HHS Public Access

Author manuscript

*Vaccine*. Author manuscript; available in PMC 2023 July 11.

Published in final edited form as:

*Vaccine*. 2020 November 17; 38(49): 7728–7740. doi:10.1016/j.vaccine.2019.07.041.

# An approach for preparing and responding to adverse events following immunization reported after hepatitis B vaccine birth dose administration ☆

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## Abstract

The success of immunization programs in lowering the incidence of vaccine preventable diseases (VPDs) has led to increased public attention on potential health risks associated with vaccines. As a result, a scientifically rigorous response to investigating reported adverse events following immunization (AEFI) and effective risk communications strategies are critical to ensure public confidence in immunization.

Globally, an estimated 257 million people have chronic hepatitis B virus (HBV) infection, which causes more than 686,000 premature deaths from liver cancer and cirrhosis. Hepatitis B vaccination is the most effective way to prevent mother-to-child transmission of HBV infection, especially when a timely birth dose is given within 24 h of birth. However, an infant's risk of

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☆[Allegations regarding vaccine-related adverse events], if not rapidly and effectively dealt with, can undermine confidence in a vaccine and can ultimately have dramatic consequences for immunization coverage and disease incidence."] [1].

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

dying is highest in the neonatal period, and thus, administering HepB-BD within 24 h of birth overlaps with the most fragile period in an infant's life.

A working group formed in July 2016 following the publication of the case reports of the effects on vaccination coverage of media reports of infant deaths after HepB-BD administration in China and Vietnam. The goal of the working group was to create a framework and describe best practices for preparing for and responding to AEFI reported after HepB-BD administration, using existing resources. The framework includes six steps, including three preparation steps and three response steps.

This document is written for national and regional immunization program staff. Prior to using the framework for preparation and response to AEFIs reported after HepB-BD administration, staff members should be familiar with how AEFI are detected, reported, and investigated in the country. The document might also be of interest to national regulatory staff members who monitor vaccine safety within the country.

**Keywords**

Hepatitis B; Hepatitis B birth dose; Adverse event following immunization; Framework; Preparedness; Response

## 1. Background

The success of immunization programs in lowering the incidence of vaccine preventable diseases (VPDs) has led to increased public attention on potential health risks associated with vaccines [1]. As a result, a scientifically rigorous response to investigating reported adverse events following immunization (AEFI) and effective risk communications strategies are critical to ensure public confidence in immunization [2]. In particular, case reports of declines in hepatitis B vaccination coverage after media reports of infant deaths after hepatitis B vaccine birth dose (HepB-BD) administration in Vietnam [3] and China [4] demonstrate the importance of being prepared for and quickly responding to AEFI reports.

Globally, an estimated 257 million people have chronic hepatitis B virus (HBV) infection, which causes more than 686,000 premature deaths from liver cancer and cirrhosis [5]. Infection at birth or in early childhood presents the highest risk of progressing to chronic HBV infection (greater than90%) compared with infection in older age groups (5%) [6]. Hepatitis B vaccination is the most effective way to prevent mother-to-child transmission of HBV infection, especially when a timely birth dose is given within 24 h of birth [6].

An infant's risk of dying is highest in the neonatal period, or the first 28 days of life. Forty-five percent of child deaths under the age of five years take place during the neonatal period, with about 2.7 million babies dying every year in their first month of life [7]. Moreover, up to half of all under-five child deaths occur within the first 24 h of life and three quarters occur in the first week, or the early neonatal period [7]. Consequently, administering HepB-BD within 24 h of birth overlaps with the most fragile period in an infant's life [3]. Thus, HepB-BD administration at birth is prone to an association with coincidental deaths, which might be reported as an AEFI.

Given WHO's universal recommendation to include birth dose vaccination in national programs [6], the establishment of hepatitis B control goals in all WHO regions, and the Global Health Sector Strategy for Viral Hepatitis, more countries are expected to introduce the HepB-BD [8]. In addition, in 2018, the Gavi alliance announced support to countries introducing HepB-BD. Therefore, it is necessary to have tools available to ensure appropriate investigation and communication after coincidental deaths or serious adverse events following HepB-BD vaccination. Responses to such events are critical for maintaining confidence in the vaccine and immunization programs.

## 2. Purpose

The goal of this document is to present a framework and describe best practices for preparing for and responding to AEFI reported after HepB-BD administration. The information contained in the document is based on the case studies in China and Vietnam of media reports of infant deaths after HepB-BD administration and information adapted from other resources. These resources include WHO's Global Manual on Surveillance for AEFI and AEFI tools, WHO's Regional Office for Europe's *Vaccination and Trust* and the Centers for Disease Control and Prevention's *Crisis Emergency Risk Communication Manual*. This document is not intended to replace any existing guidelines for vaccine safety surveillance or risk communication.

## 3. Audience

This document is written for national and regional immunization program staff. Prior to using the framework for preparation and response to AEFIs reported after HepB-BD administration, staff members should be familiar with how AEFI are detected, reported, and investigated in the country. The document might also be of interest to national regulatory staff members who monitor vaccine safety within the country.

## 4. Methods

The best practices described in this document were developed by a working group formed in July 2016 following the publication of the case reports of the effects on vaccination coverage of media reports of infant deaths after HepB-BD administration in China and Vietnam [3,4,9]. The working group included immunization program experts from four WHO regions (African, European, Southeast Asian, and Western Pacific), WHO Headquarters, and the Centers for Disease Control and Prevention (CDC). An earlier draft was reviewed by immunization program staff from China and Vietnam.

