Regional workshop on strengthening vaccine safety surveillance and capacity-building for causality assessment

Bangkok, Thailand, 20–22 September 2022
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<tr>
<td>ADR</td>
<td>adverse drug reaction</td>
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<tr>
<td>AE</td>
<td>adverse event</td>
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<td>AEFI</td>
<td>adverse event following immunization</td>
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<td>AESI</td>
<td>adverse event of special interest</td>
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<td>AVSS</td>
<td>active vaccine safety surveillance</td>
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<td>BeSD</td>
<td>behavioural and social drivers</td>
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<td>CA</td>
<td>causality assessment</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<td>COVID-19</td>
<td>coronavirus disease 2019</td>
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<td>DGHS</td>
<td>Directorate General of Health Services</td>
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<td>EPI</td>
<td>Expanded Programme on Immunization</td>
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<td>GACVS</td>
<td>Global Advisory Committee on Vaccine Safety</td>
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<td>GVSB</td>
<td>Global Vaccine Safety Blueprint</td>
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<tr>
<td>HCW</td>
<td>health-care worker</td>
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<td>HEOC</td>
<td>Health Emergency Operations Centre</td>
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<td>ITAG</td>
<td>Immunization Technical Advisory Group</td>
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<td>IVD</td>
<td>Immunization and Vaccine Development</td>
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<td>JRF</td>
<td>Joint Reporting Form</td>
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<td>MoHP</td>
<td>Ministry of Health and Population</td>
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<td>NHEICC</td>
<td>National Health Education Information Communication Centre</td>
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<td>MNT</td>
<td>maternal and neonatal tetanus</td>
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<td>NRA</td>
<td>National Regulatory Authority</td>
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<td>PIDM</td>
<td>Programme for International Drug Monitoring</td>
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<td>RCCE</td>
<td>risk communication and community engagement</td>
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<td>RVAP</td>
<td>Regional Vaccine Action Plan</td>
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<td>RVIP</td>
<td>Regional Vaccine Implementation Plan</td>
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<td>Abbreviation</td>
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<tr>
<td>SUIDI</td>
<td>sudden unexplained infant death investigation</td>
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<td>TTS</td>
<td>thrombocytopenia with thrombosis syndrome</td>
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<td>UMC</td>
<td>Uppsala Monitoring Centre</td>
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<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
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<td>VAERC</td>
<td>Vaccine Adverse Events Review Committee</td>
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<td>VITT</td>
<td>vaccine-induced thrombosis and thrombocytopenia</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<td>WISE</td>
<td>WHO Information Immunization System</td>
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1. Introduction

The main objective of the meeting was to strengthen vaccine safety surveillance and causality assessment (CA) of serious adverse events following immunization (AEFIs) for all vaccines in the South-East (SE) Asia Region. The specific objectives were:

- providing updated information on vaccine safety surveillance, including new tools developed by WHO for causality assessment and data management;
- reviewing regional and country successes and challenges with regard to AEFI surveillance for vaccines used in national immunization programmes and COVID-19 vaccines, and identifying priority actions for strengthening AEFI reporting at national and subnational levels;
- reviewing adverse events of special interest (AESIs) and other active surveillance mechanisms that have been established in the Region/globally and their contribution to further increase sensitivity of safety surveillance; and
- discussing how vaccine safety surveillance can be used to mitigate vaccine hesitancy.

Dr Jos Vandelaer, WHO Representative to Thailand, opened the meeting on behalf of Dr Poonam Khetrapal Singh, WHO Regional Director for South-East Asia and the opening address is attached as Annex 1.

The participants in the workshop included managers of national expanded programmes on immunization (EPIs), focal persons looking after vaccine safety surveillance at the national level, National Regulatory Authority (NRA) representatives, chairpersons of the national AEFI committees, EPI/AEFI surveillance focal points from WHO country offices and nominated United Nations Children’s Fund (UNICEF) Country Office staff.

The workshop was facilitated by members of the Global Advisory Committee on Vaccine Safety, the Chairperson of the Causality Assessment Subcommittee of the National AEFI Committee, India, staff members from the vaccine safety surveillance and pharmacovigilance team from WHO HQ, Immunization and Vaccine Development (IVD) unit at the WHO Regional Office for South-East Asia (WHO-SEARO), including consultants from), and the Uppsala Monitoring Centre (UMC). The agenda is attached as Annex 2 and the list of participants is attached as Annex 3.

2. Opening Session

2.1 Technical session 1: Global and Regional Progress in vaccine safety surveillance

*Brief questionnaire on vaccine safety surveillance using Slido*

The technical session began with a questionnaire on vaccine safety surveillance through interactive software that enabled the display of participant responses in real time. The responses allowed the facilitators to determine the areas for emphasis during the workshop.
Progress on vaccine safety surveillance in the SE Asia Region and linkages to the Regional Vaccine Implementation Plan 2022–2026

The Strategic Framework for the Regional Vaccine Action Plan 2022–2030 is the regional adaptation of the Immunization Agenda 2030, which was endorsed by the WHO Regional Committee for South-East Asia in September 2021. The Regional Vaccine Implementation Plan (RVIP) 2022–2026 has been developed in consultation with Member States, Immunization Technical Advisory Group (ITAG) members and partners to operationalize the Strategic Framework. The SEAR-ITAG endorsed the plan in August 2021.

Member States and partners will need to pay renewed attention to achieve the following impact goals: 1. leaving no one behind in the South-East Asia Region by increasing equitable access to and use of new and existing vaccines; 2. pursuing vaccine-preventable disease (VPD) elimination and control goals: achieving measles and rubella elimination, sustaining polio elimination, sustaining maternal and neonatal tetanus (MNT) elimination and achieving hepatitis B control; and 3. reducing the overall mortality and morbidity from VPDs across the life-course.

The Strategic Priorities (SPs) and the Key Areas of Focus of the Regional Vaccine Action Plan (RVAP) are shown in Fig. 1 below.

Fig. 1. SPs and the key areas of focus of the RVAP

<table>
<thead>
<tr>
<th>SP1. Immunization for PHC/UHC:</th>
<th>SP3. Coverage &amp; Equity:</th>
<th>SP6. Supply &amp; Sustainability:</th>
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</thead>
<tbody>
<tr>
<td>1. Immunization in primary health care</td>
<td>1. Disadvantaged populations</td>
<td>1. Innovation and affordability</td>
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<tr>
<td>2. Leadership, governance and management</td>
<td>2. Barriers to vaccination</td>
<td>2. Vaccine forecasting, procurement and supply</td>
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<td>4. Supply chain and logistics</td>
<td>4. Learning from disease-specific initiatives</td>
<td>4. Sufficient, predictable resources</td>
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<td>7. Monitoring vaccine safety</td>
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<tr>
<th>SP2. Commitment &amp; Demand:</th>
<th>SP4. Life Course &amp; Integration:</th>
<th>SP7. Research &amp; Innovation:</th>
</tr>
</thead>
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<tr>
<td>1. Commitment</td>
<td>1. Mobilizing support</td>
<td>1. Evidence for Implementation</td>
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<td>2. Subnational support</td>
<td>2. Evidence-based delivery practices</td>
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<td>5. Public knowledge and understanding</td>
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| SP5. Outbreaks & Emergencies             |                                                 |                                                  |
|------------------------------------------|------------------------------------------------|                                                  |
| 1. Coordination and integration          |                                                 |                                                  |
| 2. Local capacity                        |                                                 |                                                  |
| 3. Comprehensive health response         |                                                 |                                                  |
| 4. Community engagement                  |                                                 |                                                  |

Monitoring of vaccine safety is under the Strategic Priority of immunization for primary health care (PHC)/universal health coverage (UHC). Member States in the Region should ensure that the national immunization programmes can detect and respond to any concern over vaccine safety through continuous monitoring and coordination among relevant stakeholders. The regional indicator for vaccine safety refers to the proportion of countries with at least one documented (with the reporting form), individual, serious AEFI case per million total population. At present, four countries meet this indicator criteria.
Before the start of the COVID-19 pandemic in 2019, all countries of the Region had made substantial progress towards building capacity for the surveillance of the safety of vaccines under EPI. All of them had established national monitoring systems and set up review committees for AEFI with suitable terms of reference (ToRs) and legislative or administrative bases.

Nine out of 11 countries had reporting rates of >10 AEFIs per 100 000 surviving infants following EPI vaccination and 10 had reporting rates of >1 serious AEFI per 1 million surviving infants.

All countries of the Region have used their existing structures for safety surveillance for COVID-19 vaccination. In preparation for COVID-19 vaccination, countries had expanded their national AEFI committees to include relevant specialists, such as physicians, cardiologists, respiratory physicians, neurologists, obstetricians and endocrinologists. Regional workshops on safety surveillance for COVID-19 vaccination were organized in December 2020 and November 2021. Health-care workers (HCWs) were trained in AEFI detection and reporting through online and face-to-face sessions. Indonesia initiated surveillance for adverse event of special interest (AESI) following COVID-19 vaccination at 14 sites.

Twelve COVID-19 vaccines are being used in 10 countries that have COVID-19 vaccination programmes, with most countries using four or five different vaccines. The viral-vectorized AstraZeneca (AZ) vaccine accounts for 60% of doses administered in the Region, followed by the inactivated vaccines, Sinovac, Covaxin and Sinopharm.

