Ninth South-East Asia Regional Meeting of Virologists of the Measles and Rubella Laboratory Network

Lucknow, India, 1–2 September 2022

Theme of the meeting:
Expanding the scope with commitment to excellence
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1. Background

The Global Measles and Rubella Laboratory Network (GMRLN) is the largest internationally coordinated laboratory network providing high-quality laboratory support for surveillance to measure progress towards measles and rubella elimination. Case-based surveillance requires timely laboratory confirmation from a network of accredited laboratories. High-quality surveillance, bolstered by strong laboratory support, is necessary for verifying elimination. It is important to monitor the quality of the measles and rubella laboratory network (MRLN) by monitoring the performance of the laboratories in the network with regard to globally recommended indicators.

Elimination of measles and rubella is a Flagship Priority of the WHO South-East (SE) Asia Region. A Regional Strategic Plan for achieving this goal was developed with four objectives. One of the objectives is to develop and maintain an accredited/proficient measles and rubella (MR) laboratory network that supports every Member State. The Immunization and Vaccination Development (IVD) Department of the WHO Regional Office for South-East Asia (WHO-SEARO) coordinates a regional MRLN, comprising 58 laboratories, to provide critical support to their respective national case-based surveillance programmes and help verify the elimination status.

The MR laboratories are responsible for testing serum specimens from suspected measles cases for laboratory confirmation and throat swab specimens for establishing genetic linkages of circulating measles and rubella viruses. As case classification of suspected MR cases is based on laboratory confirmation, it is crucial to ensure that MR laboratories function at high efficiency levels and meet the globally recommended standards so that the results produced by network laboratories are internationally accepted. In addition, strict adherence to biosafety and biosecurity procedures has also become an extremely important agenda to deliberate on at a time when most laboratories are heavily involved in laboratory testing of SARS-CoV-2 as part of the COVID-19 pandemic response strategy.

2. Objectives of the meeting

The objectives are to:

- provide updates on global and regional progress towards the measles and rubella elimination goal, overall performance of the SE Asia Region MRLN and genetic sequencing of MR viruses;
- discuss and develop laboratory strategies to improve laboratory confirmation for MR surveillance programme:
  - considerations for revision in serology test algorithm;
  - broadening the use of real-time PCR for case confirmation in endemic countries in special situations/settings; and
  - timeliness indicators for reporting molecular results to the programme.
- provide orientation on how to fill the stipulated formats for external quality assessment (EQA) schemes;
- discuss revisions in reporting formats of measles and rubella molecular tests and data management challenges;
- increase awareness of various approaches to strengthening MR molecular surveillance in the Region;
provide updates on research activities; and
clarify the roles and responsibilities of national MR laboratories within the national measles and rubella surveillance programmes.

3. Updates on measles and rubella at WHO-SEARO

Fig. 1. Status of MR in the WHO SE Asia Region

During the Seventy-second session of the Regional Committee in September 2019, countries of the South-East Asia Region adopted the goal of measles and rubella elimination by 2023. A “Strategic Plan for measles and rubella elimination in WHO South-East Asia Region: 2020–2024” was endorsed by the Regional Committee. Based on the plan, five strategic objectives have been defined to eliminate MR from the SE Asia Region.

Immunization

Achieve and maintain high population immunity with >95% vaccination coverage with two doses of measles- and rubella-containing vaccines in each district of each country.

Fig. 2. Measles vaccine coverage and cases in the SE Asia Region
Fig. 3. Rubella vaccine coverage and cases in the SE Asia Region

Fig. 4. Significant increase in ‘zero dose’ children in the Region, 2019–2021; ‘zero dose’ refers to children who did not receive the first dose of the measles-containing vaccine (MCV1), ‘partially vaccinated’ refers to children who received MCV1 but not MCV2; more than 80% of ‘zero dose’ children are from India and Indonesia
Surveillance

Develop and sustain a sensitive and timely case-based surveillance system for measles and rubella.

Table 1. Surveillance performance indicators for SE Asia Region MRLN

<table>
<thead>
<tr>
<th>Countries</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2021</td>
<td>2022</td>
<td>2021</td>
<td>2022</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>1363</td>
<td>3040</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>Bhutan</td>
<td>68</td>
<td>49</td>
<td>99</td>
<td>76</td>
</tr>
<tr>
<td>DPR Korea</td>
<td>272</td>
<td>NR</td>
<td>100</td>
<td>NR</td>
</tr>
<tr>
<td>India</td>
<td>8332</td>
<td>34372</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Indonesia</td>
<td>854</td>
<td>4065</td>
<td>63</td>
<td>68</td>
</tr>
<tr>
<td>Maldives</td>
<td>9</td>
<td>3</td>
<td>56</td>
<td>100</td>
</tr>
<tr>
<td>Myanmar</td>
<td>26</td>
<td>33</td>
<td>54</td>
<td>82</td>
</tr>
<tr>
<td>Nepal</td>
<td>637</td>
<td>505</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>26</td>
<td>35</td>
<td>100</td>
<td>86</td>
</tr>
<tr>
<td>Thailand</td>
<td>191</td>
<td>93</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>Timor-Leste</td>
<td>30</td>
<td>67</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>SE Asia Region</td>
<td>11808</td>
<td>42262</td>
<td>78</td>
<td>76</td>
</tr>
</tbody>
</table>

A – Number of suspected measles cases
B – % suspected cases with adequate investigation initiated within 48 hours of notification
C – % suspected cases with serum specimens collected
D – % serum specimens received at a laboratory within five days of collection

Laboratory

Develop and maintain a proficient measles and rubella laboratory network.