A framework for preparing for and responding to clusters of events is provided in Fig. 1. These six steps may not always happen sequentially and they may even occur concurrently. A complete list of links to resources is provided in Appendix A.

### 4.1. Preparedness

1. Understand context for AEFI reported after HepB-BD administration, including local rates and causes of neonatal deaths.

2. Develop strategies for surveillance of adverse events following HepB-BD administration.
3. Develop a comprehensive risk communications strategy and build capacity to respond to an AEFI reported after HepB-BD administration.

### 4.2. Response

4. Verify and investigate the cause(s) of AEFI cases, including clinical and epidemiological investigations.
5. Proactively and regularly engage with news media and affected populations to share information on key aspects of the investigation and to respond to questions.
6. Monitor vaccination coverage and public response, and adapt the response to emerging data.

## 5. Preparedness

Information gathering and setting up mechanisms, structures, and tools for response

The information in this section provides a context for the status of hepatitis B-BD in regions and affected countries, as well as background rates and main causes of neonatal deaths. Information on the importance of AEFI surveillance and building vaccine confidence are also provided. The relevant information outlined in preparedness is critical for comprehensive and well-informed responses to clusters or isolated cases of serious AEFI. Availability of adequate resources necessary to respond to an adverse event and to verify a cluster is important for operationalizing the preparedness, surveillance, and response steps below.

### 5.1. Step 1: Understand context for AEFI reported after HepB-BD administration

**5.1.1. Background rates of known conditions occurring at birth that might be associated with AEFIs—**Knowledge of background rates for known conditions occurring at birth that might be coincidentally associated with AEFIs (e.g., neonatal deaths, seizures, anaphylaxis, and thrombocytopenia) is useful for providing context in explaining causes of AEFI clusters.

- Neonatal mortality rates vary greatly by country. (See rates at WHO).
- Approximately 45% of all deaths of children under age 5 occur among newborn infants in the first 28 days of life (neonatal period).
- 75% of all newborn deaths occur during the first week of life.
- Globally, the most common causes of neonatal deaths are prematurity and low birth weight (36%), neonatal infections (23%), and birth asphyxia or intrapartum complications (23%) [10].

**5.1.2. AEFI rates after hepatitis B vaccination and for other vaccines and biologics administered at birth—**Understanding the known AEFI rates after hepatitis

B vaccination at birth helps to interpret and elucidate whether the number of events in the cluster is excessive within an age group or location. Information on the observed AEFI rates are available at WHO's vaccine safety site.

**5.1.3. Understand vaccination status by WHO region and within the country:** Understanding hepatitis B vaccination coverage provides a baseline for assessing changes in coverage due to vaccine safety events. See WHO for more information.

### 5.2. Step 2: Develop strategies for surveillance of adverse events following HepB-BD administration

**5.2.1. Ensure an AEFI surveillance system exists or establish one where needed—**Ensuring that an AEFI surveillance system exists is a critical first step in mitigating the effects of clusters of AEFI. See the WHO *Global Manual on Surveillance of Adverse Events Following Immunization* listed in Appendix A for more information on setting up an AEFI surveillance system.

While many countries are in the process of establishing minimum capacity for monitoring AEFI though passive surveillance systems globally, active surveillance systems, while more expensive, are necessary for rigorous evaluation of AEFI. Where possible, integration of active surveillance systems into national health systems are ideal for answering important epidemiologic vaccine safety questions [1].

**5.2.2. Understand vaccine pharmacovigilance in your country or region—** Vaccine pharmacovigilance is the monitoring of vaccine safety to ensure that if any issues arise, there is a timely response to identify real safety issues and to strengthen confidence in the immunization program and vaccines. Many countries have a federal regulatory agency that also receives safety data on pharmaceutical products, including vaccines. Understanding and collaborating with the regulatory agencies may help you understand what AEFI data are available and create important bridges across agencies involved in vaccine safety within the country.

### 5.3. Step 3: Develop a comprehensive risk communications strategy and build capacity to respond to an AEFI reported after HepB-BD administration

**5.3.1. Understand the roles of vaccine hesitancy and trust**

- The document, *Vaccinations and Trust,* available at euro.who.int/vaccinetrust and visit vaccineconfidence.org, has a comprehensive overview of vaccine hesitancy and building confidence in vaccines, and lists a supporting online library with additional documents on preparedness.
- The European Center for Disease Prevention and Control document, *Let's Talk About Hesitancy*, outlines key information on commonly cited reasons for hesitancy and screening tools for monitoring vaccine hesitancy.
- The Vaccine Confidence Project with the London School of Hygiene and Tropical Medicine provides updated information on vaccine confidence by country and region. Please see the article, "The State of Vaccine Confidence

2016: Global insights through a 67-country survey," to find specific country-level data [11]. Visit vaccineconfidence.org

**5.3.2. Understand the media climate and caregiver perceptions—**The media and public are critical immunization stakeholders; maintaining their confidence in the vaccine, the vaccinator, and the vaccination program requires ongoing engagement to raise awareness about the benefits and safety of vaccines and encourage a supportive information environment for caregivers seeking guidance on immunization decisions for their children.

- One method of priming media to report accurately on vaccine-related topics is to offer training for media representatives before a crisis occurs.
- Media reports, including social media, should be monitored for public perceptions and narratives regarding HepB-BD among caregivers and community influencers.
- Collect data on a regular basis on caregiver knowledge, attitudes, perceptions and beliefs around immunization to inform communications planning. Sometimes caregiver concerns around HepB-BD are not primarily dictated by vaccine safety issues, but shaped by cultural, religious or contextual concerns that pose a barrier to accepting HepB-BD for their newborn children, concerns which can change over time.