Cumulative adverse events following immunization reports and causality assessment (CA) data are being provided to the WHO-SEARO by countries through email or monthly reporting in electronic Joint Reporting Form (eJRF) for COVID-19 data. Data are also available from the annual national ITAG reports, submitted for review by SEAR ITAG.

Four out of nine countries reported >10 AEFIs per 100 000 doses with wide variations, ranging from 1.5 to 722, following COVID-19 vaccination in 2021 and 2022. Three countries reported serious AEFIs >1 per 100 000 doses with variations, ranging from 0.03 to 11. The new indicator of one serious AEFI per million population in 2021 for COVID-19 vaccines since initiation was 8/10 countries, with variations ranging from 0.47 to 203.6, and for EPI vaccines was 4/11 countries, with variations ranging from 0.01 to 32.6.

Reporting on serious AEFIs from EPI declined in 2021, when compared with 2019. Case investigations were completed for 98% of serious AEFI cases from COVID-19 vaccination and EPIs. The number of cases that were ineligible for causality or were unclassifiable were low. However, it was concerning that causality assessment for serious COVID-19 and EPI AEFIs was far from being complete.

Causality assessment outcomes were coincidental and product-related (A1) for COVID-19 and EPI. There were no vaccine defects and a few immunization errors for EPI and COVID-19. Immunization stress-related responses (A4) were reported for COVID-19 vaccines and there were challenges to causality assessment due to lack of autopsy findings as indicated by countries. It has also been noted that the rates of thrombocytopenia with thrombosis syndrome (TTS) and myocarditis are lower in SE Asia Region countries, compared with high-income countries.
The Thirteenth ITAG recommendations regarding vaccine safety surveillance were presented and discussed to guide countries on developing their workplans for safety surveillance.

**Global update on vaccine safety surveillance**

The presentation provided a global update on the progress on vaccine safety surveillance over the past two years. The importance of moving from aggregate data to case data was highlighted. After 2020, the new performance indicator is individual serious reporting rate in million total population from a country or a subnational area per year. The initial target proposed was at least one serious reported case per one million population per year. Case-based data needed to be reported in VigiBase for documenting the cases.

Progress on general areas of vaccine safety was described. WHO/HQ developed the Global Vaccine Safety Blueprint (GVSB) 2.0 following the first version that was drawn up in 2012. This blueprint will be valid for a period of two years. Safety surveillance programmes have been moving from minimum to maturity level concepts. The Global Benchmarking Tool will be used for assessing country performance. Moving from Level 1 to Level 4 with Level 4 being the maximum performance. Based on content, there are two strategic areas, technical and enabling, that are important for accountability. The expert committees and working groups for vaccine safety include the nOPV2 subcommittee, the Expert Steering Committee on safety surveillance in pregnancy in low- and middle-income countries (LMICs), the Global Advisory Committee on Vaccine Safety (GACVS) monitoring the safety of malaria vaccine implementation programmes and the subcommittee on monkeypox.

Newer approaches to managing data include the use of VigiMobile, interoperability with existing AEFI data collection systems, creating an AEFI data dashboard at WHO and an e-learning course on AEFI data management. Publications in the past two years include one on anaphylaxis identification, case management and response, including a video on management of an anaphylaxis.

The role of the Vaccine Safety Net in facilitating internet users’ access to reliable, understandable and evidence-based information on the safety of vaccines, regardless of their geographical location and language, was described. The COVID-19 GACVS subcommittee published special modules, such as the one on TTS guidelines. The COVID-19 vaccine safety surveillance manuals were published as electronic versions only; these included the special module study protocols for safety signal detection and safety surveillance of COVID-19 vaccines concerning pregnant and breastfeeding women.

The key priorities for vaccine safety in 2022–2023 included moving from a minimal and enhanced capacity concept to a maturity level concept, as outlined in GVSB 2.0, with a focus on a) governance and systems development; b) coordination of safety systems between stakeholders and partners; c) strengthening of the regulatory framework; d) high-quality surveillance of adverse events following immunization, concentrating on case-based data; e) enhanced vaccine safety communication; and f) ensuring implementation of vaccine safety in fragile states and during emergencies.
2.2 Technical session 2: AEFI detection, reporting and analysis

What we have learnt from COVID-19 vaccine pharmacovigilance – understanding basic concepts

This presentation covered the basic pharmacovigilance concepts, which included how safety of vaccines is determined. Adverse vaccine or immunization reactions are a measure of vaccine safety. Adverse reactions are determined in pre-licensure clinical trials; however, because of the limited number of participants recruited, such trials cannot determine reactions that are rare or delayed or those that occur in subpopulations. Thus, post-licensure passive surveillance of adverse events following immunization is critical. Since symptoms or signs of an AEFI can occur in background conditions, causality assessment is required to differentiate a coincidental event from an adverse vaccine or immunization reaction. The COVID-19 vaccine programme highlighted many of these principles. Rare adverse reactions were documented through post-licensure surveillance with vaccine signals for anaphylaxis, myocarditis and TTS or vaccine-induced thrombosis and thrombocytopenia (VITT). In order to establish a myocarditis vaccine attributable rate, it was important to know the background rates of myocarditis, while for TTS/VITT, this was a unique vaccine reaction (provided heparin exposure had been excluded).

The Uppsala Monitoring Centre delivered a presentation on their role in data management and how the country programmes could benefit from sharing anonymized safety surveillance data on tools, such as VigiBase, VigiFlow and VigiLyze.

Co-coordinating Regional and global AEFI reporting and analysis by the WHO Programme for International Drug Monitoring

The Uppsala Monitoring Centre (UMC) is an independent, self-funded, non-profit foundation that was established in 1978. It oversees the technical and scientific operations of the WHO Programme for International Drug Monitoring (PIDM) under which there are 153 full Member countries and 22 Associate Members. UMC is the custodian and manager of VigiBase and the developer of WHODrug Global, the world’s most widely used drug dictionary. VigiBase contains over 32 million records of individual cases; of these six million are on vaccines, out of which 4.2 million are related to COVID-19 vaccines.

The UMC’s core areas include products, such as WHODrug, which is widely used in coding for clinical trials and is also needed to structure and code information in VigiBase services to make it analytical. The UMC offers training courses, both online and physical, on pharmacovigilance. These range from courses on basic pharmacovigilance to in-depth courses on signal detection and statistical reasoning. There is a global communications department that focuses on advocacy and raising awareness about pharmacovigilance. The scientific development activities of the UMC include signal detection as the core part of the work, clinical assessment and communicating about signals to stakeholders.

Signals that arise at the local level may not always be seen as a pattern because only a limited number are observed. However, collation of data on a global scale through VigiBase helps find rare and unexpected events that may not be detected through clinical trials.
From the start of the COVID-19 pandemic, the UMC has been focusing on providing the same kind of support and tools for vaccine safety as that for drugs. Since COVID-19 vaccines are being rolled out in large numbers, even rare events can have significant programmatic impact. Therefore, collecting and analysing the data at the global level is critical.

There is a need to move from paper forms to digital solutions for safety data collection to reduce delays in reporting and improve data quality. In the field, the available options for data collection include VigiMobile, DHIS2, MedSafety app and others being used at the local level.

The UMC provides VigiFlow for AEFI data entry. The WHO AEFI Reporting Form was digitalized into a VigiFlow interface, including all 25 core variables and available up to the district level. The analysis has different hierarchy levels so that a country can have access to the relevant subsets of the national data. The analysis is displayed as descriptive epidemiology and will show surveillance performance.

Safety surveillance data, entered by the programme through direct reporting, e-reporting or through mobile apps, flow through VigiFlow, which is the intersection between the subnational and national levels. VigiFlow is the basis for data management and analysis of adverse drug reactions (ADRs) and AEFIs. Further sharing of data with VigiBase, the WHO global database of AEFIs and ADRs, is an active choice to be made by the national programme.

VigiLyze is the analysis tool available at the national level. VigiLyze can be used for vaccine safety surveillance through statistical screening at national/regional/global levels; it allows for the prioritization of AESI and can be tailored to focus on individual vaccine and vaccine platform levels. The tool offers quantitative view, showing statistical screening at national, regional and global levels, at the general level of, say, “COVID-19 vaccine” or at the level of specific vaccines, e.g. Tozinameran (Pfizer) and Elasomeran (Moderna).

The qualitative view allows for further exploration of statistical signals with the possibility of getting aggregated disproportionality at the vaccine platform level (SDG filter). The UMC provides support for signal management and for cross-border collaboration across countries, at regional and global levels. Signals are shared by the UMC through VigiLyze with those who have access. VigiLyze can be accessed by regulators and EPIs. National authorities may similarly share information derived from VigiLyze within the country.

VigiMobile has been recently added for data collection. The app uses the standard WHO AEFI reporting form, based on the 25 core variables, recommended by the Organization for collecting AEFI data. Reports can be sent directly to VigiFlow as soon as an internet connection becomes available.
**How country surveillance systems have been adapted to collecting and processing data for decision-making at the three levels and how the methods for monitoring have changed since the introduction of COVID-19 vaccines**

The presentation highlighted how country surveillance systems have been adapted to collecting data from VigiBase and through the Joint Reporting Form (JRF). The collection and utilization of safety surveillance data for action at various stages of the surveillance cycle were highlighted.

The AEFI data are collected by interviewing the patient or parents, reviewing case records and then transcribing this information on the reporting form. Once the reporting form is completed, it is transmitted to the next level of the hierarchy. If a health worker fills out the form next, it will be sent to the district. At the district level, the District EPI Manager or the District Immunization Officer completes the reporting by reviewing the data entered and checking for mistakes and inconsistencies. If electronic software is used for reporting, this process will be completed in the software. However, irrespective of the software being used, the minimum data elements, consisting of 25 core variables, should be collected.