Fig. 5. South-East Asia MRLN laboratories

Measles and rubella laboratory network in the SE Asia Region

<table>
<thead>
<tr>
<th>Country</th>
<th>National laboratory</th>
<th>Subnational laboratory</th>
<th>Reference laboratory</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Bhutan</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>DPR Korea</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>India</td>
<td>7</td>
<td>18</td>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td>Indonesia</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Maldives</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Myanmar</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nepal</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Thailand</td>
<td></td>
<td>13</td>
<td>1*</td>
<td>14</td>
</tr>
<tr>
<td>Timor-Leste</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>SE Asia Region</td>
<td>18</td>
<td>37</td>
<td>3</td>
<td>58</td>
</tr>
</tbody>
</table>

* Regional reference laboratory
SE Asia Region MRLN detected 11,808 and 42,262 suspected measles cases in 2021 and 2022 respectively. The percentage serology results, reported within four days of receiving the specimens in laboratories were 76% and 80% in 2021 and 2022 respectively. SE Asia Region MRLN witnessed a decline in the number of genotypes submitted to measles nucleotide surveillance and rubella nucleotide surveillance (MeaNS) and (RubNS) primarily due to the COVID-19 pandemic as most of the MRLN laboratories were involved in COVID-19 molecular testing. The quality assurance indicators of SE Asia Region MRLN for 2022 are provided in Table 2.

**Table 2. Quality assurance indicators of SE Asia Region MRLN in 2022**

<table>
<thead>
<tr>
<th>Quality assurance indicator</th>
<th>#Labs</th>
<th>Passed</th>
<th>Failed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global proficiency testing (PT) panel for serology</td>
<td>55</td>
<td>54</td>
<td>1</td>
</tr>
<tr>
<td>Global molecular PT panel</td>
<td>36</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>National PT panel for serology (India and Thailand)</td>
<td>41</td>
<td>41</td>
<td>0</td>
</tr>
<tr>
<td>Laboratory proficient status for serology</td>
<td>44</td>
<td>43</td>
<td>2 (pending)</td>
</tr>
<tr>
<td>Laboratory proficient status for molecular test</td>
<td>36</td>
<td>32</td>
<td>4 (pending)</td>
</tr>
</tbody>
</table>

* DPR Korea could not be assessed for lack of data

† 13 subnational laboratories of Thailand assessed by National Institute of Health of Thailand

Nine new MR laboratories of India are accorded proficient status for serology

**Outbreak preparedness and response**

Ensure adequate preparedness and response to measles and rubella outbreaks in a timely manner. Six countries of the Region (Bangladesh, Bhutan, India, Indonesia, Myanmar and Sri Lanka) reported conducting readiness assessment and shared the findings.

**Linkages**

Strengthen support and linkages to achieve the strategic objectives above.

- Each country has a National Measles and Rubella Elimination Strategy.
- All countries have functional national verification committees (NVC) for measles and rubella elimination and provide annual reports to the South-East Asia Regional Verification Commission (RVC) for measles and rubella.
- All countries conducted subnational programmatic risk assessments in 2021 and identified high-risk areas for measles and rubella transmission.

**3.1 Key challenges to measles and rubella elimination in the SE Asia Region**

These include:

- policy barriers to vaccinating older age groups during routine sessions;
- absence of accountability mechanisms at the subnational level, as evident by the non-existence or suboptimal functioning of the state task forces or district immunization coordination committee or equivalent;
- impact of the COVID-19 pandemic – deprioritized MR activities, the pandemic recovery phase likely to last for a few more years:
  - Additional immunization and surveillance gaps emerged in several countries.
- financial insufficiency for optimal implementation of activities to achieve the 2023 target of measles and rubella elimination; and
- ensuring quality of the laboratory network as the network gets expanded.

3.2 Key observations for improving South-East Asia MRLN

(1) Internal audit activity needs to be strengthened further:
   - The best practice is to invite an auditor from a different laboratory, a few laboratories are not mentioning the names of reviewers and dates.
   - Many a time scores are deducted or answers to some of the questions are “no” or “partial” with no explanation in the comment box.
   - Sometimes, no scores are allotted.
   - Levey-Jennings (LJ) charts, vaccination records of laboratory staff and organogram are missing in the reports submitted by some of the laboratories.

(2) Equipment maintenance entails:
   - Importance of reading and interpreting maintenance certificate reports;
   - Self-maintenance of biosafety cabinets, a suggestion if service providers are not available locally; and
   - Pipette calibration, an important component of QA – calibration of pipettes should include balance calibration.

(3) ELISA worksheets – here are suggestions to include a few more variables:
   - Room temperature at the time of performing the assay;
   - Recording the time of each incubation step;
   - Calculations of reagent dilutions;
   - Internal quality control (IQC) values and range;
   - Lot numbers of positive and negative controls; and
   - Lot numbers of conjugate and substrate.

