaccine safety surveillance and should be encouraged to report AEFIs and other safety-related issues to authorities and vaccine manufacturers either directly or via healthcare workers or local authorities.

Strategies for objective 5:

5A. *Establish* mechanisms for communication between regulatory authorities, immunization programmes, ministries of education and other authorities, so that the public is informed about vaccine safety issues and are encouraged to report any concerns about vaccine safety.

STRATEGIC AREA III

Regulatory framework

Introduction

NRAs are responsible for ensuring the quality, safety, and effectiveness of medicines, vaccines, and other medical products used within a country, throughout the product life-cycle. In most countries, vaccines must be registered or authorized by the NRA before they can be used in the population. Marketing authorization is granted based on an assessment that there are adequate data to support the conclusions that the benefits outweigh the risks in the populations for which the vaccine is indicated. However, it is essential to have continuous post marketing surveillance of the quality, safety, and effectiveness of a vaccine to ensure that benefits of the vaccine continue to outweigh the potential risks (life-cycle management). Both NRAs and immunization programmes have specific roles and collective responsibility in ensuring vaccine post marketing safety.

A well-functioning regulatory system based on laws, regulations, and clear procedures is required to have effective vaccine safety monitoring throughout the product life-cycle. This requires investment in systems, processes, infrastructures, administrative support, and human capacity with relevant scientific knowledge and technical expertise. The investment in resources must be sustainable to ensure the long-term stability of the regulatory system. Approaches for ensuring vaccine safety should be practical, risk-based, fit for purpose, and continually improved to take advantage of advances in science and technology. Available tools, e.g., WHO's GBT should be used to strengthen pharmacovigilance capacity as a fundamental component of a well-functioning, integrated regulatory system.

Rationale

Legal requirements and regulations should be in place to support an effective adverse event surveillance system, with clear descriptions of roles and responsibilities, efficient coordination among public health officials and other stakeholders, adequate flow of information, and transparency in decision-making. The regulatory system should have a framework for reliance and collaboration to make effective use of resources. The GBT has criteria for assessing whether an NRA has legal provisions and regulations that allow recognition of and/or reliance on vaccine safety decisions, reports or information from other countries, regions or international bodies.

Safety monitoring of vaccines is required for both pre- and post-marketing phases and involves the engagement of manufacturers (or marketing authorization holders) and NRAs. Regulators have a key role in reviewing risk management plans prior to marketing authorization and making risk-based recommendations for post marketing safety surveillance. Safety monitoring systems, processes, and adequate investment in human resources are essential for effective safety monitoring and maintaining public confidence in vaccines.

NRAs must have the authority to act when warranted. Communication and information sharing with immunization programme and other key institutions enhances the NRA's ability to make science-based decisions to protect public health. Regulators should have the authority to mandate vaccine safety studies from manufacturers (or marketing authorization holders) and importers of vaccines, and the independence to investigate potential safety signals and ensure continued post marketing safety of vaccines. Mandatory industry reporting requirements that consider both local and foreign markets should be established and enforced in all countries.

Building pharmacovigilance capacity is fundamental for ensuring post marketing vaccine safety. The GBT is an effective tool to generate and analyse evidence of the performance of regulatory systems. WHO is developing a process intended to promote trust, confidence, with a transparent and evidence-based approach that will enable NRAs to rely on work of other NRAs, including decision making related to vaccine safety. The practice of reliance would increase efficiency and allow more effective use of regulatory resources especially in resource-limited settings.

NRAs and immunization programmes must address product quality issues, including the problem of substandard and falsified (SF) products on the market. Countries should have a mechanism in place for prevention, detection, and response to SF products, including SF vaccines, which have been cause for increasing concern. Reporting to global alert system should be encouraged, and there should be mechanisms to exchange information on SF or suspected SF products.

Objectives

Objective 1: All countries should have provisions to establish vaccine pharmacovigilance, including laws, regulations, infrastructure, and lines of accountability

Legal provisions are required to establish systems for data collection and storage. They should include mechanisms for communication of vaccine safety information to stakeholders (NRAs, immunization programmes, vaccine manufacturers or marketing authorization holders). Laws and regulatory frameworks should comply with the principles of good regulatory practices and good reliance practices *(19)*.

A well-functioning programme requires adequate human resources and technical expertise for the assessment of safety data. Decision-making and actions related to safety issues should be timely and accurately communicated to the public. In many countries, vaccine pharmacovigilance systems are supported by regulatory provisions with clearly defined lines of accountability. However, many countries still lack such provisions and have either a limited or no pharmacovigilance system. Each country should establish requirements for vaccine pharmacovigilance that allow timely identification, investigation and appropriate communication of serious vaccine safety issues. Harmonization or convergence of regulations, tools, and processes facilitates collaboration and reliance on decisions from trusted partners, e.g., other NRAs.

Strategies for objective 1:

1A. *Establish* a set of legal provisions, regulations, and guidelines which provide a mandate and guidance for the implementation of all activities related to vaccine safety monitoring over the life-cycle of a product. Legal provisions can be national or supra-national. Laws, regulations, and guidelines should comply with good regulatory practices and good reliance practices, international standards, and be publicly available for transparency.

1B. *Establish* legal provisions and regulations to allow recognition and reliance on decisions from other countries and regional networks or international bodies on vaccine safety issues

1C. *Ensure* good and effective communication, transparency and outreach to the public, regional and international partners, and accountability for the decisions and actions of the NRA

1D. *Incorporate* the principle of continuous improvement in strengthening the vaccine safety surveillance system and in the capacity to assess vaccine safety data for decision making

Building country capacity using WHO's Global Benchmarking Tool

WHO's Global Benchmarking Tool (GBT) tool and benchmarking methodology enabled the FDA in United Republic of Tanzania to:

- identify strengths and areas for improvement;
- to facilitate the formulation of an institutional development plan (IDP);
- to build on strengths and address identified gaps or weaknesses;
- to prioritize IDP interventions; and
- to monitor progress and achievements.

After having done this analysis, in 2018, the United Republic of Tanzania became the first country in Africa to achieve a confirmed well-functioning, regulatory system for medical products, following a formal evaluation by WHO.

This case study highlights Strategy 1A, i.e., to establish a set of legal provisions, regulations and guidelines and Strategy 1D, i.e., to incorporate principles of continuous improvement.

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Objective 2: Ensure vaccine pharmacovigilance is a national, regional, and international responsibility

In an increasingly globalized market, the same vaccines are being licensed in countries all over the world. This makes vaccine safety a national, regional and international responsibility. Regulatory and public health decisions should be based on all available data. Vaccine safety data from one country are important to others that are using the same or similar products. Information exchange is therefore critical for decision-makers at national, regional, and international levels

Strategies for objective 2:

2A. *Develop* and *expand* regulatory networks for the exchange of information and experience and *promote* harmonization or convergence of approaches.

2B. *Exchange* vaccine safety data through national, regional, and global platforms including WHO's Programme for International Drug Monitoring *(20)*.

Objective 3: Develop human resources to perform regulatory safety surveillance activities

Like other parts of the health system, a well-functioning regulatory system requires a qualified workforce. It is increasing complex to make scientifically sound decisions about the safety, effectiveness and quality of medical products. Regulators must stay up-to-date with the science that underpins the development and regulation of biological products, given the rapid advances in technology and methodologies. Continual, specific technical training, including e-learning courses, is essential to maintain an efficient and effective workforce.

Strategies for objective 3:

3A. *Promote* the development and implementation of a `global competency framework for regulators' *(21)* to support training and professional development of regulatory staff

3B. *Ensure* all entities that have a role in safety surveillance activities are adequately resourced with a well-trained, experienced, and skilled workforce with expertise in areas required to perform safety surveillance functions, including benefit and risk assessment for vaccine use, and appropriate managerial capacities

3C. *Encourage* sharing of expertise among technical staff from different countries to build capacity through networking.