**5.3.3. Develop relationships needed for a response to media reports of AEFI —**Developing relationships for your response ensures that you have an inner circle of colleagues who are prepared and available to assist in a response, should an event occur. The specific relationships developed will be country specific, but should include members from the news media, regulatory representatives, and other experts who would be critical in a response. Specific steps are outlined below.

- Establish relationships with the national AEFI focal person(s) and national regulatory representatives and become familiar with the AEFI surveillance system (if existent) in country.
- Identify communications experts in the Ministry of Health (MOH) or EPI program who can support your communications response.
- Establish a communications task force, including naming a media-trained spokesperson to communicate externally should an event occur.
- Build relationships with the media, key partners, stakeholders, and health staff.

**5.3.4. Develop critical materials for your response—**Developing critical materials for your response guarantees that you have messages and materials ready to share with stakeholders and the public as soon as an event occurs. It is also important for the national immunization program to have a social media presence, so that if the need arises there will be a platform from which specific responses can be delivered. Specific steps are provided below.

- Assemble information materials about AEFI.

- See the FAQ sheet on hepatitis B and the vaccine in Appendix B.
- Establish social media platforms for the immunization program, if nonexistent.
- Conduct communications assessments.
- Prepare communications and media plans.
- Develop draft press release and holding statements for a major event.
- Pre-test communications materials.
- Obtain tools to aid in strengthening communications response to events that may negatively affect confidence in vaccines. The WHO Regional Office for Europe has a comprehensive set of tools that are evidence-based and downloadable.
- Prepare a list of people who are available if a crisis situation occurs, including their contacts (make sure to update the list regularly). Determine where the operations center will be. Make sure that support staff will be available as well.

**5.3.5. Build capacity to respond to an AEFI—**Spokespersons need to be trained so that they are prepared for the strategies used by journalists, the types of questions journalists often ask in a crisis, and how to speak and behave during a press conference. They also need to be guided in how to respond when there is not (yet) sufficient evidence about the causality of an AEFI, and how to communicate to establish trust. Other responsible officers also need to be trained in crisis communication as all actions in a crisis may influence the level of trust from the public in authorities and in vaccines. Tips for spokespersons and guidance on responding to journalistic strategies are available at the WHO Regional Office for Europe's website.

**5.3.6. Implement interventions to address vaccine hesitancy—**One way to decrease the impact of vaccine-related events is to build resilience in your country or region against hepatitis B-BD vaccine hesitancy prior to the occurrence of AEFIs. This usually involves building a supportive environment around caregivers which fully promotes immunization from the interpersonal level to the national or policy level. The European Centre for Disease Prevention and Control recently published a technical report titled, Catalogue of Interventions Addressing Vaccine Hesitancy, which outlines interventions immunization stakeholders can use to counteract hesitancy in their country or region. The report includes interventions focused at the individual level as well as community-based interventions.

If possible, countries should conduct formative research to understand barriers and drivers to the vaccine, including their perceptions and beliefs. One option is to conduct a Tailoring Immunization Programmes (TIP) project, a comprehensive research and stakeholder engagement process that can help obtain an in-depth understanding of barriers and enablers to vaccination, to aid in addressing vaccine hesitancy and closing immunity gaps. Learn more about TIP.

# 6. Response

Coordination, investigation, and communications following a cluster of serious AEFI

The information in this section provides step-by-step guidance during the "response" phase of a HepB-BD-related adverse event. The goals of "Response" are to verify the AEFI cluster, identify the cause (s) of the AEFI cases, and determine if an intervention is needed (*e.g.*, remove the vaccine batch). This section also stresses the importance of using of existing reporting systems, engaging stakeholders, and ensuring that local experts or consultants are involved in verifying the cluster. It emphasizes maintaining the same positive message on the safety of HepB-BD and the importance of engaging partners to ensure transparency. It also outlines step-by step guidance for conducting clinical AEFI investigations to categorize the type of AEFIs (causality assessment) and guidance on conducting additional assessments and conducting epidemiologic studies.

## 6.1. Step 4: Verify the cluster and investigate the cause(s) of AEFI cases

**6.1.1. Engage key partners—**Engage with stakeholders, such as the national AEFI committee, local experts, or consultants, who have the responsibility to identify and manage AEFI, and ensure that spokespeople have been identified and media-trained. See this website for an overview of stakeholders.

**6.1.2. Obtain critical information—**Obtain numbers of AEFI cases of concern from the notification/reporting system in country, utilizing the national/regional database for AEFI collection and analysis. If another source such as the media provides numbers, confirm the source. As mentioned in Step One, it is important to understand the background rates of the condition in the cluster for your region and country if available. Understanding these rates helps elucidate whether the number of events in the cluster are in excess of the usual rates for an age group or within a location. The withdrawal of the Rotashield Vaccine in the United States in 1999 provides example of where obtaining the number of events aided in epidemiological studies later in the investigation—and eventually led to the discontinuation of the vaccine. You can read about Rotashield at CDC.

**6.1.3. Verify the cluster—**Conduct initial investigation to verify the existence of a cluster using active case finding and interviews. The WHO process typically used is described in Fig. 2. Verify that the cluster exists based on initial data from field investigation, number of AEFI cases in the cluster, and location. (NOTE: numbers may change as more information is obtained.)