(4) Use of electronic ELISA result-recording spreadsheet:
   - Allow accurate recording of results and outcomes.

(5) Proficiency panel samples should be tested by staff routinely performing the test in the laboratory and not only by senior or experienced staff.

3.3 Key messages

The MR laboratory network needs to be prepared to:

(1) Test a higher number of serological examinations to handle outbreak situations and rising surveillance sensitivity;
(2) Characterize measles virus in at least 80% of the chains of transmission;
(3) Populate the measles genotype database of the country;
(4) Identify imported viruses;
(5) Make participation in all external and internal quality assurance mechanisms mandatory; and
(6) Ensure timely reporting and establishing linkages with colleagues from the Expanded Programme of Immunization (EPI), deemed important for public health interventions and success of the surveillance programme.
4. Improving laboratory confirmation for MR surveillance programme

4.1 Sequential testing versus parallel testing

In a low-incidence setting, the positive predictive value of measles-rubella IgM enzyme immunoassay (EIA) decreases. This increases the possibility of false positive measles results using ELISA. As case classification and public health response to the whole measles surveillance programme is based on laboratory results (Table 3), reporting of false positive results will be a problem for field surveillance and response. A switch from sequential to parallel testing was proposed to avoid the issues raised due to false positive measles results. The algorithms for both sequential and parallel testing are provided in Fig. 6.

<table>
<thead>
<tr>
<th>Status of a country</th>
<th>Impact of a positive laboratory result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries verified as “measles eliminated”</td>
<td>Even a single positive result will lead to a lot of public health interventions and surveillance actions</td>
</tr>
<tr>
<td>Achieved low measles incidence and targeting for verification status</td>
<td>Verification status may be derailed</td>
</tr>
<tr>
<td>Countries with high measles incidence</td>
<td>There is no major impact</td>
</tr>
</tbody>
</table>

Table 3. Impact of positive measles results on public health response, based on measles endemicity

Fig. 6. Sequential testing and parallel testing algorithms for measles and rubella

Sequential testing

- Serum
- Measles IgM
  - Positive
  - Negative
- Rubella IgM
  - Positive
  - Negative

Parallel testing

- Serum
- Measles IgM
- Rubella IgM
  - Positive
  - Negative

The feasibility assessment of the switch from sequential to parallel testing was carried out. It was observed that shifting the testing algorithm would result in increased workload and rubella test kit consumption, based on measles positivity rates (Table 4). Therefore, the countries, where measles positivity is high, will have an increased workload and rubella kit requirement. While calculating rubella kit requirements for implementing parallel test algorithm, the wastage factor also needs to be considered. It is expected to be higher in low-workload laboratories, compared with high-workload ones.
Table 4. Increased workload in a laboratory, based on the annual workload and measles positivity

<table>
<thead>
<tr>
<th>The annual workload of a laboratory</th>
<th>≤ 200</th>
<th>500</th>
<th>1000</th>
<th>2000</th>
<th>≥ 3000</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% measles positivity</td>
<td>10</td>
<td>25</td>
<td>50</td>
<td>100</td>
<td>150</td>
</tr>
<tr>
<td>10% measles positivity</td>
<td>20</td>
<td>50</td>
<td>100</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>20% measles positivity</td>
<td>40</td>
<td>100</td>
<td>200</td>
<td>400</td>
<td>600</td>
</tr>
<tr>
<td>40% measles positivity</td>
<td>80</td>
<td>200</td>
<td>400</td>
<td>800</td>
<td>1200</td>
</tr>
<tr>
<td>&gt; 50% measles positivity</td>
<td>100</td>
<td>250</td>
<td>500</td>
<td>1000</td>
<td>1500</td>
</tr>
</tbody>
</table>

Some of the considerations for shifting the algorithm from sequential to parallel:

1. Sample receipt in laboratories is not evenly distributed, some months witness high workload while others show low workload.

2. Low-workload months or laboratories will not have much impact on the workload with regard to shifting from sequential to parallel testing algorithm.

3. High-workload laboratories will have relatively less difficulty in shifting to parallel testing algorithm mainly because:
   - They do not have to wait for measles test result before putting up a sample for rubella test.
   - Tracking and segregation of samples in a laboratory will become easier.
   - Meeting the timeliness of laboratory result within four days of sample receipt will entail:
     - Low measles positive rates: parallel test algorithm will be helpful.
     - High measles positivity rate (≥30%): parallel testing algorithm will increase the workload.

4. During outbreaks, laboratories witness high workloads with high measles or rubella positivity rates. Therefore, a provision should be there with regard to switching to sequential algorithm in special circumstances.

4.2 Dual reactive samples

GMRLN has started changing the algorithm from serial testing to parallel testing as countries move towards elimination. This has resulted in increased reports of double reactive samples. The “dual reactive samples” are samples positive for both measles and rubella IgM. These samples will get noticed only through parallel testing algorithm as, during sequential testing algorithm, the positive measles samples are not tested for rubella. There are multiple factors that may result in dual reactive samples:

1. Epidemiological reasons:
   - recent MR vaccination;
   - recent M vaccination and rubella infection;
   - recent M infection and current R infection; and
   - recent R infection and current M vaccination.
(2) Laboratory-based reasons:
- specificity of any test assay cannot be 100%;
- assay not performed to SOPs, e.g. RT incubation outside 18 ºC–25 ºC parameters; and
- no control antigen testing in new indirect IgM assays to rule out background noise that may arise due to various test experiment variables and may push the readings towards positivity.