Regulatory harmonization or convergence to improve access to quality-assured medicines

Harmonization or convergence of regulatory requirements can be the foundation for work sharing between regulatory authorities. The Australia-Canada-Singapore-Switzerland-United Kingdom (ACCESS) Consortium is an example of like-minded regulatory authorities working together to reduce duplication and increase each NRA's capacity to ensure the public have timely access to safe and effective, high quality therapeutic products. The ACCESS Consortium has initiatives for information sharing and work-sharing in areas including:

- generic medicines registration;
- assessment reports for new prescription medicines;
- investigations into post marketing safety of medicines;
- development of technical guidelines and;
- alignment of IT systems for information sharing.

Through the Consortium, the participating NRAs build synergies that result in enhancing the efficiency of their regulatory systems. This case study highlights Strategy 2A i.e., to develop and expand regulatory networks, Strategy 2B i.e., for exchanging vaccine safety data and Strategy 3C i.e., for sharing expertise among technical staff from different countries to build capacity.

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STRATEGIC AREA IV

Surveillance of adverse events following immunization (AEFI)

Introduction

The goal of post marketing AEFI surveillance is early detection, analysis, appropriate and timely response to minimize untoward effects of immunization on the health of individuals and ensure the highest quality of immunization programmes that maximizes benefits. Clinical trial data used by regulators for licensure and policy makers for vaccine introduction ensure that vaccine benefits outweigh the risks for the population studied. However, clinical trials cannot evaluate rare and uncommon AEFIs, delayed outcomes and reactions among subpopulations that are not included or who are underrepresented in the clinical trials. Post marketing surveillance fills these gaps. Surveillance based on spontaneous reporting can help detect unexpected vaccine reactions throughout the product life-cycle but this does not usually allow the causality to be assessed. In addition, early post marketing active surveillance (for specific conditions of interest or within subpopulations of interest) helps to evaluate possible risks.

GVSB1.0 laid the framework for minimal capacity for AEFI surveillance, including AEFI reporting, investigation, data management, causality assessment and communications. To evaluate the performance of different countries in achieving minimal capacity, WHO developed a reporting ratio for minimal surveillance capacity as a first performance indicator *(22)*. A country is said to have a minimum vaccine safety surveillance system in place if it reports at least 10 serious and non-serious AEFIs for 100 000 surviving infants per year. Although this is a crude indicator to evaluate performance, it has enabled global monitoring of AEFI reporting over the last decade. The number of countries meeting this reporting level target rose from 80 in 2010 to 120 in 2018.

Vaccine safety surveillance systems were further strengthened by the provision of support to LMICs to help them establish AEFI Review Committees and strengthen their functional capacities. This included standardizing the reporting processes through the identification of core variables, development of additional standardized tools and methods for surveillance *(23, 24)* and associated training *(25)*. Harmonization of several national surveillance systems was increased through alignment of their vaccine safety guidelines with the global vaccine safety surveillance principles *(26)*.

Aggregate vaccine safety data that are primarily transmitted by national immunization programmes using the WHO UNICEF joint reporting form *(27)* are used to calculate the AEFI surveillance indicator at the global level. Case-based data are available from multiple systems with large variations between countries. NRAs, national pharmacovigilance centres and immunization information systems are the main recipients of this information. WHO encourages the consolidation of all safety reports into a national database and sharing of case information through the WHO Programme for International Drug monitoring *(20)*.

Rationale

The 2019 landscape analysis reported that while AEFI notification and reporting were improving, more progress is needed in the areas of investigation, capacity for data analysis, causality assessment and communication *(28)*. Several participants in the survey indicated that active surveillance, causality assessment and methods for vaccine safety were key areas that should be prioritized for the next decade.

Objectives

In addition to the guiding principles outlined in GVSB1.0, there are several additional objectives to achieve high quality AEFI surveillance. These objectives may be accomplished at the local, national or regional levels.

Objective 1: Detect and assess vaccine safety signals that warrant further investigation

The past decade has witnessed the development of national reporting forms using WHO-approved core variables in many countries. Electronic reporting is also replacing paper reporting in several countries. Over time, web-based and electronic platforms that are more accurate and reliable are being adapted by countries. Free and open-source software such as Open Data Kit (ODK) *(28)* or District Health Information System 2 (DHIS2) *(29)* are enabling the integration and visualisation of vaccine safety data with overall immunization databases as well as integration with other national health programmes.

The AEFI reporting patterns over the last decade have changed so that in addition to previously described AEFIs, immunization stress-related responses (ISRRs), particularly among older children and adults, are being increasingly reported and impacting immunization programmes in several countries *(30)*. Introduction of new vaccines and use of novel vaccines for outbreak response in LMICs have brought new challenges for AEFI detection *(31, 32)*. New vaccines for administration during pregnancy to protect the mother, the baby, or both, also highlight the additional methodological challenges of vigilance *(33)*.

Vaccine safety signals typically arise when unexpected events in terms of type, frequency, severity or seriousness are identified through clinical trials, spontaneous reporting, active surveillance systems or specific studies. Surveillance based on spontaneous reporting can help identify unusual AEFI patterns or higher than expected frequencies of AEFIs. Public concerns or reports in the media can prompt immunization programmes to review surveillance data and initiate specific epidemiological studies to evaluate signals. Safety signals need to be assessed in all these situations. Signals for intussusception following RotaShield® rotavirus vaccine *(34)* and narcolepsy following Pandemrix®, the H1N1 influenza vaccine *(35)* were confirmed as true vaccine adverse reactions, although at lower rates than originally reported. In contrast, signals for postural orthostatic tachycardia syndrome (POTS), chronic fatigue syndrome (CFS) and complex regional pain syndrome (CRPS) following HPV vaccination were not found to be associated with vaccination (see box) *(36)*.

Collaboration between several countries for active surveillance using pooled data has yielded information on measles-containing vaccines and aseptic meningitis and idiopathic thrombocytopenic purpura *(37, 38)*. Similar multi-country studies were used to demonstrate the association between rotavirus vaccines and intussusception *(39)*. Specific active surveillance studies are needed when new vaccines are introduced in LMICs. Active surveillance capacity is useful for testing safety hypotheses and should be established in every country that introduces new vaccines.

Strategies for objective 1:

1A. *Use* spontaneous reporting systems as a primary pillar for AEFI signal surveillance (spontaneous reporting should be stimulated by making stakeholders aware of the system).
1B. Regularly *review* reports submitted to safety surveillance systems to identify unexpected patterns and frequencies, with special attention to serious outcomes such as death, disabilities, life threatening events, and immunization errors.
1C. *Identify* and *quantify* public concerns about vaccines through community engagement, cross-sectional surveys and monitoring community opinion and preferences, as well as social media.
1D. *Characterize* background rates of conditions that may be temporally associated with vaccination.
1E. *Develop* and *implement* a framework and process at the country level to assess vaccine safety signals and determine which should be prioritized for more rigorous evaluation and assessment of risk.

Disproving vaccine safety signals following scientific study (HPV vaccine and multiple adverse events)

A cluster analysis of serious adverse events after HPV vaccination that were reported in girls and young women between September 2009 and August 2017 in Denmark was done in a retrospective observational study. The study reviewed 963 reports of adverse events following HPV vaccination, including postural orthostatic tachycardia syndrome (POTS), chronic fatigue syndrome (CFS) and complex regional pain syndrome (CRPS) and other conditions like headache, dizziness, syncope or fatigue. The study concluded that the AE reports for POTS, CFS and CRPS resulted from stimulated reporting by the media. Causal association of these symptoms with HPV vaccine was not confirmed. The study reiterated the safety of the HPV vaccine and indicated that the interpretation of safety signals can be improved with improved validation of report details, such as vaccine type and onset time of AEs, and further understanding of the relationship between reporting patterns and media activity. Determination of background rates of POTS, CFS and CRPS among the age group receiving HPV vaccine and good-quality population-based epidemiological studies with medical record validation would facilitate the evaluation of these vaccine safety signals.