Analysis of data is essential for making programmatic decisions and communicating these to the public and stakeholders concerned. District-level analysis of data leads to the identification of programme-related issues, whereas product-related events are identified at the national level. The national AEFI data should be shared between the EPI and the National Regulatory Authority (NRA) so that each country has a uniform data set. The aggregate data, submitted through eJRF, are available in the public domain through the WHO Information Immunization System (WISE).

Collection of case-based data is similar to that of aggregate data at the initial stage. However, since it contains personal data, there is an issue with confidentiality. Hence, the data need to be encrypted through the E2B process, following which it can be entered into the global database of VigiBase. Since the data shared are confidential, only one official from the EPI and another from the NRA provide access for each country. Manufacturers also share the data with the global database manufacturers and the NRA. The information is especially important for the National AEFI Committee when it conducts causality assessment.

The challenges to making informed decisions regarding JRF data were stated as follows: it is the aggregate data that are available on an annual basis, the type of AEFI, relationship to specific vaccines, age and pregnancy status, among other issues. Challenges regarding case-based data were that: it may not be of sufficient quality to make informed decisions, most data are coming from developed countries and in several countries, the data may not have been shared with the relevant stakeholders.

Furthermore, the presentation provided examples of how data were being used to strengthen vaccine safety surveillance through the sharing of guidelines and relevant publications.

In conclusion, it was emphasized that data needed to be shared with relevant stakeholders. Analysis of data was important to identify and flag issues that were specific to the country, prepare scientific reports and share them.
**Demonstration of the resources available in the country context**

The presentation described and demonstrated the resources and tools available for safety surveillance. Vaccine safety trainings are being conducted through face-to-face sessions, e-learning and hybrid mechanisms. The resources demonstrated included: the AEFI detection and notification manual, which highlights the one-on-one communication among the patient’s mother, the vaccinator and the recipient; the standard AEFI reporting form; and VigiMobile.

There are five courses for face-to-face training: vaccine safety basics course, advanced course on AEFI and causality assessment, vaccine safety communications course, AEFI signal detection course and national AEFI guidelines dissemination course.

The vaccine safety e-learning training courses are as follows: vaccine safety basics, AEFI investigation, data management and AEFI causality assessment.

The hybrid trainings include: AEFI field investigation simulation and communications course, AEFI data management blended course and communications.

The e-learning courses are linked to AEFI rate sheets for vaccines, WHO position papers and all relevant documents for case investigation that can be automatically downloaded. The case investigation course is also connected to the causality assessment software. Thus, data can be uploaded directly on the causality assessment software. The data management basics course has three modules. The first is on data entry while the second module describes how to convert data into a line list; the third module teaches data conversion into a graph.

**Group work: lessons learnt from COVID-19 vaccines to conceptualize the approach to AEFI detection and reporting**

The countries were divided into three groups to undertake the group work. Each group discussed and documented the lessons learnt from COVID-19 vaccine AEFI detection and reporting, the factors that facilitated or were barriers to AEFI detection and reporting for COVID-19 vaccines and how AEFI surveillance could be maintained post the COVID-19 pandemic.

A summary of the action points from the groups is provided below.

The factors facilitating AEFI detection and reporting were outlined as follows:

- **system strengthening to enhance AEFI reporting:** an established and robust AEFI system that could be strengthened; training and retraining, along with motivating HCWs, who were already part of immunization systems through face-to-face, online and hybrid mechanisms; use of new tools, such as videos; sensitization of other cadres for reporting – village health volunteers, pharmacists, hospital emergency departments and clinicians; strengthening of AEFI committees – inclusion of adult medicine specialists, more frequent meetings, establishment of district (subnational) causality assessment committees; collaboration between hospital pharmacists and the regulator for AEFI/ADR reporting; media campaign to sensitize public to AEFI; and strong monitoring and review system for AEs with regular reporting to districts.
- **use of novel IT tools or methods to facilitate AEFI reporting**: development of SMS platforms for consumers to report common adverse events; AEFI waiting rooms for observation; regarding vaccines, asked about AEs when subsequent doses received and AEs captured by surveillance; and mandating reporting of AEFIs.

- **facilitation of direct consumer reporting through self-reporting mechanisms**, such as SMS platform and phone hotlines.

- **enhanced advocacy for AEFI surveillance through** political support, a high level of political commitment and involvement of religious leaders to address vaccine hesitancy, and the establishment and use of electronic vaccine registries.

### Barriers to AEFI detection and reporting

The following barriers were identified:

- **system issues**: all HCWs not trained in AEFIs, low reporting from the private sector; delayed reporting due to connectivity issues, lack of formats, etc.; mechanisms not in place for community reporting; time lag between reporting of AEs and receipt at district/higher levels – impacted timeliness of receipt and analysis of data; no KPI/benchmark for hospital-based reporting of AEFIs (some hospitals may have KPIs for ADR reporting); and shortage of staff, including high turnover and workload, as, usually, AEFI surveillance staff were also responsible for COVID-19/other disease surveillance and COVID-19 vaccination acceleration.

- **knowledge gaps**: for detection and reporting of emerging AEs, such as TTS, and myocarditis; and reporting by some health officers, particularly of deaths, needs to be increased.

- **proposed actions for strengthening detection and reporting**: conducting regular training for health workers and surveillance staff in AEFI; establishing/continuing with the IT platforms that integrate EPI and COVID-19 AEFI reporting; use of electronic vaccine records to capture all AEs, including the minor ones; creating awareness of AEFI among community and encouraging self-reporting through IT platforms; recognizing HWs for reporting AEFI; strengthening feedback mechanism; data management and data sharing; and promoting collaboration between medical associations and other key stakeholders.

### 2.3 Technical session 3: case investigation and causality assessments

**Investigation of AEFIs, including recent changes in AEFI investigation approaches due to COVID-19 (Module D)**

This presentation covered the steps in investigating an AEFI, which includes confirmation of information in the report, investigation and collection of more data, assessing the immunization service, specimen collection, where applicable, and concluding the investigation. Data should be collected with regard to the patient, the event, the vaccine(s) and other persons (vaccinated and non-vaccinated). The immunization service should be
investigated, and the practices observed. Specimens should be collected from the patient and the vaccines. Vaccines should not be tested without a hypothesis regarding the cause of the error. Final actions include reaching a conclusion regarding the potential cause and developing an action plan to take appropriate corrective action; early communication; reporting findings to national and international partners; and collecting additional information, if required. Suspension of the vaccine programme is seldom required.

**Analysis of vaccine safety data and risk assessment**

An analysis of vaccine safety data was presented. The example of increase in reports of fever following introduction of a new vaccine was presented. The reasons for this can include an increase in administered vaccines, a change in reporting, concomitant disease and an increase in vaccine reactogenicity. Analysis should determine the vaccine attributable rate of a reaction and take account of any confounding factors. It is important to use standardized Brighton Collaboration case definitions and coding dictionaries, if possible.

Determination of a numerator and a denominator is important to calculate rates and relative rates of reporting. Denominator data include those vaccinated, but this data may not be available; use of surrogate measures, such as distributed vaccine doses, may be needed. Reporting rates can then be calculated and compared. Background rates can be compared with observed rates to ascertain if there is an excess vaccine reaction rate. This evidence then informs a benefit-risk analysis. Relative risks – for example, vaccine A compared with vaccine B – can also be calculated. Confounding and modifying factors should be considered. An understanding of the investigation of a cluster was also provided.

**Update on causality assessment and introduction of group work and online demonstration of the AEFI Causality Assessment Tool**

Causality is the relationship between two events (the cause and the effect), wherein the second event is a consequence of the first. Causality assessment (CA) is carried out to determine if such a relationship exists and if it exists, to what extent. The WHO assessment process classifies an AEFI report into one of the three categories – consistent, indeterminant or inconsistent. Serious AEFI clusters, suspected signals and other AEFIs (such as those causing community concern) should be selected for causality assessment. The prerequisites should be a case investigation needs to have been performed and a valid diagnosis must be established. The process involves four steps – eligibility, checklist, algorithm and classification. The causality committee should consist of independent experts and function under the written terms of reference.

Feedback from the groups on pdf, generated by online causality assessment software, accessed at https://gvsi-aefi-tools.org/, including actions taken on the basis of CA

During this session, country groups were provided with details of AEFI cases and asked to review the cases assigned, perform an online causality assessment (https://gvsi-aefi-tools.org/) and detect the causality. Four selected groups delivered presentations during the plenary session.
Role of National Regulatory Authority in vaccine safety surveillance

The presentation described the role of the NRA in vaccine safety surveillance. The development of a vaccine is very closely monitored by the country where the vaccine is produced. The NRA has a legally mandated role in both the pre-marketing phase and the post-marketing phase. In the pre-marketing phase, the NRA provides oversight to clinical trials, regulatory inspections, marketing authorization and licensing. Laboratory testing of vaccines is essential to ensure quality. The vaccine batch, produced by each manufacturer, is sent to a national control laboratory, where the vaccine is tested, leading to the execution of a lot release; the manufacturing country must execute this.