**6.1.4. Make timely decisions about the vaccine and the need for clinical investigations—**Decisions about withdrawing the vaccine should be made following the event, and it is important that these decisions are made in a timely fashion, based on the best available data. If a death has occurred, initiating investigations immediately (ideally within 24 h) is critical. Clinical investigations are often difficult and require substantial resources and time. Specific actions may include the following:

- Conduct the investigation to confirm a reported diagnosis of an AEFI and clarify details and outcome (using appropriate case investigation forms); determine whether unimmunized persons are experiencing similar events; determine if case is isolated or part of a cluster and ensure administration of the appropriate medical care.
- If the vaccine is implicated, decide if you should quarantine the vaccine for testing and prevent further use until the investigation is concluded. If you decide to quarantine the vaccine, supply a replacement vaccine to ensure continuity of vaccination (if different manufacturers of the same vaccine are available within country).
- If there is a lapse in available vaccine, ensure there is guidance in place for what health workers should do and what vaccines should be offered shortly after birth until the supply issue is resolved.
- Conduct tests such as specialized studies on tissues (isolation of vaccine-derived virus, if applicable) or lot testing.
- If a death has occurred, autopsies may be needed. However, they should be conducted only if they are appropriate within the local context. If it is not possible to conduct an autopsy, a verbal autopsy can be conducted where caregivers or next of kin are interviewed to ascertain cause of death.
- Review the quality of the vaccine and manufacturing regulation history and practices. The regulatory agencies in your country may have access to this information.
- Report results of the investigation to all partners, including the media and healthcare workers.

**6.1.5. Conduct a causality assessment, according to WHO guidance—**It is important to ensure that a causality assessment is completed, as described in Fig. 3, using WHO's tool. Historically, causality assessment has been conducted at an individual based-level by clinical experts such as the US-based Clinical Immunization Safety Assessment Network [13] or at a population-based level by epidemiologists like the National Academy of Medicine, formerly – the Institute of Medicine [14]. Specific considerations for assessing causality include temporal association, exclusion of alternative explanations, prior evidence, proof of association, and biological plausibility. After completing the causality assessment, determine if the identified cluster comprises a vaccine safety signal by referencing the available literature on the condition (i.e., if the cluster indicates a potential link between a vaccine and an event, if previously known or unknown). However, if the signal identified is new, it will not be available in the literature.

Ideally, the country will have established either a national expert committee for AEFIs or an equivalent independent panel that could help conduct the causality assessment using clinical results from the investigation mentioned above to establish the link between vaccine given and the AEFI. A National Immunization Technical Advisory Group (NITAG), if established,

could discuss and review the safety data from a causality assessment or AEFI investigation and make recommendations for the country.

**6.1.6. Make decisions to conduct epidemiologic studies and disseminate findings—**When a cluster occurs, it is important to determine causal associations in a robust, well-planned epidemiologic study so the evidence can identify risks associated with a particular vaccine. However, epidemiological studies are often difficult and require substantial resources and time. If established in a country, active surveillance greatly reduces the time to assess AEFI in populations. These studies identify causal associations between adverse events and specific recommendations may be made based on the data generated. Following release of the results of the study, findings should be disseminated in a timely manner through various platforms, such as at stakeholder or expert meetings or in news media releases or a publication. Specific steps may include the following:

- Verify safety signal before conducting an epidemiological study—determine whether previous studies detected a similar signal.
- Decide whether to also conduct an epidemiological impact study to determine changes in coverage due to an event or cluster (if needed)—an example is shown in a case study in *Step 6*.

**NOTE:** The above decisions require careful consideration of in-country expertise, resources, and availability of time. Not all countries have the subject matter expertise or resources to conduct signal verification or impact studies of AEFIs. WHO has a pool of national, regional, and global experts available to assist in this effort and support capacity building.

The diagram above shows categorization of the type of AEFI based on availability of information during the investigation. In 2013, WHO revised the methodology for causality assessment of individual AEFI, allowing evaluators to review AEFI cases and guide them on their determination of the appropriate category of causal association. A companion electronic software application also is available and provides step-by-step guidance in the causality assessment, minimizing chances of making errors. The latest causality assessment guidance is available at WHO.

## 6.2. Step 5: Proactively and regularly engage with news media and affected populations to share information on key aspects of the investigation and to respond to questions

**6.2.1. Develop your response—**WHO has provided information on how to quickly and appropriately respond to vaccine safety events. The specific steps are outlined below and should provide a useful starting point for your initial response. Here, capitalizing on the resources and relationships developed in the Preparedness section above is critically important.

### 6.2.2. Follow the immediate steps recommended by WHO: [16]

1. Gather your inner circle developed in Step Two.
2. Understand the vaccine safety issue.
3. Liaise with key stakeholders.

4. Communicate externally to stakeholders and the public – both the general public and the local health workers and communities affected.*

   *Ensure that you acknowledge the event *with empathy*.

Ensure that the media representatives and other partners are provided with accurate and relevant information on the following:

1. Vaccine safety issues.
2. The immunization program.
3. The benefits and risks of vaccines and immunizations.

**6.2.3. Avoid dismissing the event and use consistent messages—**Media coverage (particularly via the Internet) and social media can quickly fuel public fears about the safety of vaccines. Government and responsible agencies must respond immediately and appropriately with accurate facts to prevent a loss of confidence in vaccination due to misinformation about an adverse event. CDC's 2014 *Crisis Emergency Risk Communication Manual* recommends that the following should occur during a crisis:

- Those who respond should not dismiss outrage at what has occurred, even if the magnitude of the crisis seems small or the outrage is unfounded.
- Responders should use consistent messages and ensure that these messages originate from a source that is credible.