This case study highlights Strategy 1C i.e., to identify and quantify public concerns, Strategy 1D, i.e., characterize background rates of conditions that may be temporally associated with vaccination, and Strategy 3B, i.e., to conduct special studies when indicated.

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Objective 2: Investigation of AEFIs

The frequency of AEFI investigations has improved over the last decade. Capacity to investigate serious AEFIs has been built in many countries. However, the field investigations that are conducted do not always provide sufficiently high-quality data for AEFI causality assessments.

The clinical diagnosis and circumstances of occurrence, particularly of serious AEFI and deaths, should be investigated with the participation of local health leaders and a group of experts who are independent from the immunization programme, the regulatory agency and the vaccine manufacturer, to avoid any real conflicts of interest. However, these latter stakeholders can be requested to assist the AEFI investigations as they can provide relevant information.

Strategies for objective 2:

2A. *Strengthen* capacity in countries for investigation of serious AEFIs and for providing high quality data for causality assessment.

2B. *Establish* intra- and inter-country processes to evaluate vaccine safety signals rapidly and rigorously for further assessment of risk.

Confirming a vaccine safety signal using specific studies: example of Pandemrix® and narcolepsy)

An association between the H1N1 influenza vaccine Pandemrix® and narcolepsy was initially reported in 2010 in Finland. A retrospective database study to assess the incidence of narcolepsy in Finland showed a 17-fold increase in narcolepsy in children under 17 years of age in 2010, compared with 2002-2009. The majority (50/54) of these children in 2010 had received Pandemrix® 6 to 242 days (median 42 days) before the sudden onset of narcolepsy. A human leukocyte antigen (HLA) analysis in 34/54 children showed that all 34 children had a specific HLA type with the narcolepsy specific allele DQB1*0602/DRB1*15. The study concluded that it was likely that Pandemrix® vaccination contributed, perhaps with other environmental factors, to this increased incidence of narcolepsy in genetically susceptible children. Narcolepsy had never been previously associated with the use of any vaccine.

This case study highlights Strategy 2A i.e., to strengthen investigation for serious AEFIs, Strategy 3B to conduct special studies when indicated and Strategy 3D to coordinate existing active surveillance studies.

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Objective 3: Conduct individual and population level AEFI causality assessment

AEFI causality assessment is the systematic evaluation of the information obtained about an AEFI to determine the likelihood that an event might have been caused by a vaccine or vaccination. At the individual-level, clinical assessment can determine if a vaccine or vaccination-related error caused the AEFI. These assessments should be conducted by national AEFI committees and other expert groups *(40)* that are independent and who have no conflicts of interest associated with the ministries of health, industry or the immunization programme.

Determining whether an individual AEFI is associated with a vaccine or vaccination can be difficult and requires varied approaches. In some instances, laboratory testing can determine with high certainty that the AEFI is a vaccine reaction, e.g., aseptic meningitis with mumps vaccine virus *(41)*. In most situations, more rigorous studies are needed to determine if the vaccine is causally associated with the AEFI and to explore potential biological mechanisms. Procedures for AEFI causality assessment have been streamlined in the last decade and national AEFI committees in several countries use the revised WHO AEFI causality assessment classification *(42)* and the online tools *(43)* for assessment. Standardized case definition tools and algorithms such as those developed by the Brighton Collaboration are essential to ensure standards and specificity *(44, 45)*.

Population causality assessments can be used to assess if an AEFI can be attributed to a vaccine or vaccination-related event and, if so, what the rate is. Factors considered in population level causality assessments include temporal association, exclusion of alternative explanations, prior evidence, proof of association, consistency of the association, specificity, and biological plausibility. Associations can be explored using methodological approaches such as cohort, case-control, and self-controlled study designs *(46)*. These study designs can be conducted on an ad hoc basis. Timeliness, study validity and efficiency can be improved through active vaccine safety surveillance (AVSS) *(47)*.

Different data sources may be accessed for conducting AVSS, including large-linked automated databases (LLDB), registries and sentinel site-based surveillance. LLDBs can combine data about vaccine exposure, health outcomes and socio-demographics at the individual level from different sources using unique patient identifiers. By combining multiple databases, LLDBs allow quick analysis of large, heterogeneous study populations, increasing the statistical power and enabling investigations for rare AEFIs *(48, 49)*. An alternative approach to AVSS may be collection of data from sentinel sites that may be populational or hospital based *(50)*.

Strategies for objective 3:

3A. *Establish and develop* expert committees, with clear terms of reference, for causality assessment of serious AEFIs, clusters of AEFIs and other vaccine-related events that cause public concerns.

3B. When indicated, *conduct* specific studies (e.g., evidence-based case and epidemiological investigation) under the guidance of the expert committees (strategy 3A), to determine if a confirmed signal is a true vaccine adverse reaction.

3C. *Develop* active surveillance and hospital-based sentinel surveillance systems aimed at providing data on vaccine safety risks and benefits.

3D. *Coordinate* existing active surveillance studies nationally, regionally or globally to increase power and timeliness.

Objective 4: Prevent vaccination adverse reactions

Vaccine-product and quality-defect-related reactions can be minimised by rigorous quality control during the manufacturing processes. Industry should maintain the highest standards of rigorous testing in the prelicensure clinical development phase (1 to 3), as well as active surveillance during phase 4. Traceability helps identify falsified vaccine. Risk management plans are the backbone of post marketing monitoring.

At immunization centres, managing vaccine-product related reactions such as anaphylaxis requires emergency kits and trained staff to identify and respond in a timely manner. A conducive environment will reduce the incidence of ISRRs. Behavioural and pharmacological approaches help to alleviate pain and anxiety. Vaccine recipients and their parents, when the recipient is a child, should be informed about how to identify and manage common minor reactions (e.g., fever and pain at the site of injection) and counselled on seeking medical care for severe symptoms, using appropriate communication strategies by vaccinators.

Immunization-related errors can be serious, resulting in death or long-term disabilities. They can also have a negative impact on confidence in immunization programmes. However, immunization-related errors are fully preventable with adequate training, supervision, monitoring, and tools. Suitable training of all relevant staff on the principles of vaccine storage, handling and administration is critical. Supportive supervision and suitable documentation should help to ensure that proper procedures are followed. Updated technologies need to be used for maintaining and monitoring cold chain compliance. Innovative engineering and product design of vaccine packaging, vaccine storage, and vaccination devices can help eliminate potential sources of immunization-related errors.

Strategies for objective 4:

4A. *Use* information from vaccine safety signal detection, investigation, and causality assessments to prevent immunization errors and associated vaccination-related injuries.

4B. *Promote* research and development for innovative technologies for vaccine packaging, vaccine storage and vaccination devices to reduce immunization errors.

4C. *Provide* appropriate training and resources to health staff to ensure that vaccines are administered in a safe and conducive environment.

4D. *Communicate* about the risks and benefits in a clear and concise manner prior to vaccination and addresses concerns of the vaccine recipient, their caregivers and the public.

Objective 5: Strengthened capacity to address vaccine-related adverse events and communication response

Immunization in a routine setting or under special conditions, such as population or school vaccination campaigns should be accompanied by appropriate vaccine safety messages. It is also necessary to prepare suitable communication plans to anticipate and address specific situations, such as clusters of AEFIs, and maintain cooperation with communities and vaccine recipients.

Strategies for objective 5:

5A. *Develop* a vaccination safety communication plan that includes both routine benefit-risk communication and crisis communication components:

- risk communication prior to vaccination which includes information about known vaccine reactions and addresses the concerns of vaccine recipients and their caregivers;
- messages and frameworks to facilitate a rapid response to any event;
- identification of channels for information dissemination to reach audiences across a diverse range of stakeholders and population groups;
- sufficient and appropriate human and financial capacity;
- coordination processes, including stakeholder engagement plans.