Member States vide World Health Assembly resolution WHA67.20 requested WHO to strengthen the national regulatory systems. WHO has the global benchmarking tool, which is a universal tool for all kinds of products. They apply the valuation tool and evaluate peer-to-peer-based performance. The evaluation leads to an institutional development plan. WHO also provides technical support to NRAs and governments to ensure that the national regulatory authorities achieve appropriate benchmarking.

The role of WHO includes the following: setting norms and standards for all vaccines; capacity-building in developing countries; coordinating formation of networks; regulation of medical devices, including diagnostics; and international and regional collaboration of drug laboratory authorities and WHO prequalification (PQ) programme. The PQ programme supports UNICEF in procuring medical products, including vaccines, through a prequalified manufacturer. Through overall health system strengthening programmes, WHO has international and regional collaborations, wherein it is either coordinating or participating as an observer. Finally, WHO plays a key role in the regulation of complex biologicals through hand-holding the manufacturing country NRA.

WHO provides technical support for the formulation of the institutional development plan; it monitors the progress and impact. This is performed in collaboration with the interested partners, such as Gavi, The Vaccine Alliance and UNICEF. Many countries have conducted the benchmarking of their regulatory systems through WHO or independently. Self-benchmarking has been carried out by 57 countries and WHO has conducted this in 31 countries. A maturity level rating of three and four means the NRA is functional and vaccine production can take place in the country. A total of 98 countries are at maturity level one; 40 countries are at maturity level two; and only 29 countries are at maturity levels three and four.

The presentation described the challenges faced while strengthening the regulatory system. The main challenges include lack of national policies and long-term strategies; unclear vision; insufficient commitment, both political as well as bureaucratic, to ensure that the NRAs achieve the maturity level; inadequate resources; and improper regulatory practices. The resources available for NRA strengthening, covering all nine functions through guidance/policy documents, were described. The earlier system of stringent regulatory authority is being replaced by the WHO listed framework and within five years, all Member States, which have been listed as transitional, have to achieve the benchmark, as per the policy and operational guidance document.
The functioning of NRAs in the SE Asia Region countries can be placed in three main categories: smaller countries with a population of one million or less with NRAs ensuring essential functions; larger countries with less mature vigilance systems in which NRAs perform essential and intermediate functions; and still larger countries with more mature vigilance systems, where the NRAs perform essential, intermediate and advanced functions. The NRA actions for detection and surveillance, assessment and prevention of safety surveillance were described.

**Verbal autopsy for deaths following immunization**

The presentation highlighted the importance of verbal autopsy for cases of unexplained child deaths following immunization. The current infant mortality rate in India is 27 per 1000 live births. Therefore, many coincidental deaths may be temporally linked to vaccination, leading to erosion in confidence in vaccine safety.

Deaths following immunization are commonly reported among infants. Typical case histories have revealed previously normal children going to bed on the night of the vaccination and being found dead the next morning or dying in their sleep after a variable period of time. Such cases are usually not seen by a doctor and a health-care worker, and a post-mortem examination is often not undertaken or remains incomplete. Sudden infant death syndrome (SIDS) is a probable cause, but sudden deaths can also result from suffocation, sedative overdose, snake- or insect-bite and infanticide. Hence, verbal autopsy is a critical tool to understand “what happened” and reach a valid diagnosis. It provides a clear sequence of events, from vaccination till death. The investigator gains insight into the child and family’s circumstances. It is invaluable in the case of deaths for which no post-mortem examinations have been performed and it also complements post-mortem, especially if the quality of the examination was poor. In the absence of a post-mortem, it is a critical tool that helps differentiate SIDS from sudden, unexplained deaths.

Verbal autopsy was introduced in India when the National AEFI Guidelines were revised in 2015. The tool is based on the WHO and Centers for Disease Control and Prevention (CDC), Atlanta, forms for sudden unexplained infant death investigation (SUIDI). It is to be filled in when investigating any report of AEFI death, where inadequate information is available regarding the terminal event.

The presentation informed attendees about the key components of the child verbal autopsy form and its different sections, beginning with the basic details and then moving on to other relevant elements, including information on the circumstances of death in exact vernacular words for the onset of symptoms and chronology of events, treatment provided before the event, respondent/witness interview, family history, interviewer’s observations, case summary and final diagnosis. The details of the interviewer and copies of all available documents should be attached.

The programme introduced a new form for reporting AEFI deaths among adults/persons above 15 years of age in 2021 for COVID-19 vaccination. It is based on the verbal autopsy forms, developed by the Population Health Metrics Research Consortium and the WHO international standard verbal autopsy questionnaires.
Like the paediatric autopsy form, it provides critical inputs regarding the sequence of events, comorbidities, past illnesses, treatment details, medication history, relevant obstetrics and gynaecology history among women, addictions, lifestyle, and social and family history. Also included is information regarding systemic involvement, such as the role of the respiratory system, the cardiovascular system, the gastrointestinal system, the central nervous system and the genitourinary system; information regarding COVID-19 infection/past COVID-19 vaccination; any treatment or medication details during the current event before death; and relevant risk factors, such as smoking, drinking and drug abuse.

Since February 2021, filling in a verbal autopsy form has become mandatory, even if a postmortem examination has been conducted.

The challenges to a verbal autopsy are: it is not conducted in cases of death following immunization; it is poorly administered; a verbatim account from the informant is not recorded; all sections are not recorded; there are changes in teams conducting AEFI investigation; and there is a considerable time gap between case investigation and CA.

The challenges should be addressed through training in administering verbal autopsy as part of investigation training, supportive supervision and feedback, encouraging causality assessment at the state, instead of the central, level and ensuring verbal autopsy for adult deaths reported as AEFIs.

The main causes of sudden deaths in India are cardiac and neurological. Verbal autopsy helps in differentiating death from pre-existing morbidity from that due to an event that could be linked to vaccination. Thus, it helps differentiate cases that are coincidental from possible signals. Verbal autopsy is a powerful tool in AEFI case investigation and should be considered only one of the tools for arriving at a diagnosis for death. The quality of information provided through the tool is dependent on the investigator. Also, it should not be the sole basis for causality assessment. The information in the verbal autopsy form must be viewed in the context of AEFI investigation reports and other relevant laboratory/hospital records.

**Active vaccine safety surveillance**

Active vaccine safety surveillance (AVSS) is defined as a data collection system that seeks to ascertain as completely as possible the number of adverse events following immunization in the population via a continuous organized process. Passive surveillance is triggered by an AEFI while active surveillance is often event-based (regardless of vaccination status). The methods of AVSS include sentinel surveillance, data linkage, use of mHealth and cohort event monitoring. Each of these methods has advantages and disadvantages. Active surveillance has a role in meeting a knowledge gap – for example, delayed and serious events and AVSS have been established in some jurisdictions as part of COVID-19 surveillance. It is important to define the utility of AVSS to inform the sustainability of these surveillance systems.
2.4 Technical session 4: role of communication in vaccine safety surveillance

The role of communication in vaccine safety surveillance was explained through three main presentations and discussions: what drives vaccine uptake; resilience and risk communication; and media engagement. Using a template provided, country-specific groups explored the application of the content per country, relative to their national plans and priorities. They applied the tools, frameworks and guidance that had been presented in the earlier sessions. These included questions on integrating priority indicators for behavioural and social drivers (BeSD) into existing routine monitoring activities, identification of the next steps to gather data on BeSD, updates to national plans on risk communication and related activities to strengthen workforce capacity and engagement of key champions/advocates, and lastly, steps to build strong collaboration with local media. Completed group work templates were later gathered for analysis and will be used as a basis for follow-up actions in countries of the SE Asia Region.

3. Country presentations

Bangladesh – national safety surveillance for detection, reporting and causality assessment for EPI vaccines, including global data sharing

The presentation described the evolution of EPI and vaccine safety surveillance in the country. Passive safety surveillance at the government health facility level began in 2003 and was gradually scaled up to be operational at the community level since 2006. Community field workers notify cases to the district or the city corporations. The district AEFI committee is activated for case confirmation and investigation. The country has eight divisions, each with a Divisional Causality Assessment Committee that has been constituted recently. The investigation reports are shared with the respective Divisional Committee for causality assessment. The causality assessment and case data are forwarded to the National AEFI Expert Review Committee for reconfirming the classification, potential signal detection, further investigations, if required, and global data sharing. Serious AEFIs are notified and investigated as a priority.

The National AEFI Committee members include pediatricians, microbiologists/virologists, epidemiologists, pathologists, medical specialists, neurologists, pharmacologists, forensic experts and representatives from Directorate General of Drug Administration (NRA). The Committee has the option to call for additional experts, if required.

AEFI reporting rates started to decline from 2019 and this continued during the COVID-19 pandemic. Besides underreporting of AEFI cases, other challenges for vaccine safety surveillance include delays in completion of online reporting, delayed case investigation leading to recall bias and late submission of AEFI investigation reports, mobilization of multidisciplinary investigation team, inadequate laboratory investigation and lack of autopsy for death cases.
Recent initiatives to strengthen vaccine safety surveillance include publication of revised AEFI surveillance and response operational guidelines, ongoing trainings of health staff in revised guidelines, online reporting of AEFIs from 2021, approval for use of adrenaline, hydrocortisone and chlorpheniramine in managing anaphylaxis, availability of AEFI management kit at all levels, completion of WHO NRA benchmarking, formation of causality assessment committees at the divisional level, and review of surveillance and immunization.