**6.2.4. Refer to the timeline of national response after notification of AEFIs [17]—**A suggested timeline is provided below. This timeline outlines which actions should be taken within 24 and 72 h and which should continue throughout the event. Each vaccine safety event is unique, but having an idea of the specific steps to be taken immediately afterwards can streamline the communications and response. Additionally, ensuring that the communications response reaffirms the benefits of vaccines is important, regardless of the status of the AEFI investigation. AEFI investigations can take several months or even years; thus, affirming the general safety of the Hepatitis B vaccine throughout the entire investigation and response is critical. If a new safety concern is identified, it should be communicated to relevant stakeholders.

Within 24 h

1. To address the public's concerns, assess the clear need for immediate internal and external communications and implement the communications plan.
2. Alert the spokesperson identified in Step Two.
3. Select the media platforms for your response (social media, radio, TV, print media).
4. Prepare or update media and communications materials.

Within 72 h

1. Consider handing out a media release.

2. Consider hosting a media conference—it may not be necessary or appropriate to hold a media conference or release for every event.

#### Ongoing—from 72 h to Resolution of Event

1. Monitor activities and ongoing responses of various groups and communications critics.
2. Counteract rumors by giving factual information and avoiding repeating rumors.
3. Supply communications tools to health workers and partners, including the public.
4. Provide updated information to stakeholders and the public.

**6.2.5. Communicate results of the investigation to relevant stakeholders—** Providing a continuous communications response is critical for sharing information on the key aspects of the response, including the results of the clinical and epidemiological investigations, as well as responding to potential questions from the media and the public. This communicates to the public and stakeholders that you have taken the event seriously and provides a platform for updating them on the final status of your investigation.

- The timeline for communications will depend on the length of the investigations, including the conduct of epidemiologic studies.
- The audience for these activities includes the general public, the local community affected, healthcare workers locally and nationally, and the local and mass media—messaging should be tailored to specific groups.

### 6.3. Step 6: Monitor vaccination coverage and public response, and adapt the response to emerging data

**6.3.1. Monitor the media and public response—**Continuously monitoring the media and public response – including their fears and concerns, their support and interests – will help inform the EPI program on what to communicate or clarify to the public, contributing to maintaining confidence in the immunization program. (See “Preparedness” steps above.) Monitoring hesitancy in a systematic manner requires regular data collection before, during and after an event, preferably over several years, to understand how events may have impacted vaccine acceptance; however, media and social media coverage can be a short-term proxy for understanding general sentiment regarding a vaccine event. Following the event, preparations on risk communications messages to various audiences should be refined or developed, as appropriate. Specific steps may include the following:

- If investigations identify program errors as the cause of the cluster, strengthening capacity among healthcare workers with supportive supervision is critical for preventing future occurrences.
- Evaluate communications, behavior of initiators of AEFI concerns, and feedback to guide future responses.

**6.3.2. Implement strategies to reduce the risk for a future event and improve risk communications—**Strengthening and improving the surveillance system will ensure that events are identified more quickly in the future. Document lessons learned. Monitoring coverage can be resource intensive and might not be timely if there is not a registry.

- Use lessons learned to revisit risk and crisis strategies and plans, training needs of frontline personnel and spokespersons, and plans for stakeholder relations management.
- Communicate results of the impact study, if conducted [3], and the results of any signal evaluated or other studies or assessments conducted. An example of an impact study is provided below.
- Plan ongoing communications activities to continue reassuring the public and caregivers the value and safety of immunization, and any monitoring systems to detect changes in perceptions over time.

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Impact Study Example: Li, X., Wiesen, E, Diorditsa S., et al. Impact of adverse events following immunization in Viet Nam in 2013 on chronic hepatitis B infection. Vaccine 2016;34.6:869 873.

Following a cluster of serious AEFI in Vietnam, hepatitis B birth dose vaccine coverage dropped from 75.6% to 56.0% in 2013. Li, X., Wiesen, E, Diorditsa S., et al. estimated the impact of the reduction in vaccination coverage in 2013 on hepatitis B transmission and future deaths using a mathematical model. An excess of 17,456 future deaths and 90,137 chronic HBV infections were attributed to the drop in coverage of HepB-BD. The authors tried to refocus the country on the value of the vaccine and add perspective to how low vaccine coverage had an effect on disease occurrence among adults and pregnant women. These data were published in an open access journal and presented at various speaking events, including for the news media.

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## Acknowledgement

We would like to thank Lance Rodewald, Eric Wiesen, Brent Wolff, Dang Thi Thanh Huyen, Sigrun Roesel, Stephane Guichard, Laura Conklin, Abigail Shefer, and Linda Elsner for their contributions to this document.