Refer to Strategic area V – Enhanced vaccine safety communication for more detailed guidance on communication.

STRATEGIC AREA V

Enhanced vaccine safety communication

Introduction

Vaccine safety communications and social engagement are essential components of every step in the interactions between an immunization programme and healthcare workers, their vaccine recipients, caregivers, religious, traditional and community leaders, the media and the public. Vaccine safety concerns are strongly associated with vaccine hesitancy, acceptance and demand. These concerns impact the degree of trust and confidence of the public, healthcare community and decision-makers in vaccines and vaccination programmes. Therefore, ensuring that every country has the capacity, infrastructure and resources to educate and communicate about vaccine safety, vaccine benefits and the diseases they prevent is critical for building trust as well as maintaining and increasing immunization coverage *(51)*.

Rationale

Increasing the number of vaccines delivered through routine immunization will prevent more deaths and diseases, and reduce the incidence of devastating consequences of vaccine-preventable diseases. However, this is usually associated with increased scrutiny of AEFIs and other vaccine safety concerns. These concerns must be tracked, taken seriously and any misconceptions corrected. This includes prompt and appropriate advice to regulators, to healthcare workers and to communities, who have a right to know about any potential vaccine risk, no matter how small it may be, including very rare risks. Vaccine recipients and their caregivers, as well as the public, also have a right to know about any uncertainties, particularly uncertainties when a new vaccine is launched. It is also important to promote media and health literacy among the public, so that they can discern between well-founded medical information and misinformation. Misinformation can contribute to vaccine hesitancy, particularly if it is spread rapidly online during a crisis. Localized insights, through behavioural research and communication science, can be used to inform the development of an evidence-based, enhanced vaccine safety communication strategy. At the national level, dedicated financial and technical resources are required to communicate effectively about AEFIs *(52)*.

Strategies for vaccine safety communication are necessary throughout the life-cycle of all vaccine products, not only as part of a crisis management plan. Vaccine safety risk communication involves communicating the benefits of vaccination, as well as potential risks before and during a vaccination session (in preparation for potential AEFIs). Vaccine safety crisis communication involves communicating about vaccine safety updates and benefits of immunization, after a vaccine-related event. The vaccine-related events can include other events that can damage vaccine confidence, usually linked to vaccine safety, and which can trigger public concern. Strategies for vaccine safety communication should be available throughout the vaccine life-cycle, and crisis management strategies should be understood as mutually reinforcing strategies that aim to mitigate future negative outcomes affecting the immunization programme.

The media, as an amplifier of information about vaccine safety, benefits and concerns and, sometimes, misinformation, plays a crucial role in vaccine safety and crisis communication. They can potentially disseminate spurious concerns across borders and have a regional or global impact on immunization programmes. Authorities should use social and media channels to evaluate public sentiment appropriately and effectively. This requires understanding traditional, social and digital media, monitoring real-time emergence of vaccine safety concerns and facilitating informed dialogue and discussion with media and social media gatekeepers. By doing so, they will be able to communicate in a timely fashion and ensure accurate media reporting of vaccine-safety-related events. Engaging all media channels as an ally and ensuring that reliable vaccine safety information is accessible and appropriate for the health literacy of the target audience is critical in any context. During crises, it is critical that the communication is first, right, credible, empathetic, respectful, consistent and that it provides clear messages and calls to action, when necessary. Admitting to being wrong or having made mistakes is also essential for maintaining public confidence in the immunization programme.

Ultimately, proactive vaccine safety communication aims to build individual and public trust, empower individual decision-making and protect immunization programmes. In this way, vaccine safety communication contributes significantly to addressing concerns related to vaccine safety that may contribute to hesitancy. The goal of vaccine safety communication is to ensure that stakeholders are part of a real-time feedback loop, especially in case of an AEFI. Vaccine safety communication provides stakeholders with access to information they need to trust vaccines, to have access to the services and authorities that deliver them and to make informed choices.

Objectives

Objective 1: Strengthen the capacity and infrastructure to communicate vaccine safety information and manage the communication response to vaccine safety related events

An effective approach to vaccine safety communication requires integrating all component of vaccine safety. This includes AEFI preparedness, surveillance, response and causality assessment. Communication about safety should be part of healthcare workers' training, immunization policies and mandates. Strong coordination and capacity are required (including a dedicated budget) to ensure adequate preparedness. The response to a vaccine-safety-related event should mitigate any negative consequences for confidence in immunization programmes. Ownership of and demand for immunization by the communities reflects trust that can be achieved through adequate communication of benefits and risks. Some Members States are promoting demand and awareness to make vaccination programmes a 'people's programme'.

Strategies for objective 1:

1A. *Establish* vaccine safety communications capacity through existing and novel structures at national level. This should include medical, communications and behavioural expertise with a scope of work to formulate a shared communication strategy *(53)*.

1B. *Conduct* capacity needs assessments on a regular basis with follow-up training and education activities for healthcare workers, the media and decision-makers.

1C. *Upgrade* healthcare workers curricula and continuing education programmes on vaccine safety related topics including risk and interpersonal communication.

1D. *Engage* the media and civil society regularly about vaccine safety, particularly prior to introducing new vaccines.

1E. *Support* the development of trustworthy websites and other social media for vaccine safety information and link with the WHO Vaccine Safety Net (https://www.vaccinesafetynet.org/).

1F. *Invest* in the development of innovative tools for engaging with stakeholders and support initiatives and interventions for effective management and dissemination of vaccine safety information in the digital space.

Averting vaccine safety crisis with effective communications

In England, a routine programme for human papillomavirus (HPV) vaccination targeting 12 to 13-year-old girls (school year 8) and a catch-up programme for adolescents aged 17 to 18 years (school year 13) was implemented during the 2008 and 2009 academic years. On 28 September 2009, a 14-year-old girl died shortly after receiving a dose of HPV vaccine at her school in Coventry. There was no evidence of acute allergic reaction or cardiac arrest immediately after the dose. The relevant local and national health authorities were informed. An investigation was started. A press statement was issued informing about the death and the vaccination programme. It was decided not to suspend the vaccination programme during the investigation. The school sent a letter to parents that said: "An unfortunate incident occurred and one of the girls suffered a rare, but extreme reaction to the vaccine." Even though the school corrected this information on their website later that evening, it caused confusion and concern among the parents and media.

Local and international news programmes broadcast details of the girl's death shortly after HPV vaccination. The government was accused of having selected a poor-quality vaccine by political opponents. The manufacturer voluntarily recalled the vaccine batch that had been used. Communications officers briefed journalists to avoid speculation until further information was known. When the preliminary autopsy results showed that the girl's death was due to a rare, serious underlying medical condition and that the vaccination did not play a role in her death, communication officers contacted the audio-visual and print media to reverse the negative headlines in the next day's papers. Media attention died down rapidly and HPV vaccination in schools continued. Tests on the vaccine at the UK National Institute for Biological Standards and Control showed that the vaccine conformed fully to its specifications and had not been contaminated.

This case study highlights Strategy 1A i.e., to develop a vaccine communication strategy that crisis components and Strategy 1D, i.e., regularly engage the media on vaccine safety-related topics.

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Objective 2: Identify and characterize vaccine safety concerns among the public, healthcare workers and other stakeholders as potential safety signals that warrant further investigation and a communication response

Vaccine safety concerns expressed by the public, healthcare workers and other stakeholders, are potential safety signals that may warrant additional investigations. Vaccine safety systems must be able to detect these safety signals rapidly and characterize them so that those that need to be investigated can be prioritized and scientifically addressed. There is substantial variability in approaches for the effective identification and characterization of these vaccine safety concerns. The optimal approach depends on the setting (sub-national or national) as well as the population or subpopulation of interest. Research and evidence-based assessments can help inform interventions to address safety concerns and guide communication responses.