Completion of causality assessments that was lagging in 2022 is being addressed. The next steps for programme strengthening include constitution of the National AEFI Communication Committee, refresher trainings in AEFI reporting and case Investigation, capacity-building of the AEFI investigation team for verbal autopsy, counselling and motivating health workers for reporting AEFI, data-driven supervision, and monitoring and timely submission of AEFI data in DHIS2.

**Bhutan – strengthening case investigation for AEFIs following COVID-19 vaccination**

The presentation from Bhutan focused on the strengthening of case investigations for AEFIs following COVID-19 vaccination. A country profile of Bhutan was presented. In summary: there are 20 districts; the population is 963,249 in 2021; 2.3 million doses of COVID-19 vaccines have been administered as of August 2021; and 14,449 minor AEFIs and 59 serious AEFIs have been reported. The key milestones in the COVID-19 pandemic and vaccination campaign were presented. The vaccine coverage is high for the first and second doses (92%), but it gets reduced with booster doses (third – 75%, fourth dose – 45%). Strengthening was achieved by the daily zero reporting of AEFIs from all vaccination posts; minor AEFIs were reported and recorded through the dedicated hotline number while serious AEFIs were reported immediately to focal persons. Investigation within 72 hours, and daily review and updation of AEFIs by NITAG and RITAG members were carried out during the campaign period and causality assessment was conducted at the end of the campaign in collaboration with the WHO Country Office.

Serious AEFIs were referred to the national hospital in Thimpu for management. AEFIs on the part of the vaccine brands were presented, but not rates. Serious AEFIs included anaphylaxis, seizures and alcohol withdrawal, accounting for 65% of reports. The rates of AEFI per 100,000 doses are: Covishield 7.4, Pfizer 0.2 and Moderna 1.4. Causality assessment was reported for 19 patients. The reported challenges included the following: geographical terrains/sparse population, inadequate doctors/HR, AEFI reports on EPI vaccines not getting submitted adequately, communication gap and lack of coordination, and VigiBase not being used by the country.

The presentation concluded that no amount of preparedness was adequate for emergencies and that leadership played a vital role in the preparation and rollout of vaccination. It also noted that effective risk communication was very critical to maximize community participation and vaccination coverage while multisectoral coordination was the key to successful vaccination campaign. It also stressed that the use of a web-based, real-time AEFI reporting system was a game changer in tracking real-time reported AEFI cases, follow-up and management, including referral, and that instituting regional ITAG/AEFI committee had helped in workload sharing while the deployment of clinicians in vaccination posts had made a difference in AEFI case management.
**India – strengthening causality assessment**

The presentation described the country profile and the AEFI surveillance system in the country. The National Immunization Programme is one of the largest programmes in the world with 419 million doses from 11 antigens being delivered annually for RI. Supplementary immunization activities (SIAs) are also carried out for polio, measles, rubella and Japanese encephalitis.

The vaccine safety surveillance system includes district, state and national AEFI committees. The country has IT-based system for reporting AEFI cases, including case investigation. CA is conducted at the state level and reviewed at the national level. The national level has been strengthened with the addition of the AEFI Secretariat, which includes four zonal consultants, helping in expediting report collection and causality assessment. CA results are shared with the Ministry of Health and Family Welfare (MoHFW) by the Chairperson, National AEFI Committee, following which line-listed, anonymized results are displayed on the MoHFW website and shared with the drug regulator and the states for further action.

Following the COVID-19 crisis, the following initiatives were undertaken to strengthen CA for COVID-19 and EPI: AEFI surveillance guidelines revised for COVID-19; AEFI committees expanded to include internal medicine specialists, cardiologists, neurologists, obstetrician-gynaecologists, respiratory medicine specialists; capacity-building for AEFI surveillance and causality assessment undertaken; the number of investigation forms reduced from two to one, timelines reduced for investigations (three days to complete the case reporting form) and causality assessments (three days for completion of case records); verbal autopsy form introduced for AEFIs in adults; directives issued to improve quality of postmortems at medical colleges through a panel that included pathologists and clinical specialists, videography included in the protocol; and results for histopathology and toxicology tests followed up on. Additional workforce at national and state levels was mobilized for following up on and expeditiously conducting CA.

Results from the causality assessment of EPI and COVID-19 vaccines were presented; these included the challenges faced due to COVID-19. The plans to strengthen safety surveillance in the country include: improved reporting of all AEFIs, including the non-serious ones; direct reporting by health-care service providers and vaccine beneficiaries; increase in reporting for all ages; covering non-paediatric vaccines; reducing timelines for investigation and causality assessments; causality assessments by state AEFI committees with the national level undertaking quality checks for CA; signal management systems using automated processes; more efficient data sharing processes with the national regulator; use of IT-enabled systems for reporting of AEFI cases by health workers/medical officers (learnings from COVID-19 vaccination rollout); and involvement of medical professional bodies, such as Indian Academy of Paediatrics and Indian Medical Association (IMA), to facilitate reporting of AEFI cases.

**Indonesia – AESI surveillance for COVID-19 vaccination**

Sentinel surveillance for adverse events of special interest (AESIs) has been established in Indonesia for COVID-19 vaccination. More than 430 million doses of COVID-19 vaccines have been used in Indonesia; 32 diagnoses listed with case definitions were
adopted and 14 hospitals selected for surveillance. Self-controlled risk interval analysis was performed with a risk assessment conducted for the period of 42 days following vaccination. Risk intervals are currently being analysed for ischaemic stroke, heart failure, coronary heart disease and Gillian in 2021-Barre Syndrome. The challenges include limited reference in developing and/or conducting AESI surveillance, including data analysis. The lessons learnt include the need for conducting a pre-assessment prior to determining hospitals as sentinel sites, setting up a regular feedback mechanism to maintain sensitivity and completeness/timeliness of reporting/recording, involvement of department/unit at sentinel sites and preparation of a statistical analysis plan.

Maldives – analysis of safety signals following COVID-19 vaccination

Maldives has a population of 545,847 in 2021, with 71 AEFI cases investigated up to August 2022 and 68 cases undergoing causality assessment with the following outcomes: vaccine product-related event – 17; immunization anxiety-related – 3; indeterminant – 15; and inconsistent – 28. Importantly, 45 deaths and 13 cases of anaphylaxis (Brighton Collaboration Level 1–1, Level 2–5, Level 3–4) were reported. A line listing was provided for indeterminate reports. Challenges include incomplete forms, delay in reporting serious AEFIs and inadequate awareness among health-care professionals about reporting all AEFIs.

Myanmar – country plans for improving AEFI surveillance

Myanmar consists of 14 states and has a population of 54 million in 2022. The EPI was established in 1978. Currently, the programme delivers 13 antigens with rotavirus and HPV vaccines have been introduced most recently.

The National AEFI Committee was established in 2002 and revised in February 2022. The Committee consists of 13 members, who are independent experts from the fields of paediatrics, medicine, forensic science and pathology. The Chair of the Committee is a high-level decision-maker from the Ministry of Health (MoH). The state and regional EPI team leaders and township medical officers are responsible for conducting AEFI field investigations, supervised and supported by the central EPI, as needed. Minor AEFIs are reported through a monthly report in the first week of each month. Serious AEFIs are reported immediately within 24 hours. The country has developed guidelines for AEFI surveillance and training was conducted in 2020.

The challenges to AEFI detection, reporting and causality assessment are as follows: recent large turnover of health-care workers and staff shortage; inadequate knowledge of AEFI reporting and management among new recruits; limited interpersonal communication skills among health workers; at present, the AEFI surveillance system functioning suboptimally, capturing mainly serious AEFI cases; some serious AEFI cases not reported due to lack of awareness among clinicians; issues of data quality in reported cases; no AEFIs reported from the private sector and areas under ethnic health organizations; rapid spread of misinformation on social media; weak supervision for AEFI surveillance in routine immunization; limited information from verbal autopsy; and limited laboratory capacities, particularly for cases from far-flung areas.
The country plans for strengthening vaccine safety surveillance are provided below.

- **AEFI Committee**: AEFI Committee members and the Secretariat will be trained in field investigation and causality assessment and will generate regular communication with all stakeholders.

- **Training**: there will be capacity-building for newly recruited health workers; township, state and regional supervisors/focal points will be trained in AEFI surveillance, investigation and risk communication; the private sector will be trained in AEFI reporting; and competent and trained staff will be assigned to perform vigilance activities.

- **AEFI reporting**: AEFI reporting is to be strengthened for routine immunization, covering minor and serious AEFIs.

- **AEFI investigation and management**: there will be operational and technical support for field investigation of serious AEFI cases through partners.

- **Data**: data management and analysis will be strengthened for early detection of safety signals and the programme will identify secure channels of data sharing.

- **Meetings**: advocacy and orientation meetings for pediatricians and clinicians, including those from the private sector, will be held.

- **Communication**: media monitoring will be conducted to identify and address rumours, community concerns and other vaccine safety issues; there will be real-time consultation with the AEFI Committee and NITAG.

**Nepal – communication plans for vaccine safety crisis in routine immunization and supplementary immunization activities**

Nepal is a landlocked country with a population of 29,192,480 (as per the 2021 census) and 126 ethnic groups spread across three ecological zones – mountains (Himalayas), hills and plains (Terai). The National Immunization Programme is a priority programme of the Government of Nepal. Currently, it provides vaccination against 13 vaccine-preventable diseases. A well-functioning safety surveillance system has been in place since 2003. Training in AEFI surveillance was conducted in 2004; this was followed by a refresher course in 2008. AEFI training is integrated into all SIAs and new vaccine introductions.