## Appendix A:. Resources

## Hepatitis B and Hepatitis B vaccine

- World Health Organization. Hepatitis B vaccines: WHO position paper—July 2017. Weekly Epidemiological Record 2017;92:369–392.World Health Organization.
- World Health Organization. Implementation of hepatitis B birth dose vaccination—worldwide, 2016. Weekly Epidemiological Record 2017;92:369–392. Available at: http://apps.who.int/iris/bitstream/handle/10665/260207/WER9307.pdf?sequence = 1
- World Health Organization. Preventing perinatal hepatitis B virus transmission: a guide for introducing and strengthening hepatitis B birth dose vaccination. 2015. Available at: http://apps.who.int/iris/bitstream/handle/10665/208278/9789241509831_eng.pdf?sequence = 1

## Vaccine safety

- World Health Organization. Global vaccine safety: WHO vaccine reaction rates information sheets [online]. (2018) [December 6, 2018]. Available at: http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/
- World Health Organization. Safety of mass immunization campaigns. [cited June 22, 2017] Available at: http://apps.who.int/iris/bitstream/handle/10665/67726/WHO_V-B_02.10_eng.pdf?sequence = 1.
- Vaccine Safety Basics course: WHO and its partners developed an E-learning course on Vaccine Safety Basics on the origin and nature of adverse events, the importance of pharmacovigilance, and risk and crisis communications. The course is designed to serve a broad range of individuals involved in vaccine safety: health professionals, national regulatory staff, immunization staff, etc. It teaches the steps in verifying AEFI (including a cluster). Available at: http://vaccine-safety-training.org/.

## AEFI surveillance

- For standard procedures, forms, and methodologies for AEFI surveillance, please consult WHO's Vaccine Safety Tools.
- World Health Organization. Global manual on surveillance of adverse events following immunization [online]. 2014. [cited June 22, 2017] Available at: http://www.who.int/vaccine_safety/publications/Global_Manual_on_Surveillance_of_AEFI.pdf
- World Health Organization. Vaccine Safety Basics E-Learning Course. [cited June 22, 2017] Available from URL: http://vaccine-safety-training.org/
- World Health Organization. AEFI Core Variables [online]. 2015. [cited June 22, 2017] Available from URL: http://www.who.int/vaccine_safety/initiative/tools/AEFI_core_variables_basics_EN_Dec2015.pdf?ua = 1
- World Health Organization. AEFI Reporting Form [online]. 2016. [cited June 22, 2017] Available from URL: http://www.who.int/vaccine_safety/initiative/tools/AEFI_reporting_form_EN_Jan2016.pdf?ua = 1

## AEFI investigations

- World Health Organization. Aide-Memoire on AEFI investigation [online]. [cited June 22, 2017] Available from URL: http://www.who.int/vaccine_safety/initiative/investigation/New_aide-memoire_AEFI.pdf?ua = 1
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## AEFI and risk communication responses

The UNICEF AEFI Communication eLearning course provides a basic overview of AEFIs and example of possible AEFI events. It discusses the importance of gauging the impact of AEFIs and the decision of if, when, and how to respond. It also covers approaches for preparedness and developing communications responses to AEFI. The course is approximately 75 min long and provides a strong foundation for preparing a response to clusters of serious AEFI. This course is recommended for non-communicators in the immunization program, but also for professional communicators who support the Ministry of Health and may be unfamiliar with the specifics of AEFI responses. The course is available at this website.

### Other resources:

- World Health Organization Regional Office for Europe. Four immediate steps when responding to an event that may erode trust [online]. 2017. [cited June 22, 2017] Available from URL: http://www.euro.who.int/__data/assets/pdf_file/0018/333135/VSS-4-steps-trust.PDF?ua = 1
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## Appendix B:. Frequently asked questions

The following may be useful in developing information sheets and training materials. Modify to suit your needs; it is not an exhaustive list of FAQs.

## What is hepatitis B?

Hepatitis B is a serious infection of the liver caused by the hepatitis B virus (HBV). HBV is present in the blood and body fluids of infected individuals. HBV infection is mostly asymptomatic, especially in children. Adults may present with an acute infection consisting of non-specific symptoms that manifest as any of the following:

- Loss of appetite (not wanting to eat).
- Nausea, diarrhea, and vomiting.
- Dark urine.
- Yellow skin and eyes.

## What are complications of hepatitis B virus disease?

- HBV can cause long-term infection that can be undetected for decades and is the leading cause of these conditions, which ultimately can lead to death:
- Permanent liver damage, also known as cirrhosis.
- Liver cancer.

## Why is hepatitis B a public-health problem?

HBV infection is a major cause of chronic liver disease. More than 257 million people worldwide have chronic HBV infection, which can lead to complications such as liver cirrhosis, cancer, and ultimately death in 15% to 25% of chronically infected people.

## Who can get hepatitis B infection?

Anyone can get hepatitis B.

## Who is most at risk?

In areas of moderate to high HBV transmission (>2% of the general population chronically infected), newborns and young children are most at risk of getting infected and developing chronic infection, with complications developing many years later. Besides infants born to HBV-positive mothers, other at-risk groups include men who have sex with men, heterosexual persons with multiple sex partners, injection drug users, hemodialysis patients, and healthcare workers at risk for occupational exposure, among others.

## How does hepatitis B spread?

Hepatitis B virus spreads through blood or other body fluids that contain small amounts of blood from an infected person. People can spread the virus even when they have no symptoms. Babies and children can get hepatitis B in the following ways:

- At birth from their infected mother.
- Through direct contact with the blood or open sores of an infected person.

- Through exposure to blood from sticks by needles or other sharp instruments.

## Is there a cure for HBV infection?

No, there is currently no cure for hepatitis B infection, although people with chronic HBV infection can be treated with antiviral drugs to reduce the risk of progression to cirrhosis or liver cancer.

## Who should get the hepatitis B vaccine?

To prevent mother-to-child transmission of HBV, all newborns should receive the hepatitis B vaccine within 24 h of birth, followed by 2–3 additional doses before the age of 1 year. Adults at high risk for HBV infection, such as healthcare workers, injection drug users, people who get frequent blood transfusions, and those who handle blood and blood products (laboratory workers), should also be vaccinated with 3 doses of hepatitis B vaccine.