Strategies for objective 2:

2A. *Conduct* qualitative and quantitative multidisciplinary implementation research on healthcare workers, the public, and other potential stakeholders to understand their concerns about vaccine safety.

2B. *Leverage* other existing opportunities to collect and analyse data related to vaccine safety perceptions, e.g., reviews of expanded programmes on immunization, post-campaign monitoring, mass immunization campaign surveys, regional and global metrics, tools and best practices *(54)*.

2C. *Monitor* traditional and social media to identify public vaccine safety concerns *(55)* and provide real-time information on a dedicated VSN platform *(7)*.

Objective 3: In a crisis, provide timely, short and clear messages to all stakeholders describing what is known, what is not known, and what is being done to fill these gaps

AEFI surveillance systems, investigation of signals, and causality assessments require timely communications to all interested parties. NRAs and NITAGs require this information to determine if there are any changes to the risk-benefit profile of the vaccine. Vaccine manufacturers require this information for similar reasons, including making changes to the product and conducting their own analyses and communications. Healthcare workers, the media and the public will be interested in this information and can expect that such information will be shared with them in a timely manner. This vaccine safety communication must be evidence-based and tailored to the target audience through appropriate channels. Vaccine safety communications are often incorporated into broader vaccine communications that includes an explanation of vaccine benefits. Nonetheless, the purpose of vaccine safety communications in the context of a crisis must focus on what is known, what is not known and what is being done to fill these gaps.

Strategies for objective 3:

3A. *Develop* a vaccine safety communication strategy that includes both routine risk communication and crisis communication components (severity grading, standard messaging, identification of channels for dissemination to target audiences).

3B. *Develop, evaluate* and *implement* widely effective vaccine communication strategies that take advantage of insights from social sciences, psychology, social and news media, science communication and other disciplines.

3C. *Develop* specific strategies for outreach to vaccine-hesitant and other vulnerable communities, working through engagement with established community, traditional and religious leaders.

3D. *Develop* and *implement* a monitoring and evaluation framework.

3E. *Ensure* there is sufficient human and financial capacity to handle communication-related issues, especially during crises.

Rapid and effective responses maintain public confidence

In 2017, the death of an adolescent girl in Fiji after she received a dose of human papillomavirus (HPV) vaccine was reported to the public and media. A careful postmortem investigation concluded within weeks that the death was not due to the vaccine. In the meantime, the Fiji Ministry of Health used information on the safety of the HPV vaccine compiled by WHO and decided to continue the vaccination programme. They provided regularly reassuring communication to the public through press releases. This rapid and effective response enabled Fiji's HPV vaccination efforts to continue despite the coincidental event of the tragic death of an adolescent.

This case study highlights Strategy 3A i.e., develop a vaccine communication strategy that includes crisis preparedness and response components.

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STRATEGIC AREA VI

Fragile states and emergencies

Introduction

Fragile states have substantially impaired economic and social performances. This may be due to weak governance, limited administrative capacity, chronic humanitarian crises, persistent social tensions, and often, violence or the legacy of armed conflict and civil war *(56)*. Emergency is defined as a situation impacting the lives and well-being of many people or a significant percentage of a population and requiring substantial multi-sectoral assistance. For WHO to respond, there must be clear health consequences and this requires threshold values, rules of engagement and an exit strategy to be defined *(57)*.

Rationale

Vaccine safety monitoring in fragile states and emergencies poses specific challenges as it must be conducted in a setting with weakened routine health services, including vaccination programmes. In this context the occurrence of immunization errors can be another source of disruption. Although many of these challenges need to be addressed on an emergency basis, prevention of medical errors is particularly important in a protracted crisis. Security and logistics issues are also more challenging in such situations. They may affect the population's access to health services and healthcare workers' ability to provide quality-assured safe vaccines to the population. This may result in the inability to deliver full vaccination series. Ensuring vaccine safety, particularly when additional strategies, such as mass vaccination campaigns, expanded target age groups, and reduced vaccination courses, are in place, requires greater consideration than under usual circumstances *(58, 59)*. Greater attention is required for staff preparedness and training to minimise avoidable immunization and programmatic errors and avoid vaccine safety crises. Deployment of innovative vaccine delivery and packaging to reduce risks of errors in vaccine handling, reconstitution, and administration can help reduce the risk of vaccine safety crises in these settings.

Many different vaccines can be considered, depending on the assessment of risk for possible outbreaks e.g., cholera, diphtheria, hepatitis, measles, meningococcal disease, poliomyelitis, typhoid fever, and yellow fever. Healthcare workers should be familiar with the safety profiles of each vaccine, as well as their administration. Vaccines supplied and donated during emergencies may not have undergone standard lengthy and rigid regulatory evaluations and are often approved in fast track for emergency use and their use may be off-label. Labelling of packages in a language not used in the country is an additional risk for immunization errors. Vaccines procured for use in these situations, even from non-conventional sources, should meet international standards of quality and safety, and preferably have obtained WHO prequalification *(60)*.

Vaccinations (both routine and disease specific) must also be considered in the face of emerging infectious diseases such as cholera, Ebola, Zika, Middle-East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), and novel human coronavirus (2019-nCoV) among others. Often no licensed vaccines are available for use against such outbreaks and healthcare workers are involved in the emergency response. Prevention and control of emerging infectious diseases in fragile states during emergencies are highly challenging due to prevailing disrupted infrastructure, healthcare services and, sometimes, even general insecurity. High risk for frontline healthcare workers and immediate contacts of infected patients may justify regulatory emergency

use authorization for novel vaccines with limited data on use in humans. In this setting it is essential that vaccine administration is accompanied with active vaccine and vaccination safety monitoring.

Vaccine and vaccination safety monitoring needs to be incorporated into microplanning processes for vaccination roll out in these situations. Specific follow-up and communication strategies should be embedded to ensure that populations are not only aware of the beneficial protection offered but also of the risks involved. The risk of public outrage and media criticism over serious vaccine safety events can be politically extremely sensitive. It is, therefore, critical that health authorities clearly recognize the need for vaccine safety surveillance and be prepared to support it. Support and assistance from national and international partner agencies, non-governmental organizations, civil societies and donors are crucial for the government responsible for vaccine and vaccination safety.

Objectives

Objective 1: Use vaccine safety monitoring as a quality assurance mechanism for vaccination activities in fragile states and in emergency situations

Interruption of routine health services and infrastructure problems often occur in fragile states and emergency situations. Nonetheless, there may be sufficient infrastructure and resources remaining that can be used to assure partially or completely the necessary components of vaccine safety surveillance.

Strategies for objective 1:

1A. *Ensure* that only WHO prequalified or approved quality-assured vaccines are used in fragile states or in emergency situations.
1B. *Ensure* that national guidelines and micro plans, incorporating safety surveillance, communications and vaccine safety response processes are in place in fragile states or in emergency situations.
1C. *Ensure* continuing spontaneous reporting of AEFIs as part of the vaccination activity, and wherever possible, enhanced or active surveillance in sentinel sites to supplement spontaneous reporting.
1D. *Enhance* staff capacity for safe immunization practices and AEFI surveillance in fragile states and in emergency situations.

Improving vaccination practices and engaging community leaders during emergencies to address barriers to vaccination

By January 2018 several sessions of a diphtheria vaccination campaign had been held in Cox's Bazar, Bangladesh to reach hundreds of thousands of displaced Rohingya children, following a diphtheria outbreak that was thought to have infected 4000 people, killing 40. Despite achieving an estimated 81% administrative coverage in the second session, reports of vaccine hesitancy and community concerns had surfaced. Qualitative data collection from caregivers, influential community and religious leaders and healthcare workers revealed a complex web of concerns causing hesitancy, including:

- low awareness about the benefits of immunization;
- vaccine safety and fear about multiple injections
- lack of sensitivity to cultural and gender norms; and
- mismatch in community perceptions of needs and provision of health services.