Crisis communication plans are incorporated into all vaccination campaign plans and guidelines. There is no separate crisis communication plan for RI and SIA. A weekly press conference is held to share the policies, programmes and strategies of the Ministry of Health and Population (MoHP) with the public. A designated spokesperson is responsible for the weekly press briefing.

Capacity-building with regard to risk communication and community engagement (RCCE) for spokespersons and other health professionals at the federal, province and local levels has been undertaken. Designated spokespersons have been identified for provincial and local levels. More than 500 radio journalists, health journalists and others have been oriented to AEFI and AEFI media reporting for COVID-19 vaccination.
The National Health Education Information Communication Centre (NHEICC) is the focal point for national risk communication and community engagement activities. A Crisis Media Hub has been established at the NHEICC to develop, pre-test and disseminate communication materials. The Media Hub, in coordination with the divisions and experts concerned, has developed and disseminated various communication materials on vaccine safety through social media platforms; these have also been shared with different online and offline media publications in Nepali and English. Regular RCCE partner meetings are held to discuss issues and key priority messages. Verification of rumors is undertaken and shared with the MoHP for media briefing. The centre is working collaboratively with partner agencies and mobile service providers (Ncell, NTC).

The Health Emergency Operations Centre (HEOC) is functioning with designated focal points to manage dissemination of information through regular MoHP press releases. Hotline numbers were functioning and provided information on COVID-19 to the public.

In 2021 and 2022, 63 radio journalists were trained in assessing public concerns related to COVID-19 vaccination, RI and Typhoid Conjugate Vaccination campaign. Following this, more than 263 community meetings were organized to address public concerns, including those over vaccine safety.

Community perceptions of COVID-19 acceptance was also gathered through the three rounds of a telephone survey, covering more than 6000 respondents. Less than 3% respondents cited fear of fever as the reason for not getting vaccinated. In a qualitative study conducted with caregivers of children to understand the vaccination behavioural drivers in the Kathmandu Metropolitan City, 26% of the caregivers of under-vaccinated children cited fear of children falling ill (fever) as one of the reasons for not vaccinating them.

Sri Lanka – using national safety surveillance for detection, causality assessment and management of TTS

Sri Lanka has an established AEFI surveillance system for routine immunization (RI), which has been an integral part of the EPI since 1995. AEFI is an agenda item at Sri Lanka NITAG meetings. The AEFI reporting system is regularly monitored and evaluated during the district-level EPI reviews.

The existing AEFI surveillance was adopted to detect and report AEFIs following COVID-19 vaccination, which began with the introduction of the AstraZeneca (AZ) vaccine. Later, a special reporting form was developed to capture suspected TTS cases. Following reports of early cases of TTS from other countries, awareness among vaccine recipients and health-care workers about TTS was raised. The Director-General of Health Services (DGHS) sent a communique to all clinical settings, requesting stakeholders concerned to report all hospital admissions due to any medical reason within three weeks of vaccination with AstraZeneca to the Epidemiology Unit of Ministry of Health through a hotline. A team of doctors at the Epidemiology Unit followed up on the reported cases over the phone.

The DGHS constituted an expert panel (EP-MoH) to investigate severe AEFIs following COVID-19 vaccination. The panel consisted of the chief epidemiologist, epidemiologists, physicians, neurologists, immunologists, virologists, haematologists, forensic pathologists and pharmacologists. The expert panel formulated guidelines on diagnosis and management of TTS, which were disseminated to all clinical settings.
The following steps were undertaken for detection and management of TTS:

- A national-level multidisciplinary team (MDT), consisting of physicians, neurologists, neurosurgeons, neuro-anesthetists, haematologists and radiologists, was appointed by the DGHS to manage severe AEFI’s following COVID-19 vaccination;
- All patients suspected of TTS were expected to be transferred to the National Hospital of Sri Lanka (NHSL) in Colombo following initial management and stabilization;
- A “COVID-19 management cell”, consisting of a physician, a paediatrician, a haematologist, an anaesthetist, a radiologist and a virologist/microbiologist, was established at all hospitals as part to advise on case management.
- Management of severe AEFI’s, including TTS, was carried out by the COVID-19 cells at their respective hospitals with advice from the national MDT until they were transferred to the NHSL or otherwise; the EPI-MoH was available round the clock to offer MDT support to manage TTS patients; all suspected cases were immediately reported to the Epidemiology Unit via a 24-hour hotline; a team of doctors at the central Epidemiology Unit followed up on the progress of TTS patients; and all suspected cases were investigated by the expert panel (EP-MoH) and causality assessed.

The COVID-19 vaccination programme administered 2,898,224 doses of AZ vaccines with an AEFI reporting rate of 33.1 per 100,000 doses. Serious AEFI’s reported following AZ amounted to 51; serious AEFI reporting rate was 1.76 per 100,000 doses. Furthermore, 100% of serious AEFI’s were investigated and causality had been assessed for 96%. Brighton Collaboration’s case definition was used to diagnose TTS. Classifications following causality assessment are as follows:

<table>
<thead>
<tr>
<th>Consistent with causal association with immunization (vaccine product-related)</th>
<th>Inconsistent with association with immunization</th>
<th>Unclassifiable</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTS</td>
<td>Anaphylaxis</td>
<td>Coincidental</td>
<td>Adequate data not available</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>39</td>
<td>2</td>
</tr>
</tbody>
</table>

The TTS incidence was 0.21 per 100,000 doses. The median age of TTS cases was 42 years with equal number of men and women being affected. The average time between vaccination and hospital admission was 13.6 days. Two cases recovered and four died.

The challenges faced by the COVID-19 vaccination programme were as follows: vaccine hesitancy due to community concerns over adverse effects; justifying offering the AZ vaccine to the younger population since the risk of TTS was higher while older people gained more benefits from the vaccine; difficulties in accurate diagnosis of TTS since true cases of TTS from COVID-19 needed to be filtered out as other viral diseases also cause low platelet counts.
The lessons learnt include: addressing adverse media publicity since cases unrelated to the vaccine were giving undue publicity to AEFI; risk communication had to be executed carefully while informing the public about the true risks of the vaccine, while being careful to not create undue panic among them, which would have led to vaccine hesitancy; early detection sensitizing clinicians and the field health staff to the new adverse events of this new vaccine, thus putting them on alert to detect any possible AEFI; creating awareness among people of unusual AE due to probable TTS; optimal management of TTS by creating awareness among treating clinicians of proper management of this new syndrome; liaison between treating clinicians and the central MDT; and lack of diagnostic facilities at some hospitals. The strengthened AEFI surveillance should not be scaled down for EPI-related AEFIs.

**Thailand – communication lessons from management of stroke-like syndrome, following COVID-19 vaccination**

The presentation from Thailand focused on communication lessons from the management of stroke-like syndrome following COVID-19 vaccination. Thailand has a population of 66.17 million in 2021, with both passive reporting and self-reporting (using a mobile app) systems for AEFIs in place.

In late April 2021, a cluster of HCWs presented with numbness and weakness soon after Sinovac vaccination. The same lot of vaccine was distributed to all provinces, but similar events were reported only from three provinces at that time. A total of 456 cases were reported (the rate per 100 000 doses for Sinovac was 1.3, for AstraZeneca, it was 0.18, for Sinopharm 0.03 and for Pfizer 0.04). Time to onset of symptoms was two days (0–23) and all were classified as immunization stress-related responses (ISRR). Multivariable analysis with conditional logistic regression of a case control study demonstrated an adjusted odds ratio of 8.55 (1.36–53.9) for having menstrual period at the time of presentation.

Communication challenges were addressed through the following interventions: timely response to the serious AEFI event was deemed crucial; having a designated spokesperson to assure the public about vaccine safety was critical; engagement of relevant partners, such as medical councils, universities and media, would help in conveying a message to the public; there was regular training of the public health workforce in vaccine administration, vaccine safety and AEFI case investigation; and clinical practice guidelines on how to prevent and manage a patient’s stroke-like symptoms/ISRR were developed, together with the Neurological Society of Thailand.

**Timor-Leste – addressing immunization errors**

The presentation outlined the EPI schedule and the AEFI reporting and investigation mechanism in the country. Only moderate and severe AEFIs are expected to be reported, as per national guidelines. The country used the existing RI AEFI system for reporting AEFIs from COVID-19 vaccination.
From 2012 to 2016, 16 AEFI cases were reported; of these 10 had abscess following vaccination. The AEFI reporting rates by vaccine for 2020 and 2021 were presented.

In 2020 and 2021, 421 AEFIs were reported with a reporting rate of 2 per 10,000 immunizations. The reporting rate of AEFIs for COVID-19 vaccine was 2.8 per 10,000 vaccinations, 82% AEFIs were due to COVID-19 vaccines and 18% due to RI vaccines. Out of 77 RI AEFIs reported, nearly all were following hepatitis B birth dose and pentavalent vaccines. Out of 77 RI AEFIs, 52 (68%) were following hepatitis B birth dose and all of them were injection site abscesses with a rate of 9.5 per 10,000 vaccinations.

The AEFI reporting picked up from 2020 due to increased awareness, trainings and emphasis on COVID-19 vaccine safety surveillance. However, immediate and easily detectable AEFIs, such as abscesses at injection sites, and deaths following immunization were mainly reported. Injection site abscesses were reported following alum-containing hepatitis B birth and pentavalent vaccines. No abscesses were reported after non-alum-containing vaccinations were introduced. Reported abscesses were sterile abscesses due to reactogenicity of alum-containing vaccine and improper administration technique.