Double reactive (DR) samples will pose challenges to interpretation and case classification; hence, DR samples need to undergo troubleshooting at the National Laboratory or Reference Laboratory level. The guidance for troubleshooting for such samples include:

(1) National Laboratory:
- epidemiological/surveillance investigation;
- following testing protocols (time and temperature);
- repeat test;
- second sample; and
- real-time RT-PCR.

(2) Regional Reference Laboratory:
- capture assay;
- avidity testing;
- ruling out other etiological agents, such as HHV-6, Parvo and dengue; and
- RT-PCR (on T/S).

4.3 Real-time RT-PCR assay

Real-time PCR assay may add value in specific scenarios in countries that are approaching the verification status of measles and rubella elimination (Fig. 7).

**Fig. 7. Utility of serology and real-time PCR assay in case classification, based on MR endemicity in the country**

<table>
<thead>
<tr>
<th>Endemic countries</th>
<th>Approaching elimination</th>
<th>Eliminated measles</th>
</tr>
</thead>
<tbody>
<tr>
<td>The country has lots of measles and rubella cases.</td>
<td>There are sporadic measles cases with low incidence.</td>
<td>There is no measles transmission in the country.</td>
</tr>
<tr>
<td>Serology is mainly used for case confirmation.</td>
<td>Serology remains the primary method for case confirmation.</td>
<td>Case confirmation should be based on both serology and real-time PCR assay results.</td>
</tr>
<tr>
<td>Real-time PCR assay may not add value in public health response.</td>
<td>Real-time PCR assay may add value in specific scenarios.</td>
<td></td>
</tr>
</tbody>
</table>


Various scenarios wherein real-time PCR assay is useful for non-endemic countries include:

(1) Scenario 1: Cases with no adequate serum sample
   - Serum sample could not be collected (denial of parents, infants, logistic issues, etc.)
   - Serum sample is collected within three days of rash onset (IgM detection has reduced sensitivity).
   - Poor serum sample: it is grossly hemolyzed or contaminated or less in quantity.

(2) Scenario 2: IgM results not conclusive
   - The final IgM result is equivocal.
   - There is dual reactive serum.
   - Doubtful negative result (based on epidemiology and clinical information) is observed.

(3) Scenario 3: Troubleshooting genotype PCR results, such as
   - measles or rubella IgM-positive serum with negative results in corresponding genotype PCR assay or vice versa.

In endemic countries, real-time PCR assay should be diligently used and all surveillance samples received in laboratories should be reported to the programme. For endemic countries, the testing scenarios are provided in Table 5.

**Table 5. Utility of real-time PCR and genotype PCR for the diagnosis of a suspected measles case in an endemic country**

<table>
<thead>
<tr>
<th>SN</th>
<th>Serology result</th>
<th>Real-time PCR</th>
<th>Genotype PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Measles/rubella positive</td>
<td>Test not required</td>
<td>Measles/rubella genotype test</td>
</tr>
<tr>
<td>2</td>
<td>Measles/rubella equivocal</td>
<td>Measles/rubella test</td>
<td>If real-time assay positive, then measles/rubella genotype test</td>
</tr>
<tr>
<td>3</td>
<td>Negative</td>
<td>Serum collected between 4 and 28 days</td>
<td>Test not required as the serum result is conclusive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum collected within three days of rash onset</td>
<td>Measles/rubella test</td>
</tr>
<tr>
<td>4</td>
<td>Not available</td>
<td>Measles/rubella test</td>
<td>If real-time assay positive, then measles/rubella genotype test</td>
</tr>
</tbody>
</table>

*Bhutan, DPR Korea, Maldives, Sri Lanka and Timor-Leste will test all throat swab samples for real-time PCR irrespective of serology result.

5. **Updates on MR serology and molecular EQAS**

5.1 Development of national proficiency test (PT) panels

With an aim to develop the ability of SE Asia Region countries, WHO-SEARO organized a workshop on “Training for the development of a National Proficiency Test scheme for measles and rubella” in collaboration with the Victorian Infectious Diseases Reference Laboratory
The Ninth South-East Asia Regional Meeting of Virologists of the Measles and Rubella Laboratory Network (VIDRL) at The Doherty Institute in Melbourne, Australia. It was held on 13–17 May 2019. The aim of the workshop was to strengthen the capacity of SE Asia Region countries for developing MR national PT panels to monitor the quality of the MR laboratory network in the following aspects:

1. to assess proficiency of MR laboratories more frequently within a country;
2. to support new laboratories coming on board by providing practice panels; and
3. to assess proficiency of newer laboratories as and when they join the network.

To this end, Thailand and India have successfully developed national PT panels.

**National MR Serology PT panel of Thailand**

THAI NIH, the Regional Reference Laboratory of the SE Asia Region, has ISO 17043 certification as an MR serology PT provider.