In complex humanitarian emergencies, marginalized communities who may already have poor access to health services may have to deal with additional language, cultural and social barriers to seek healthcare services in unfamiliar settings. In this context, successfully addressing vaccine safety fears starts with getting the basics of community engagement and community dialogue right to be able to inform appropriate healthcare service delivery strategies and support higher uptake of vaccines.

This case study highlights Strategy 1B i.e., ensure plan incorporating communications on vaccine safety are in place.

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Objective 2: Monitor the safety of novel vaccines for emerging infectious diseases during emergencies

Introduction of novel vaccines in emergency situations requires oversight by NRAs. The response to emerging infectious diseases would benefit from additional resources from regional and international partners for prevention and control responses. Using additional resources to establish and implement active safety surveillance of vaccine recipients would be appropriate as there will be limited data about the novel vaccine used in the emergency.

Strategy for objective 2:

2A. *Develop* guidelines and standard operating procedures with national, regional and global regulatory networks for safety surveillance for novel vaccines used in emergency settings.

2B. *Ensure* that active vaccine safety surveillance is set-up prior to introducing a novel vaccine in an emergency setting.

2C. *Ensure* regulatory preparedness for emergencies, including simulation, as well as coordination, regulatory cooperation and reliance on use of quality-assured vaccines and enhanced vaccine safety surveillance.

Accelerated production, introduction and evaluation of preventive vaccines to help control Ebola outbreak

In response to the unprecedented Ebola outbreak in West Africa, in August 2014, WHO called for accelerated production of preventive vaccines that could potentially help control the outbreak. Two vaccines were developed initially, one was the replication incompetent chimpanzee adenovirus 3 (ChAd3) vector vaccine and the other a vesicular stomatitis virus (VSV), which was genetically engineered to express a glycoprotein from the Zaire Ebola virus (rVSV-ZEBOV-GP). Following an outbreak of Ebola virus disease (EVD) in North Kivu province in the Democratic Republic of the Congo (DRC) in August 2018, the rVSVZEBOV-GP vaccine was used for expanded access in a ring vaccination strategy. The safety profile of its use in DRC that was reviewed by the GACVS in December 2019, was found to be reassuring although areas that required further study were identified.

This case study highlights Strategy 1B i.e., to ensure that micro plans incorporating safety surveillance, communication and response on vaccine safety are in place during emergencies and Strategy 2B, i.e., to ensure that active surveillance is setup prior to introducing novel vaccine in an emergency response.

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Accountability framework

Rationale

The United Nations Sustainable Development Goal 3, 'ensure healthy lives and promote well-being for all at all ages', was an ambitious goal when launched in 2015, with many immunization-relevant targets to be achieved by 2030. These included specific, measurable targets, to enable monitoring and accountability of progress. Likewise, to both assist and assess the success of the implementation of GVSB2.0 strategies, an accountability framework is required for each strategic area.

Global vaccine safety surveillance is a complex network of multiple interconnected systems. Within each of these systems, including health, legislative, regulatory, governmental, industry, media and community, multiple levels and multiple stakeholders are typically involved, ranging from local community, jurisdictional, national, regional and global levels. At each level, healthcare workers, ranging from local immunization teams to clinicians treating potential AEFIs, patients, parents and other community members need to be engaged and motivated, using a variety of strategies. Additionally, the level of maturity of these systems varies widely across settings, with challenges for vaccine safety surveillance that varying accordingly.

For countries to be able to benchmark their maturity levels, measure progress and develop practical strategies for improving that maturity, a framework for accountability has been recognised as a practical and effective way of identifying and measuring the key steps leading to improved vaccine safety surveillance capacity. Additionally, there are ways that these outputs and outcomes can be displayed, with highlighted illustrations of successful activities that led to them being achieved.

The accountability and indicators will also be guided by the WHO Global Benchmarking Tool for evaluation of national regulatory system of medical products *(8)* and the WHO practical manual for the assessment of pharmacovigilance system *(61)*.

Each strategic area will identify:

- beneficiaries;
- primary stakeholders; and
- accountability: roles and responsibilities of stakeholders and partners, their relationships, including coordination of vaccine safety surveillance systems between industry and government bodies.

They will develop a high-level logic model with:

- activities – what is done with the resources;
- outputs – the direct products of the activities; and
- outcomes – changes in behaviour, knowledge, skills, level of functioning, etc.

The GVSI strategic priority group will coordinate monitoring of the accountability framework and report their assessment at each annual general meeting. An independent GVSI Observatory will be established. The GVSI Observatory will include resources from academia, technical agencies, and research networks who will share their methods and findings to enhance their dissemination. These resources, including case studies relevant to each of the GVSB2.0 chapters, links to training and support, will be categorized as global and regional, to enable

Member States to access those that are most relevant to their situation. Vaccine Safety Net *(7)* member sites will supply many of the resources linked to by the Observatory. Under its terms of reference, the aims of the Observatory are to identify data sources and present them in a useful format to document:

- the status of vaccine safety monitoring in all countries;
- the ability of countries to evaluate vaccine safety signals;
- the availability of vaccine safety communication plans at the country level to ensure awareness of vaccine risks and benefits, understanding of the perceptions of risk, and preparation for managing any AEFIs and crises promptly;
- the legal, regulatory and administrative frameworks to ensure compliance with vaccine safety surveillance requirements at national, regional and international levels;
- the availability of regional and global technical support platforms for strengthening vaccine safety surveillance systems that meets countries' expressed needs; and
- the efforts to improve systems for appropriate interaction between national governments, multilateral agencies, and manufacturers at national, regional and international levels.

ANNEX 1

GVSB1.0: minimal and enhanced capacity

The **minimal capacity** for vaccine safety described in the Global Vaccine Safety Blueprint 1.0 drew on the model proposed for other pharmacovigilance activities *(62)*. It includes:

- a national dedicated vaccine pharmacovigilance capacity, with designated staff for this purpose, stable basic funding, clear mandates and well-defined structures and roles, that collaborate with the WHO Programme for International Drug Monitoring;
- healthcare workers and others who are encouraged to report vaccine safety issues;
- a reporting form for individual case safety reports (i.e., a national reporting form for AEFIs);
- a national database or system for collating, managing and retrieving AEFI reports;
- a national AEFI review committee (ARC) to provide technical assistance on causality assessment of serious AEFIs, and clusters of AEFIs, so that unwanted risk can be managed;
- a clear strategy for risk communication that identified risks and benefits to prepare healthcare workers, caregivers and the public for possible vaccine reactions, by explaining potential coincidental events, encouraging the monitoring of AEFIs by all concerned, with preparedness plans in place to address vaccine safety crises (risk communication is dynamic and needs a feedback loop to all relevant stakeholders); and
- implemented and harmonized methods and tools for the monitoring and investigation of AEFIs.

The managerial elements listed as strengthening minimal capacity for vaccine safety and ensuring its functionality included:

- a regulatory framework that defined the provisions for monitoring and management of AEFIs;
- clear lines of accountability identified for the conduct of vaccine safety work;
- an institutional development plan in place for the implementation of activities and development of performance indicators; and
- periodic evaluation and revision of the institutional development plan to ensure continuous quality improvement of national vaccine safety activities; and a commitment to sharing information on vaccine safety with other countries.

In addition to the basic and managerial requirements for minimal capacity described above, **enhanced capacity** for vaccine safety activity includes the following:

- the ability to carry out active surveillance of adverse events of special interest (AESIs) rather than relying solely on spontaneous reporting of AEFIs for signal detection; and
- the ability to carry out epidemiological studies to test hypotheses.