The country has developed plans for strengthening AEFIs with a focus on prevention of immunization errors. The plans include capacity-building for vaccinators, including medical doctors, midwives and nurses, for correct injection techniques; identification of AEFI and case investigation; regional capacity-building for AEFI focal points at national and municipality levels; review of AEFI surveillance activities at municipality and national levels every month and annually; and strengthening monitoring and supportive supervision at all municipality levels.
4. Closing session

**Conclusion and follow-up actions**

The participants were well engaged in the discussions throughout the workshop and provided feedback to the points discussed; group exercises were conducted. The presentations and the discussions during the workshop highlighted the fact that all countries, participating in the meeting, have functioning national vaccine safety surveillance systems. All participants were requested to immediately report back the information collected during the workshop to their respective national immunization programmes, members of the vaccine adverse events review committees and national regulatory authorities.

The specific follow-up action points for each National Vaccine Adverse Events Review Committee (VAERC) and WHO are as follows:

- **vaccine adverse events review committees:** each VAERC to review the composition and add additional expertise, as necessary; special attention to be paid to including communication experts in VAERC; orientation of new members to be undertaken through workshops;
- **WHO Regional Office for South-East Asia (WHO-SEARO):** supporting countries to conduct national vaccine safety surveillance workshops; and
- **WHO headquarters:** assisting WHO-SEARO and countries with technical information and relevant tools, and providing facilitators, when requested.

a. **Strengthening AEFI detection and reporting**

The Thirteenth meeting of SEAR ITAG recommended

- that countries strengthen vaccine safety surveillance through:
  - Developing workplans for 2022–2023 for strengthening AEFI reporting, investigation and causality assessments with support from WHO; and
  - ensuring that the countries that did not meet the AEFI surveillance sensitivity indicator of one serious AEFI per million population for EPI antigens focus particularly on improving their AEFI reporting.

The lessons learnt from the institution of safety surveillance following COVID-19 vaccination should be used to implement approaches to strengthening AEFI detection and reporting. The participants identified the presence of established and functioning AEFI surveillance systems in all countries as an important facilitatory factor for COVID-19 vaccine deployment. The other factors included:

- training, retraining and motivation of HCWs, who are part of the immunization systems, through face-to-face, online and hybrid mechanisms;
- use of new tools, such as videos, for vaccine safety training;
- sensitization of other cadres, such as village health volunteers, pharmacists, hospital emergency departments and clinicians, for reporting;
strengthening of AEFI committees through inclusion of adult medicine specialists and others with frequent meetings and establishment of provincial (subnational) causality assessment committees;

- collaboration between hospital pharmacists and the regulator for AEFI/ADR reporting;
- a strong monitoring and review system for regular reporting of adverse events to the next higher level;
- vaccines asked about AEs when administered subsequent vaccine doses with capture of reported data;
- waiting room for observation of AEFI;
- high level of political commitment and involvement of religious leaders to address vaccine hesitancy; and
- the immunization programmes using novel IT tools or methods to facilitate reporting for all AEFIs (non-serious and serious ones) following COVID-19 vaccination; establishment and use of electronic vaccine registries to register vaccination and report AEFIs, and setting up self-reporting mechanisms through SMS platforms, hotlines, etc., further facilitating reporting.

The following system barriers were observed in some countries and areas:

- Despite efforts to train HCWs through online and face-to-face sessions, all HCWs could not be trained in AEFI reporting due to the COVID-19 outbreak.
- There had been weaker involvement and low reporting of AEFI from the private sector even before the COVID-19 pandemic; this continued to persist.
- There was delayed reporting due to network connectivity issues, lack of formats, etc.
- The mechanisms for community reporting were not in place in some countries.
- There was a time lag between reporting of an AEFI and receipt at district/higher levels; this impacted timeliness of receipt and analysis of data.
- There was fear of punitive action for vaccinators, if they reported an AEFI.
- There were shortage of staff (high turnover) and high workload as AEFI surveillance staff were also responsible for COVID-19/other disease surveillance and COVID-19 vaccination acceleration.

The following barriers due to gaps in knowledge were observed in some areas:

- recognition, detection and reporting of emerging adverse events, such as TTS, myocarditis, among HCWs and doctors;
- underreporting of deaths by some health officers due to lack of awareness of some AEs; and
- with “confidence” in COVID-19 vaccinations emerging, minor AEFIs not being reported.
These follow-up actions should be undertaken by countries to strengthen reporting and investigation:

- Regular training of health workers and surveillance staff should be conducted with regard to AEFI.
- Establish/continue with the IT platforms that integrate EPI and COVID-19 AEFI reporting. Electronic tools should be used to capture all adverse events and vaccine exposure, including minor AEFIs.
- Awareness about reporting of AEFI should be created in the community and self-reporting through IT and SMS platforms should be encouraged.
- HCWs who report AEFIs should be recognized.
- Feedback mechanisms for reporting and investigation should be strengthened.
- Data management and data sharing should be improved.
- Collaboration between medical associations and other key stakeholders should be promoted.

b. Strengthening AEFI detection, reporting and causality assessment, and communication within the Region

The 13th ITAG recommended that:

- national AEFI committees conduct timely causality assessments for serious AEFIs for COVID-19 and EPI antigens and regularly share data on AEFIs with NITAGs, WHO and the Uppsala Monitoring Centre through ViGiBase; and
- data from serious events be shared on time among vaccine manufactures, national regulatory authorities and EPIs.

Conclusion

Overall, countries have attempted to conduct causality assessment of serious AEFIs. However, out of nearly 11 000 serious AEFIs reported following COVID-19 vaccination, causality assessment was completed for only 51%; out of 1828 serious AEFIs reported following routine immunization, only 11% had been assessed for causality. It is evident that causality assessment of serious AEFIs following routine immunization has been compromised during the COVID-19 pandemic.

The following follow-up actions were recommended:

- The National AEFI Committee should be strengthened by involving more specialities and larger countries should consider establishing subnational committees.
- The frequency of AEFI Committee meetings should be adjusted as per workload.
- The quality of investigation for serious AEFIs should be improved through trainings in comprehensive investigation and execution of causality assessments.
The findings from case investigations should be documented; accessibility to relevant members of the committees, national programmes and NRAs should be ensured.

The feedback to the programme, vaccine regulators and manufacturers should be improved.

c. Safety surveillance data management

VigiFlow is a “PIDM member benefit”, which is to be used as a national data management system to collect and analyse AEFI reports. It includes dashboards with descriptive epidemiology and surveillance performance. Four countries from the Region are sharing data with the UMC.

The follow-up actions recommended include:

- Following discussions at the national level, countries should consider implementation of UMC IT systems for AEFI reporting and analysis. VigiMobile can be used to collect data on the 25 core variables from the field, districts are already mapped in the programme, and it supports offline reporting when access to internet is limited. VigiFlow can be used as a data management system. VigiLyze can be used as a global data reference for assessing the Immunization Agenda 2030 performance indicator for vaccine safety. Serious and non-serious AEFIs may be shared with VigiBase, the WHO PIDM global database, after approval from the national level.

- SE Asia Regional data reporting:
  - Countries should regularly report anonymized line list of serious AEFI cases through Excel file to the Regional Office if AEFI data are not being shared with the UMC.
  - The Regional Office needs to continuously monitor completeness of causality assessment and provide technical support to improve the quality of investigations and ensure completeness of causality assessment.

- AESI surveillance and other surveillance activities:
  - The experience from AESI surveillance in Indonesia should be evaluated to assess the benefits for initiation of AESI surveillance in other countries.
  - In countries planning to undertake AESI surveillance, the focus should be on manageable number of conditions at selected sentinel sites.
  - Countries may plan special active surveillance studies, such as cohort event monitoring.

d. Strengthening communications

The Thirteenth meeting of ITAG recommended that countries integrate risk communication and community engagement into the AEFI response activities and consider inclusion of a communication expert in the National AEFI Committee. Countries should enhance risk communication and community engagement in relation to adverse events and responses to misinformation regarding vaccination.
Follow-up actions on communication

a. Countries should plan to review and update existing plans:
   ➢ National plans for communication and demand generation for immunization should consider added activities on support for health workers, community engagement and collaboration with media, and gather data on behavioural and social drivers (BeSD).
   ➢ Risk communication plans should be updated within or separate to the plans for demand generation, including plans for new and enhanced activities.
   ➢ The Communications Working Group on EPI should be debriefed on the safety surveillance workshop. The ToRs of the group and the membership of the group should be strengthened with inclusion of NRA and experts.
   ➢ The National AEFI Committee should include communication/social science experts.

b. Strengthening the coordination between EPI programmes and NRAs
   ➢ Countries should define the roles of EPI and NRA for vaccine safety surveillance.
   ➢ The roles of the staff of the EPI, from the vaccination level to the subnational and national levels, and the staff of the NRA in AEFI case reporting, investigations and causality assessments should be identified.
   ➢ Joint discussion of the EPI and the NRA should be conducted before the causality assessment meetings and the information needs to be shared.
   ➢ WHO should facilitate discussions between NRAs and EPIs by sharing tools and country experiences through virtual meetings.

c. Vaccine safety surveillance evaluations
   ➢ Countries should conduct safety surveillance self-evaluations by adopting the pharmacovigilance field assessment with regard to the country context, involving NRAs and national EPI programmes.
   ➢ WHO-SEARO will conduct external evaluation of national AEFI committees.
Annex 1

Opening address by Dr Poonam Khetrapal Singh, Regional Director, WHO South-East Asia

Welcome to this regional workshop on strengthening vaccine safety surveillance and capacity-building on causality-assessment.