**National MR Serology PT panel of India**

The King Institute of Preventive Medicine and Research, Chennai, has successfully rolled out MR serology EQAS panels, as per the requirements. This has facilitated the expansion of MRLN in India from 19 laboratories in 2020 to 27 laboratories in 2021 – they are all proficient in MR serology.

### 5.2 Molecular EQA of MRLN

In 2021, 28 laboratories participated in molecular EQA (mEQA) for both measles and rubella. These included 14 laboratories from India, five laboratories from Thailand, three laboratories from Indonesia and one laboratory each from Bangladesh, Bhutan, Maldives, Myanmar, Sri Lanka and Timor-Leste. The overall performance of MRLN in molecular testing is provided in Table 6.

**Table 6. Molecular EQA performance of MRLN**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measles</th>
<th>Rubella</th>
</tr>
</thead>
<tbody>
<tr>
<td>mEQA passes</td>
<td>89% laboratories</td>
<td>93% laboratories</td>
</tr>
<tr>
<td>Use of negative extraction control</td>
<td>96% laboratories</td>
<td>96% laboratories</td>
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<tr>
<td>Perfect FASTA files</td>
<td>96% laboratories</td>
<td>92% laboratories</td>
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<tr>
<td>Correct genotyping</td>
<td>100% laboratories</td>
<td>96% laboratories</td>
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Areas of improvement for MR molecular diagnosis include:

1. Real-time RT-PCR
   - The threshold is not set in an ideal location.
   - Should have positive and negative extraction controls.
   - Invalid samples are interpreted:
     - If the MV/RV target and RNase P targets are both undetectable, the sample is invalid.
(2) Late submissions
- initial submission within two months of receipt of panel; and
- retests within six weeks of notification.

(3) Incomplete forms
- Points are deducted if information is not provided.

(4) Conventional RT-PCR
- Gel images are not labelled correctly.

(5) Genotyping
- failure to correctly identify named strains;
- topology-only phylogenetic trees;
- failure to remove -AA at the beginning of rubella FASTA file (two nucleotides added by ReCall);
- incorrect WHO names; and
- chromatogram quality.

6. Strengthening measles and rubella molecular surveillance in the SE Asia Region

6.1 Importance of molecular surveillance

The two criteria for verification of measles/rubella elimination are:

(1) documentation of interruption of endemic measles or rubella transmission for a period of at least 36 months from the last known endemic case;

(2) presence of high-quality, laboratory-supported surveillance system that:
- is sensitive and specific to detect, notify and investigate suspected cases/outbreaks in a timely manner;
- can classify cases as confirmed or discarded;
- can classify cases by source (indigenous, imported or import-related); and
- can inform the country to undertake appropriate public health actions to curtail further transmission and prevent future transmission.

The five lines of evidence for measles/rubella elimination include:

(1) detailed description of current and past epidemiology of measles, rubella;

(2) analysis of molecular epidemiology to document viral transmission patterns and duration of circulation of viruses of specific lineages;

(3) quality of surveillance and monitoring systems for measles, rubella;

(4) population immunity presented as a birth cohort analysis, including evidence on adults and underserved, migrant and refugee groups; and

(5) accountability and sustainability.
Molecular surveillance can aid in identification of the source of the outbreak as indigenous or imported and help in establishing the transmission patterns or duration of circulation for specific measles and rubella virus lineages. Therefore, molecular surveillance has vital a role to play in measles and rubella elimination.

Based on genotype information submitted by MRLN in MeaNS, the distribution of circulating genotypes between 2017 and 2022 are shown in Table 7.

**Table 7. Measles genotypes reported from the SE Asia Region between 2017 and 2022**

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<td>238 D8</td>
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### 7. SE Asia Region country updates

The country-wise presentations were formulated by country laboratory coordinators, based on the following points:

1. the current measles and rubella situation and how a laboratory is providing support to the surveillance programme:
   - Countries presented the trends of measles and rubella incidence and the number of serum and throat swab specimens tested and reported to the programme. Genotype information was provided to the programme.

2. laboratory performance and quality assurance indicators:
   - Presented timeliness indicators, findings of internal audits and follow-up actions taken by the laboratory, external and internal quality assurance indicators, ISO certification or major changes initiated by the laboratory for quality improvement.

3. challenges laboratories faced with regard to preparation of annual updates for respective national verification committee, if any, and the way forward in this regard; and

4. the support needed from IVD, WHO-SEARO and the way forward.
The following countries had presented during the meeting: Bangladesh, Bhutan, India, Indonesia, Maldives, Nepal, Sri Lanka, Thailand and Timor-Leste.

Countries with multiple MR laboratories, such as India, Indonesia, Nepal and Thailand, and laboratory focal persons at WHO country offices or the National Reference Laboratory had collated the information from their respective laboratories and presented it as a single country report.

8. Storage policy for precious material in MR laboratories

(1) Clinical samples under MR surveillance, such as serum, throat swab, urine and nasopharyngeal swab, are sensitive to heat. These samples must be placed in leak-proof containers and transported in cold chain to a laboratory.

(2) Storage of clinical specimens:
- sera at $\geq 20 ^\circ C$
- throat swabs/urine/nasopharyngeal swab at $-70 ^\circ C$
- extracted RNA at $-70 ^\circ C$
- PCR product at $4 ^\circ C$.