ANNEX 2

Current WHO Benchmarking Tool sub-indicators per maturity levels

	MATURITY LEVELS			
INDICATORS	**Level 1 sub-indicators**	**Level 2 sub-indicators**	**Level 3 sub-indicators**	**Level 4 sub-indicators**
VL01 Legal provisions, regulations and guidelines required to define regulatory framework of vigilance	VL01.01: Legal provisions for a national vigilance system exist VL01.02: Legal provisions and regulations require the manufacturers and/or MAHs to set up a vigilance system of their medical products and periodically report vigilance data to the NRA VL01.03: Guidelines ensure that distributors, importers, exporters, healthcare institutions, consumers and other stakeholders are encouraged to report adverse drug reactions (ADRs) and AEs to the MAH and/or NRA VL01.07: Legal provisions and regulations allow recognition and/or reliance on vigilance-related decisions, reports or information from other countries or regional or international bodies.	VL01.04: Legal provisions and regulations allow NRA to require manufacturers and/or MAHs to conduct specific studies on safety and effectiveness under specific conditions	VL01.05: Legal provisions, regulations and guidelines require manufacturers and/or MAHs to designate an individual person to be in charge of vigilance system VL01.06: There are guidelines for planning, conducting, monitoring, and reporting of vigilance activities	
VL02 Arrangement for effective organization and good governance		VL02.01: There is a defined organizational structure with clear responsibilities to conduct vigilance activities	VL02.02: Documented procedures and mechanisms are implemented to ensure the involvement, coordination and communication among all stakeholders relevant to vigilance activities	

	MATURITY LEVELS			
INDICATORS	**Level 1 sub-indicators**	**Level 2 sub-indicators**	**Level 3 sub-indicators**	**Level 4 sub-indicators**
VL03 Human resources to perform vigilance activities			VL03.01: Sufficient competent staff (i.e., education, training, skills and experience) are assigned to perform vigilance activities VL03.02: Duties, functions, and responsibilities of the staff in charge of vigilance activities are established and updated in the respective job descriptions VL03.03: Training plan developed, implemented and updated at least once a year for staff in charge of vigilance activities VL03.04: The NRA generates and maintains records of staff training activities and training effectiveness verification	
VL04 Procedures established and implemented to perform vigilance activities	VL04.05: Staff access to information resources relevant to vigilance processes (e.g., safety information sources and reference materials) is ensured		VL04.01: Vigilance procedures and tools are in place and implemented for collection and assessment of ADRs and AEs VL04.02: Vigilance procedures and tools are in place for investigation, interpretation of and response to ADRs and AEs VL04.04: Risk approach is considered throughout different vigilance activities, including timely response to detected signals for risks or benefit VL04.06: The NRA has access to expert committees for review of serious emergent safety concerns, when needed	VL04.03: Standard procedures exist and are implemented for enforcement of the national vigilance system VL04.07: With respect to vigilance data, assessment of the risk-benefit balance of medical products is regularly conducted VL04.08: Active vigilance activities, as well as proactive monitoring programmes (when needed) have been developed and implemented

	MATURITY LEVELS			
INDICATORS	**Level 1 sub-indicators**	**Level 2 sub-indicators**	**Level 3 sub-indicators**	**Level 4 sub-indicators**
VL05 Mechanism in place to monitor regulatory performance and output			VL05.01: Vigilance information is used in timely manner to amend existing regulatory decisions or to issue new regulatory decisions or actions	VL05.02: Performance indicators for vigilance activities are established and implemented
VL06 Mechanism exists to promote transparency, accountability and communication		VL06.01: Vigilance activities and relevant feedback are appropriately communicated to the public	VL06.02: Mechanism for regular feedback to all stakeholders on vigilance events exists and is complemented with a risk communication plan VL06.03: Vigilance data and findings are shared with relevant regional and international partners	

Source: *(8)*.

ANNEX 3

Objectives and strategies for each strategic area

STRATEGIC AREA I **GOVERNANCE AND SYSTEMS DEVELOPMENT**	
GOVERNANCE	
Objective	**Provide the structure for effective decision-making in support of vaccine safety**
	Strategies for governance objective: A. Strengthen the GVSI by providing dedicated secretarial resource and an enhanced structure B. Report on the accountability framework at each GVSI general meeting and disseminate the assessments
SYSTEM FUNDING AND FINANCING	
Objective 1	**Encourage provision of adequate resources for the operations undertaken by public vaccine safety systems**
	Strategies for objective 1: 1A. Develop clear vaccine safety system use cases for communications with budget authorities 1B. Systematically document vaccine safety crises and successes and their consequences for use in communications with budget authorities
Objective 2	**Describe public vaccine safety funding options appropriate for the maturity level of the regulatory system in a country**
	Strategies for objective 2: 2A Establish a financial task force that will advise WHO on regional and collaborative funding mechanisms for the GVSI and their oversight 2B. Develop guidance for countries on mobilizing funding for vaccine safety work aligned with country maturity level
Objective 3	**Address injuries caused by vaccine reactions or vaccination errors**
	Strategies for objective 3: 3A. Encourage appropriate analysis and handling of injuries caused by vaccines or vaccination 3B. Develop guidance on addressing injuries from vaccine adverse reactions based on available evidence and national circumstances

STRATEGIC AREA II **COORDINATION OF SAFETY SYSTEMS**	
Objective 1	**Coordination for exchange of information between vaccine manufacturers (or marketing authorization holders) and national regulatory authorities at local, regional and global levels**
	Strategies for objective 1: 1A. Develop and implement mechanisms and guidance for systematic and timely exchange of vaccine safety related information (individual case reports, safety signals, findings from post marketing studies and any changes in the risk-benefit profile of the vaccine) between vaccine manufacturers (or marketing authorization holders) and public health authorities at local, regional and global levels, to ensure that the safety profile of each product reflects the most recent information at all levels
Objective 2	**Coordination and information exchange between health authorities and other stakeholders at each level**
	Strategies for objective 2: 2A. Develop and implement guidance for vaccine safety surveillance (harmonized with regional and global standard guidelines), defining the roles and responsibilities of health system stakeholders, including regulatory authorities, immunization programmes, services providers and national and global pharmacovigilance stakeholders involved in vaccine safety 2B. Define respectful, innovative and effective mechanisms of collaboration and exchange of information between stakeholders and regulatory authorities and foster partnerships and collaborative networks in support of vaccine safety surveillance at national, regional and global levels
Objective 3	**Coordination and exchange of information between health authorities and advisory bodies at local, regional and global levels**
	Strategies for objective 3: 3A. Develop independent national and regional advisory bodies for vaccine safety that are functionally aligned with NITAGs, regional immunization technical advisory groups (RITAGs) and other bodies involved in vaccine safety. 3B. Promote global alignment of methods and collaboration between national and global advisory bodies and examine the need and relevance of similar regional committees. 3C. Promote global expert collaborative networks in support of vaccine safety surveillance.
Objective 4	**Collaboration between the scientific community and health authorities**
	Strategies for objective 4: 4A. Establish registries of vaccine safety studies at appropriate levels, until a suitable global model can be proposed. 4B. Establish a periodic review of these study registries by the GACVS to ensure the quality and potential impact of studies. 4C. Develop technical cooperation and build capacity to help countries to adapt and implement standards for post marketing safety studies.
Objective 5	**Communication between health authorities and the populations they serve**
	Strategies for objective 5: 5A. Establish mechanisms for communication between regulatory authorities, immunization programmes, ministries of education and other authorities, so that the public is informed about vaccine safety issues and are encouraged to report any concerns about vaccine safety.