## What is the schedule for hepatitis B vaccination in infants and children?

WHO recommends a birth dose within 24 h of delivery followed by two or three additional doses given 4 weeks apart. The vaccine is given via an injection in the thigh for infants or in the arm for older children.

## Why does the first hepatitis B vaccine dose need to be given within 24 h of birth?

The first dose should be given within 24 h of birth to prevent the newborn from being infected by its mother. If the mother has a chronic HBV infection, the infant is likely to be exposed to HBV-infected blood or body fluids from the mother during birth, but a timely birth dose of the vaccine can prevent the baby from being infected.

## Is the hepatitis B vaccine safe?

The hepatitis B vaccine is very safe, and it is effective at preventing hepatitis B virus infection. Vaccines, like any medicine, can have side effects. Other than the very rare occurrence of allergic shock, which happens approximately one time per million vaccinations, there are no serious side effects known to be caused by the hepatitis B vaccine.

## What are the side effects of hepatitis B vaccination?

The most common side effects are redness or darkening, swelling, and pain at the injection site; these may affect about 1 in every 11 children vaccinated. These side effects usually start within a day after the vaccine is given. Less commonly, in about 1 in every 14 children vaccinated, fever may occur for a short time after the vaccine is given. Serious allergic reactions (hives or rashes and difficulty breathing, shock) are rare—about 1 in every million doses—and are treatable, once recognized.

## Is there a reason why a child should not be given a hepatitis B birth dose vaccine?

There are no contraindications for a timely hepatitis B birth dose vaccine, although one precaution is delay its administration if the infant has moderate to severe illness.

The only contraindication to hepatitis B vaccine is a severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component. Since the birth dose is the first dose of hepatitis B vaccine that is given, this contraindication does not apply.

*These FAQs have been adapted from WHO's* Preventing Perinatal Hepatitis B Virus Transmission: A Guide for Introducing and Strengthening Hepatitis B Birth Dose Vaccination, 2015; *CDC's* Information for Parents: Hepatitis B and the Vaccine (Shot) to Prevent It (2014); *and* Hepatitis B FAQs for Health Professionals *(updated April 2018).*

## Communications case studies: China and Vietnam's experience with clusters of deaths following HepB-BD

China responded quickly using comprehensive communications plans to address loss of confidence in vaccines and its ability to handle unexpected vaccine safety concerns with multiple audiences. The government suspended the vaccine from the market immediately, yet the vaccine turned out to have no defects. However, the policy change to withdraw the vaccine had already caused major, although temporary, loss of confidence in the vaccine.

In Vietnam, reports of clusters of immunization errors related to AEFIs were published in the news media, leading to a decrease in hepatitis B birth dose coverage. Stakeholders had to refocus the country on the value of the vaccine by conducting impact studies to indicate how coverage had an effect on disease occurrence among adults and pregnant women. These data were published in an open access journal and presented at various speaking events, including to the news media.

### Details regarding these two experiences are outlined in the following articles:

1. Yu W, Liu D, Zheng J, et al. Loss of confidence in vaccines following media reports of infant deaths after hepatitis B vaccine in China. Int J Epidemiology 2016;45:441–449.
2. Wiesen E, Li X. Commentary: assessing the impact of temporally associated adverse events on neonatal hepatitis B vaccination. Int J Epidemiology 2016;45:449–450.
3. Li X, Wiesen E, Diorditsa S, et al. Impact of adverse events following immunization in Viet Nam in 2013 on chronic hepatitis B infection. Vaccine 2016;34:869–873.

| Case Studies: Lessons Learned | |
|---|---|
| **Vietnam** | **China** |
| Response to events took approximately a year, which reduced vaccine confidence. Li X, Wiesen E, Diorditsa S, et al. estimate that the reduction in coverage in 2013 led to more than 17,000 future deaths and more than 90,000 chronic hepatitis B virus infections. | A timely and comprehensive communications plan was key—Chinese officials regularly held briefings with the public and the news media. Involving WHO early in the AEFI investigations helped to mitigate skepticism. |
| Negative media reports can lead to a reduction in immunization coverage. (See the 2016 article by Li X, Wiesen E, Diorditsa S, et al. above). This suggests that both negative media reports and punitive actions may lead to longer-term consequences for vaccine coverage and confidence. | During the suspension of the vaccine under investigation, the government supplied an alternative vaccine, limiting the decline in birth dose coverage. |
| When communicating about adverse events, transparency, especially with the news media, is critical in building trust. | However, suspending the vaccine did impact vaccine confidence, and this impact on vaccine confidence should be considered in decisions regarding vaccine suspension following AEFI. |

## Nomenclature

List of Acronyms

| | |
|---|---|
| **AEFI** | Adverse Events Following Immunization |
| **CDC** | Centers for Disease Control and Prevention |
| **EPI** | Expanded Program on Immunization |
| **ECDC** | European Center for Disease Prevention and Control |
| **GVSI** | Global Vaccine Safety Initiative |
| **HepB-BD** | Hepatitis B vaccine birth dose |
| **HBV** | hepatitis B virus |
| **LMIC** | Low and Middle-Income Countries |
| **MOH** | Ministry of Health |
| **NITAG** | National Immunization Technical Advisory Group |
| **UNICEF** | United Nations International Children’s Emergency Fund |
| **VPD** | Vaccine-preventable disease |
| **WHO** | World Health Organization |