(3) Discard policy:
- Measles- and rubella-negative samples can be discarded after 12 months of reporting.
- Measles- and rubella-positive or equivocal samples should be considered precious samples and should not be discarded. If a laboratory is facing constraints on storage, then inform laboratory coordinators or the Reference Laboratory, arrangements will be made to shift positive samples to other laboratories for long-term storage or use.
- Extracted RNA is to be discarded once results are reported.

(4) Inventory:
- Box-wise inventory of all types of samples, consisting of freezer ID, rack number, box number and position number of samples, should be available.
- Prepare SOP for storage policy and inventory management.

(5) Shipment:
- PCR products are to be clearly labelled and shipped at room temperature along with a hard copy of the line list.
- Prior information about shipment is to be provided to the receiving laboratory.

9. Meeting action points

The meeting recommendations are categorized under the following headings:

- Measles and rubella serology;
- Measles and rubella real-time RT-PCR assay;
- Molecular surveillance;
- External quality assurance and accreditation;
- Good laboratory practices; and
- Miscellaneous.
Measles and rubella serology

(1) Measles and rubella incidence is likely to increase following the relaxation of COVID-19 mitigation efforts. Laboratories should prepare for expected outbreaks of measles and rubella and a return to the workload experienced prior to the start of the COVID-19 pandemic. Countries are also introducing enhanced surveillance (rash-fever), as a result, laboratories are expected to witness increased workload and thus should be prepared and consider increasing the capacity for serology tests.

(2) Countries currently following a serial testing algorithm should consider a shift to a parallel testing algorithm. It is expected that adopting parallel test algorithm in low-measles incidence setting will improve the timeliness of reporting both measles and rubella results with minimal or nil burden on resources.

- Countries that have been certified as “eliminated measles (Bhutan, DPR Korea, Maldives, Sri Lanka and Timor-Leste)” should continue parallel test algorithm for measles and rubella serology.
- Countries where measles is endemic but incidence has reduced to low levels should consider adopting parallel test algorithm – for instance, Bangladesh, Nepal and Thailand.
- The laboratory focal points of India and Indonesia will work out a plan for shifting from sequential to parallel test algorithm, based on laboratory workload and measles positivity rate. The timeline for submission of the plan is 30 September 2022.
- In measles or rubella outbreak situations, laboratories may switch to sequential test algorithm as deemed appropriate.

(3) Parallel testing may generate a small proportion of samples, which is dual reactive (measles and rubella IgM positive). These samples should not be recorded as dual infection. Dual reactive samples can be a result of multiple possibilities, most of which can be resolved through additional testing and collaboration with the EPI/surveillance programme.

- Check the vaccine history of the case concerned.
- Repeat IgM testing on the same assay with strict adherence to SOPs.
- Compare test optical densities OD/ratios.
- Repeat IgM with capture IgM.
- Check IgG and/or avidity.
- Ensure testing for diseases, which may increase non-specific reactions.
- Confirm case through real-time RT-PCR tests.

(4) Some of these double reactive (DR) resolving assays can be performed by NLs and some may need to be performed by RRLs.

(5) Countries, which have eliminated measles and rubella, should report any positive serum to the regional laboratory coordinator within 24 hours, in addition to routine reporting requirements.

(6) It is imperative that the instruction for use, as provided by the kit manufacturer, is followed strictly as even a slight deviation from the protocol may profoundly affect the result of the assay. Extra attention should be paid to the temperature at which...
the assay is performed as well as to the stringency of the ELISA washing steps wherein any remaining wash buffer can be causing a negative effect. Room temperature should be monitored throughout the procedure and not just at the beginning.

**Measles and rubella real-time RT-PCR assay**

1. Detection of IgM continues to be the gold standard for measles and rubella case confirmation. Real-time RT-PCR tests may be considered an adjunct for enhancing case confirmation in elimination countries, but, importantly, a negative result in real-time RT-PCR assay does not exclude a case as non-measles, non-rubella.

2. Introduction of real-time RT-PCR will be considered for some countries of the Region to increase the sensitivity of detecting measles cases when virological samples are collected in the first seven days after the rash onset. T/S or other respiratory samples or urine samples can be used.

3. Countries that have been certified as “eliminated measles (Bhutan, DPR Korea, Maldives, Sri Lanka and Timor-Leste)” will continue testing all throat swabs or urine specimens by real-time RT-PCR assay.

4. Countries, where measles is endemic, may consider introducing real-time RT-PCR assay, based on serology results or in some specific situations, such as:
   - **Cases with no adequate serum sample:** Serum sample could not be collected due to parents’ denial, infants or logistic issues. Serum sample is collected within three days of rash onset (IgM detection has reduced sensitivity) or there is a poor-quality serum sample (grossly hemolyzed or contaminated or less in quantity).
   - **IgM results not conclusive:** The final IgM result is equivocal, there is dual reactive serum or doubtful negative result (based on epidemiology and clinical information).
   - **Troubleshooting genotype PCR results:** There is measles or rubella IgM positive serum with negative results in corresponding genotype PCR assay or vice versa.
   - **Timeliness of reporting molecular results** to the programme is also introduced to SE Asia Region MRLN. The new timeliness indicators to be monitored by laboratories are:
     - reporting real-time RT-PCR results within seven days of sample receipt;
     - reporting genotype RT-PCR results within 14 days of sample receipt; and
     - reporting sequencing results to the programme and submissions in MeaNS and RubeNS within 60 days of sample receipt.