STRATEGIC AREA III **REGULATORY FRAMEWORK**	
Objective 1	**All countries should have provisions to establish vaccine pharmacovigilance, including laws, regulations, infrastructure, and lines of accountability**
	Strategies for objective 1: 1A. Establish a set of legal provisions, regulations, and guidelines which provide a mandate and guidance for the implementation of all activities related to vaccine safety monitoring over the life-cycle of a product. Legal provisions can be national or supra-national. Laws, regulations, and guidelines should comply with good regulatory practices and good reliance practices, international standards, and be publicly available for transparency. 1B. Establish legal provisions and regulations to allow recognition and reliance on decisions from other countries and regional networks or international bodies on vaccine safety issues 1C. Ensure good and effective communication, transparency and outreach to the public, regional and international partners, and accountability for the decisions and actions of the NRA 1D. Incorporate the principle of continuous improvement in strengthening the vaccine safety surveillance system and in the capacity to assess vaccine safety data for decision making
Objective 2	**Ensure vaccine pharmacovigilance is a national, regional, and international responsibility**
	Strategies for objective 2: 2A. Develop and expand regulatory networks for the exchange of information and experience and promote harmonization or convergence of approaches 2B. Exchange vaccine safety data through national, regional, and global platforms including WHO's Programme for International Drug Monitoring
Objective 3	**Develop human resources to perform regulatory safety surveillance activities**
	Strategies for objective 3: 3A. Promote the development and implementation of a 'global competency framework for regulators' to support training and professional development of regulatory staff 3B. Ensure all entities that have a role in safety surveillance activities are adequately resourced with a well-trained, experienced, and skilled workforce with expertise in areas required to perform safety surveillance functions, including benefit and risk assessment for vaccine use, and appropriate managerial capacities 3C. Encourage sharing of expertise among technical staff from different countries to build capacity through networking.

STRATEGIC AREA IV **SURVEILLANCE OF ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFIS)**	
Objective 1	**Detect and assess vaccine safety signals that warrant further investigation**
	Strategies for objective 1: 1A. Use spontaneous reporting systems as a primary pillar for AEFI signal surveillance (spontaneous reporting should be stimulated by making stakeholders aware of the system) 1B. Regularly review reports submitted to safety surveillance systems to identify unexpected patterns and frequencies, with special attention to serious outcomes such as death, disabilities, life threatening events, and immunization errors 1C. Identify and quantify public concerns about vaccines through community engagement, cross-sectional surveys and monitoring community opinion and preferences, as well as social media 1D. Characterize background rates of conditions that may be temporally associated with vaccination 1E. Develop and implement a framework and process at the country level to assess vaccine safety signals and determine which should be prioritized for more rigorous evaluation and assessment of risk
Objective 2	**Investigation of AEFIs**
	Strategies for objective 2: 2A. Strengthen capacity in countries for investigation of serious AEFIs and for providing high quality data for causality assessment 2B. Establish intra- and inter-country processes to evaluate vaccine safety signals rapidly and rigorously for further assessment of risk
Objective 3	**Conduct individual and population level AEFI causality assessment**
	Strategies for objective 3: 3A. Establish and develop expert committees, with clear terms of reference, for causality assessment of serious AEFIs, clusters of AEFIs and other vaccine-related events that cause public concerns 3B. When indicated, conduct specific studies (e.g., evidence-based case and epidemiological investigation) under the guidance of the expert committees (strategy 3A), to determine if a confirmed signal is a true vaccine adverse reaction 3C. Develop active surveillance and hospital-based sentinel surveillance systems aimed at providing data on vaccine safety risks and benefits 3D. Coordinate existing active surveillance studies nationally, regionally or globally to increase power and timeliness
Objective 4	**Prevent vaccination adverse reactions**
	Strategies for objective 4: 4A. Use information from vaccine safety signal detection, investigation, and causality assessments to prevent immunization errors and associated vaccination-related injuries 4B. Promote research and development for innovative technologies for vaccine packaging, vaccine storage and vaccination devices to reduce immunization errors 4C. Provide appropriate training and resources to health staff to ensure that vaccines are administered in a safe and conducive environment 4D. Communicate about the risks and benefits in a clear and concise manner prior to vaccination and addresses concerns of the vaccine recipient, their caregivers and the public
Objective 5	**Strengthened capacity to address vaccine-related adverse events and communication response**
	Strategies for objective 5: 5A. Develop a vaccination safety communication plan that includes both routine benefit-risk communication and crisis communication components: • risk communication prior to vaccination which includes information about known vaccine reactions and addresses the concerns of vaccine recipients and their caregivers; • messages and frameworks to facilitate a rapid response to any event; • identification of channels for information dissemination to reach audiences across a diverse range of stakeholders and population groups; • sufficient and appropriate human and financial capacity; • coordination processes, including stakeholder engagement plans

STRATEGIC AREA V **ENHANCED VACCINE SAFETY COMMUNICATION**	
Objective 1	**Strengthen the capacity and infrastructure to communicate vaccine safety information and manage the communication response to vaccine safety related events**
	Strategies for objective 1: 1A. Establish vaccine safety communications capacity through existing and novel structures at national level. This should include medical, communications and behavioural expertise with a scope of work to formulate a shared communication strategy 1B. Conduct capacity needs assessments on a regular basis with follow-up training and education activities for healthcare workers, the media and decision-makers 1C. Upgrade healthcare workers curricula and continuing education programmes on vaccine safety related topics including risk and interpersonal communication 1D. Engage the media and civil society regularly about vaccine safety, particularly prior to introducing new vaccines 1E. Support the development of trustworthy websites and other social media for vaccine safety information and link with the WHO Vaccine Safety Net 1F. Invest in the development of innovative tools for engaging with stakeholders and support initiatives and interventions for effective management and dissemination of vaccine safety information in the digital space
Objective 2	**Identify and characterize vaccine safety concerns among the public, healthcare workers and other stakeholders as potential safety signals that warrant further investigation and a communication response**
	Strategies for objective 2: 2A. Conduct qualitative and quantitative multidisciplinary implementation research on healthcare workers, the public, and other potential stakeholders to understand their concerns about vaccine safety 2B. Leverage other existing opportunities to collect and analyse data related to vaccine safety perceptions, e.g., reviews of expanded programmes on immunization, post-campaign monitoring, mass immunization campaign surveys, regional and global metrics, tools and best practices 2C. Monitor traditional and social media to identify public vaccine safety concerns and provide real-time information on a dedicated VSN platform
Objective 3	**In a crisis, provide timely, short and clear messages to all stakeholders describing what is known, what is not known, and what is being done to fill these gaps**
	Strategies for objective 3: 3A. Develop a vaccine safety communication strategy that includes both routine risk communication and crisis communication components (severity grading, standard messaging, identification of channels for dissemination to target audiences) 3B. Develop, evaluate and implement widely effective vaccine communication strategies that take advantage of insights from social sciences, psychology, social and news media, science communication and other disciplines 3C. Develop specific strategies for outreach to vaccine-hesitant and other vulnerable communities, working through engagement with established community, traditional and religious leaders 3D. Develop and implement a monitoring and evaluation framework 3E. Ensure there is sufficient human and financial capacity to handle communication-related issues, especially during crises

STRATEGIC AREA VI **FRAGILE STATES AND EMERGENCIES**	
Objective 1	**Use vaccine safety monitoring as a quality assurance mechanism for vaccination activities in fragile states and in emergency situations**
	Strategies for objective 1: 1A. Ensure that only WHO prequalified or approved quality-assured vaccines are used in fragile states or in emergency situations 1B. Ensure that national guidelines and micro plans, incorporating safety surveillance, communications and vaccine safety response processes are in place in fragile states or in emergency situations 1C. Ensure continuing spontaneous reporting of AEFIs as part of the vaccination activity, and wherever possible, enhanced or active surveillance in sentinel sites to supplement spontaneous reporting 1D. Enhance staff capacity for safe immunization practices and AEFI surveillance in fragile states and in emergency situations
Objective 2	**Monitor the safety of novel vaccines for emerging infectious diseases during emergencies**
	Strategies for objective 2: 2A. Develop guidelines and standard operating procedures with national, regional and global regulatory networks for safety surveillance for novel vaccines used in emergency settings 2B. Ensure that active vaccine safety surveillance is set-up prior to introducing a novel vaccine in an emergency setting 2C. Ensure regulatory preparedness for emergencies, including simulation, as well as coordination, regulatory cooperation and reliance on use of quality-assured vaccines and enhanced vaccine safety surveillance

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