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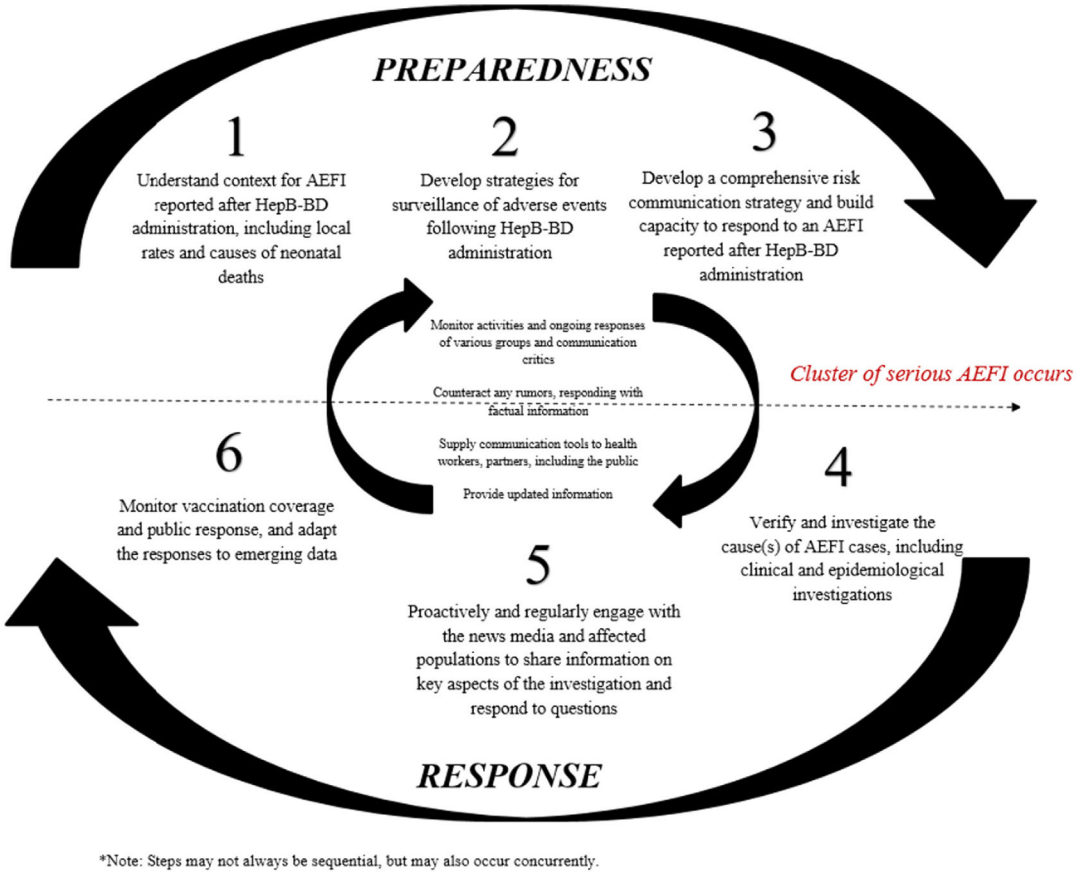


**Fig. 1.**

A framework for preparing and responding to AEFIs reported after Hepatitis B vaccine-birth dose administration.


**Fig. 2.**
From WHO Aide-mémoire on Causality Asessment [12].

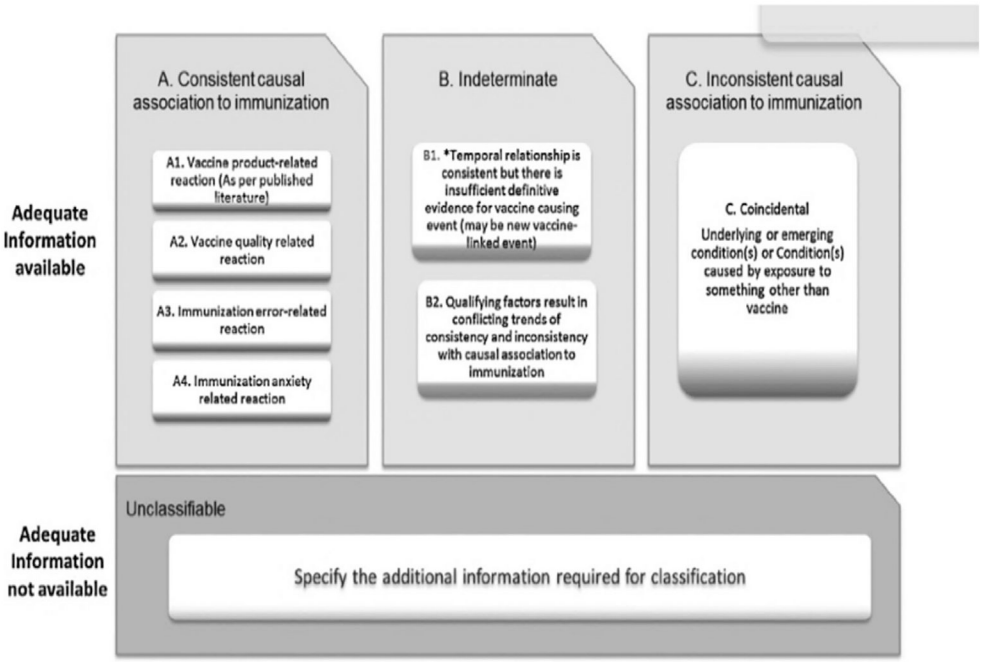


**Fig. 3.**
Categories of Causal Associations from Tozzi et al. [15].