5. A new monthly reporting format for reporting aggregated results of molecular tests to IVD, WHO-SEARO is introduced; it is attached as Annex 1. The new format is to be introduced from the first quarter of 2023 by all MR laboratories in the Region.

6. As per the new reporting scheme for molecular tests, proposed for the Region, the following guidelines should be considered:
   - All samples, received in a laboratory, should be reported to the surveillance programme, even if not tested. Throat swabs not requiring RT-PCR assay in measles-endemic countries can be reported as “test not required”.


- For sharing case confirmation results by serology or RT-PCR assay, the casewise primary reporting is to be delivered to the surveillance programme for public health interventions and actions. The secondary reporting of aggregated data in monthly formats is to be delivered to IVD, WHO-SEARO.

- For sharing sequence analysis information with the programme, the primary reporting will be delivered to RRL and the regional lab coordinator at IVD, WHO-SEARO.

**Molecular surveillance**

(1) A marked reduction in sequence detection has been reported in the Region. Laboratories are reminded that measles viruses should be characterized in at least 80% of chains of transmission and there is a need for increasing the collection of virological specimens.

(2) The global reduction in measles genetic diversity requires an improved genotype analysis for verification of elimination to be provided to NVC/RVC. Sequencing laboratories should provide detailed genetic analysis and interpretation, including identification of distinct sequence identifiers (DSIds) and named strains. Combining molecular data with epidemiological data (e.g. imported cases) is crucial to provide a comprehensive description of the situation in the country.

(3) In some countries, a higher resolution of sequence analysis is needed to rule out endemic circulation of measles. Sequencing laboratories may consider using MF-NCR sequencing to aid in molecular surveillance.

(4) Many countries have reported very few or no rubella sequences and should focus on collecting molecular samples from all rubella outbreaks. Congenital rubella syndrome (CRS) cases may continue to shed virus for up to one year after birth and can be a good source of samples for molecular data.

(5) Timely submission of sequences to MeaNS and RubeNS (within two months of receipt of the sample in the laboratory) is critical for improving global measles and rubella surveillance and is an essential component of accreditation.

(6) Appropriate transport media should be used for collecting samples for molecular detection. Molecular transport medium (MTM) should not be used for samples collected for virus culture but can only be used for molecular testing.

**External quality assurance and accreditation**

The WHO accreditation programme is critical for evaluating the performance of MRLN and a fully proficient laboratory is essential to support the verification of measles and rubella elimination.

(1) The external quality assurance programme (EQAS) is an essential component of the accreditation programme and participation is not optional. Laboratories are responsible for timely ordering of panels and facilitating the importation into their country.

(2) Any EQA resulting in a deficiency should be investigated and corrective action/preventive action (CAPA) completed.
(3) The option of “retest” is offered to a laboratory as an opportunity to score passing marks in the global EQA scheme. If a “retest” is offered to a participating laboratory by panel providers, then action from the participating laboratory should be immediate, else the initial score will be considered final.

(4) The Thai NIH e-learning internal audit training tool has proven to be highly beneficial for accreditation assessors (https://openwho.org/courses/SEAR-MR-lab-audits-EN). All assessors should strongly consider completing this programme before carrying out their assessments.

(5) The most recent accreditation assessment has confirmed the high quality of SE Asia Region MRLN. However, the internal audit can be further strengthened if all audits are carried out by an auditor from a different laboratory, all QA/QC documents are provided and equipment validation and maintenance records are completed.

(6) Collection of sera in larger volumes for serology panel preparation and kit performance evaluation will be helpful for developing EQA panels and laboratories with such samples should consult their RRL and the RLC.

(7) The accreditation checklist is currently being revised and will likely be in an Excel format to expedite its completion and facilitate the scoring process.

**Good laboratory practices**

(1) SOPs should be completed for all relevant protocols. Validated SOPs will be an essential component for gaining full accreditation with the revised checklist.

(2) Document control within the laboratory is important to ensure that information is accurate, up-to-date, accessible and aligned with the nature of laboratory services, and should be implemented in all laboratories.

(3) Compliance with MR-testing protocols, particularly incubation times and temperature and removing all wash buffer from ELISA plates, is critical to ensure sensitive and accurate test results. The MR Laboratory Manual and annexes, containing all WHO laboratory protocols, can be accessed at https://www.technet-21.org/en/topics/laboratory-measles-rubella-manual.

(4) The WHO Laboratory Biosafety Manual 4th Edition (2020) is available on the WHO website and should be referenced for all biosafety issues.

(5) Equipment maintenance – balance calibration, reading calibration certificates, self-maintenance of biosafety cabinets – can be carried out by laboratory staff, if service providers are not available locally. But full maintenance and calibration should be performed by a certified agency. This is because all equipment to be used for biosafety cabinet (BSC) calibration and performance must be calibrated and carried out by trained (certified) persons.