In 2021 the WHO South-East Asia Region averted an estimated 933 000 deaths through childhood immunization. In 2022 vaccination is expected to avert an additional 964 000 deaths in the Region.

Vaccination saves lives, improves life-long health and well-being, and is one of the most high-impact, cost-effective public health and development interventions that exist. Although vaccines are very safe, no vaccine is entirely without risk.

Adverse events following immunization (AEFI) occasionally occur and range from non-serious reactions to – in rare cases – serious reactions. This can be a source of vaccine hesitancy, which if unaddressed, can then expose children to disabling and/or life-threatening vaccine-preventable diseases.

Maintaining public trust in vaccine safety is therefore critical to the success of all national immunization programmes and the public health and development benefits they yield.

The Region has in recent years made commendable progress to strengthen AEFI monitoring. All countries of the Region have developed national vaccine safety surveillance guidelines; have implemented an AEFI reporting system; and have convened a national committee for vaccine safety surveillance and causality assessment.

By 2019, all countries had achieved the expected target for AEFI reporting indicator, and in 2020, were able to rapidly develop systems for COVID-19 vaccine safety surveillance.

Gaps and challenges nevertheless persist, several of which were highlighted at the Thirteenth Meeting of the South-East Asia Regional Immunization Technical Advisory Group (ITAG), held last month.

For example, although vaccine safety surveillance indicators for COVID-19 vaccines are at acceptable levels, in 2021, the reporting of adverse events for Expanded Programme on Immunization (EPI) antigens had declined when compared to 2019.

The ITAG noted that, at present, the carrying out of causality assessments in the Region for serious adverse events is inadequate, and must therefore be increased, along with the sharing of data between EPI programmes, national regulatory authorities, and vaccine manufacturers.

Moreover, we see that not all Member States are taking full advantage of VigiBase, WHO’s unique global database of reported potential side effects of medicinal products, including vaccines, for sharing individual case safety reports.
I urge all countries to fully utilize this key tool, which is at the heart of the global drive for safer use of medicines, and therefore patient safety.

Over the course of this three-day meeting, you have four formal objectives: First, to provide updated information on vaccine safety surveillance, including new tools developed by WHO on causality assessment and data management.

Second, to review Regional and country successes and challenges, and to identify priority actions for strengthening AEFI reporting at national and sub-national levels.

Third, to review adverse events of special interest and other active surveillance mechanisms that have been established in the Region and globally, and to assess their contribution to the sensitivity of safety surveillance.

And fourth, to discuss how vaccine safety surveillance can be used to mitigate vaccine hesitancy. For this, you must consider how best to leverage risk communication and community engagement, including by potentially appointing a communication expert to national AEFI committees.

In pursuing each of these objectives, my message to you is to exemplify and even expand on the tremendous commitment, technical excellence and solidarity you have shown throughout the COVID-19 response, ensuring that together we build back better immunizations systems that achieve maximum safety, trust, participation and coverage, for every person everywhere.

I wish you productive and engaging deliberations and look forward to being apprised of the outcomes. Thank you.
### Annex 2

## Agenda

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<th>Dr Madhava Balakrishnan, WHO HQ</th>
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<td>Professor Michael Gold, WHO SEARO</td>
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<td>Group Work 1: Lessons learnt from COVID-19 to conceptualize approach for AEFI detection and reporting</td>
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<td>o Discuss what factors facilitated/barriers to AEFI detection and reporting, for COVID-19</td>
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<td>o How can AEFI surveillance be maintained post COVID-19</td>
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<td>o Summary of action points to strengthen AEFI detection and reporting</td>
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<td>Investigation of AEFIs including recent changes in AEFI investigation approaches due to COVID-19 (Module D)</td>
<td>Ms Kristine Macartney, GACVS Member</td>
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<td>India - Strengthening of causality assessment</td>
<td>Dr Veena Dhawan, MoH India</td>
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<td>Myanmar – Country plans for improving AEFI surveillance</td>
<td>Dr Khaing Khaing Gyi, Country representative</td>
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<tr>
<td>Analysis of vaccine safety data and risk-assessment (Module E)</td>
<td>Ms Kristine Macartney, GAVCS Member</td>
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<td>Professor Athula Liyanapathirana, MoH Sri Lanka</td>
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<td>Timor-Leste – Addressing immunization errors</td>
<td>Dr Celeste Cham, VAERC Timor-Leste</td>
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<td>Discussions</td>
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<tr>
<td>Update on causality assessment (CA) and introduction of group work and online demonstration of AEFI Causality Assessment Tool</td>
<td>Dr Madhava Balakrishnan, WHO HQ</td>
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<td>Introduction of Group work 2</td>
<td>Professor Michael Gold, WHO SEARO</td>
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**DAY 2: Wednesday 21 September 2022**

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<td>- 4 groups of 2–3 countries – 60 minutes discussion</td>
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<td>Each group to discuss one case of serious AEFI allocated to the group for causality assessment</td>
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<tr>
<td>Feedback from groups on pdf generated by online causality assessment software accessed at <a href="https://gvsi-aefi-tools.org/">https://gvsi-aefi-tools.org/</a> including actions taken based on CA 10–12 min per group</td>
<td>Professor Michael Gold, WHO SEARO</td>
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<td>Role of National Regulatory Authority (NRA) in vaccine safety surveillance</td>
<td>Dr Anil Kumar Chawla WHO/SEARO</td>
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<td>Discussions on strengthening coordination between EPI programme and NRAs</td>
<td>Moderator: Dr Jayantha Liyanage</td>
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<td>- Why do media?</td>
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<td>- How to engage with the media?</td>
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<td>- Tips for interviews</td>
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### DAY 3: Thursday 22 September 2022

#### Group work per country (45 mins)
- What needs and gaps exist to understand and address reasons for low uptake?
- Planning and response to events – what programme areas could be enhanced?
- Building strong collaborations with journalists – who and how to engage?

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<th>Short presentation per country on standard PPT template on Rapid risk assessment:</th>
<th>Country representatives</th>
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<td>Verbal autopsy in deaths following immunization</td>
<td>Ms Anju Seth, Chairperson, National AEFI CA sub-committee, India</td>
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#### Discussions

**Indonesia** – AESI surveillance for COVID-19 vaccination

| Professor Dr dr Hinky Hindra Irawan Satari, MoH Indonesia |

#### Closing session

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<td>Rapporteurs, WHO SEARO</td>
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Annex 3

List of participants

Ministry of Health

**Bangladesh**

- Dr Mohammad Shamsul Haque
  - Line Director
  - Maternal, Newborn, Child & Adolescent Health
  - Directorate General of Health Services
  - Dhaka, Bangladesh

- Dr Md Shibbir Ahmed Osmani
  - Deputy Secretary
  - Health Services Division
  - Ministry of Health and Family Welfare
  - Dhaka, Bangladesh

- Dr Md Tanvir Hossen
  - Deputy Program Manager
  - EPI & Surveillance
  - Maternal, Newborn, Child & Adolescent Health
  - Directorate General of Health Services
  - Mohakhali
  - Dhaka, Bangladesh

**Bhutan**

- Mr Pelden Wangchuk
  - Medical Superintendent
  - Eastern Regional Referral Hospital
  - Mongar, Bhutan

**India**

- Dr Veena Dhawan
  - Additional Commissioner (Immunization)
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  - New Delhi, India

**Indonesia**

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  - Focal Point of National AEFI Committee
  - Ministry of Health of the Republic of Indonesia
  - Jakarta, Indonesia

- Dr Cornelia Kelyombar
  - Focal Point of National AEFI Committee
  - Ministry of Health of the Republic of Indonesia
  - Jakarta, Indonesia

**Maldives**

- Ms Hawwa Guraisha
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  - Health Protection Agency
  - Male, Maldives

- Ms Aishath Shuda
  - Project Officer
  - Ministry of Health
  - Male, Maldives

**Nepal**

- Dr Bibek Kumar Lal
  - Director
  - Family Welfare Division
  - Department of Health Services
  - Kathmandu, Nepal

- Mr Janak Adhikari
  - Senior AHW Officer
  - Office of Minister of Health and Population
  - Ramshahpath
  - Kathmandu, Nepal

**Sri Lanka**

- Dr TME Dabrera
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  - Epidemiology Unit
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- Dr A. Liyanapathirana
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**Thailand**

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Regional workshop on strengthening vaccine safety surveillance and capacity-building for causality assessment

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Regional workshop on strengthening vaccine safety surveillance and capacity-building for causality assessment

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Centers for Disease Control and Prevention
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Uppsala Monitoring Centre
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Product Specialist
Uppsala Monitoring Centre
Uppsala, Sweden
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Head of PV portfolio
Uppsala Monitoring Centre
Uppsala, Sweden
Dr Matthew Barwick
Communications officer/Video producer
Uppsala Monitoring Centre
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Demand and Behavioural Sciences
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Medical Officer
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WCO
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WHO Country Office
Dhaka, Bangladesh
Regional workshop on strengthening vaccine safety surveillance and capacity-building for causality assessment

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WHO Country office
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**WCO Indonesia**
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National Professional Officer (VPD Surveillance)
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