(6) Control samples should be used in all assays, ELISA and RT-PCR. ELISA IQC samples should be plotted using LJ format and test runs not meeting Westgard rules should be examined, resolved and repeated.

(7) A positive extraction control should be used for real-time RT-PCR assays. For all countries performing real-time RT-PCR, all positive controls should be plotted using LJ format (one for each control, including RNAse P).

(8) All test runs, which have controls outside expected values, should be documented as corrective action/preventive action.
Miscellaneous

(1) A huge investment has been made in building laboratory capacity to support COVID-19 control. Utilizing this capacity can be beneficial for GMRLN laboratories and this should be explored.

(2) Evaluation of the performance of global measles and rubella IgM kits will be completed as soon as possible.

(3) Rapid diagnostic tests (RDTs) have an important role for the rapid identification of measles and rubella. A framework for introduction and use of RDTs in the programme will be developed.

(4) Strengthening coordination between surveillance and laboratory through regular meetings is needed.

(5) Storage of clinical specimens
   - Storage temperatures. Store clinical samples at recommended conditions (-20 °C for serum, -70 °C for throat swabs/urine/NPS, -70 °C for extracted RNA and 4 °C for PCR products).
   - Discard policy. Measles- and rubella-negative samples can be discarded after 12 months of reporting. Measles- and rubella-positive/equivocal samples are not to be discarded and, if no storage is left, can be transported to the Reference Laboratory for storage. Extracted RNA is to be discarded once the results are reported.
   - Sample Inventory. Maintain inventory of stored samples with details, including freezer ID, rack number and box number, to ensure the traceability of the samples.
Annex 1

Laboratory molecular test monthly reporting format: Measles

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<th>#Urine sp. received</th>
<th>#RS sp. tested</th>
<th>#Urine tested</th>
<th>#RS measles positive</th>
<th>#Urine measles positive</th>
<th>#Real time PCR products sequenced</th>
<th>Genotype(s)</th>
<th>#submitted in MeaNS</th>
<th>#Genotypes of PCR result reported within 14 days</th>
<th>Submission in MeaNS within 60 days</th>
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### Annex 2

**Laboratory molecular test monthly reporting format: Rubella**

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<td>Date of reporting:</td>
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| SN | Months | #Respiratory sp. (RS) received | #Urine sp. received | #Resp. sp. tested Real time PCR | #Urine tested Real time PCR | #RS Rubella positive Genotype PCR | #Urine Rubella positive Genotype PCR | # +ve PCR products sequenced Genotype PCR | #submitted in RubeNS Genotype PCR result reported within 14 days | Carrontype PCR result reported within 60 days | Submission in RubeNS within 60 days |
|----|--------|-------------------------------|-------------------|---------------------------------|-------------------------------|----------------------------------|----------------------------------|------------------------------------------|------------------------------|-------------------------------|
| 1  | Jan    |                               |                   |                                 |                               |                                  |                                  |                                          |                              |                               |
| 2  | Feb    |                               |                   |                                 |                               |                                  |                                  |                                          |                              |                               |
| 3  | Mar    |                               |                   |                                 |                               |                                  |                                  |                                          |                              |                               |
| 4  | Apr    |                               |                   |                                 |                               |                                  |                                  |                                          |                              |                               |
| 5  | May    |                               |                   |                                 |                               |                                  |                                  |                                          |                              |                               |
| 6  | Jun    |                               |                   |                                 |                               |                                  |                                  |                                          |                              |                               |
| 7  | Jul    |                               |                   |                                 |                               |                                  |                                  |                                          |                              |                               |
| 8  | Aug    |                               |                   |                                 |                               |                                  |                                  |                                          |                              |                               |
| 9  | Sep    |                               |                   |                                 |                               |                                  |                                  |                                          |                              |                               |
| 10 | Oct    |                               |                   |                                 |                               |                                  |                                  |                                          |                              |                               |
| 11 | Nov    |                               |                   |                                 |                               |                                  |                                  |                                          |                              |                               |
| 12 | Dec    |                               |                   |                                 |                               |                                  |                                  |                                          |                              |                               |
| 13 | Total  |                               |                   |                                 |                               |                                  |                                  |                                          |                              |                               |
Annexure 3

Agenda

(1) Opening session:
- Welcome and opening remarks from WHO-SEARO
- Remarks from WHO HQ
- Remarks from WHO country office for India
- Remarks from the Additional Chief Secretary, Medical Health, Uttar Pradesh
- Remarks from US CDC
- Lamp lighting.

(2) Introductions and objectives of the meeting

(3) Session 1 – Providing updates:
- Regional update on measles and rubella elimination goal;
- Global Measles Rubella Laboratory Network (GMRLN): An update;
- SE Asia Region MRLN update and report findings of detailed desk review by experts for quality assurance; and
- Method under development for measles sequencing.

(4) Session 2 – Improving laboratory confirmation for MR surveillance programme:
- Measles and rubella IgM ELISA evaluations: Literature review;
- Challenges of dual reactive sera: A global update;
- Changing serology test algorithm from sequential to parallel, measles-rubella testing: Implementation feasibility and cost implications;
- Addressing dual reactive results in the laboratory network; and
- Broadening use of measles-rubella real-time PCR assay for case confirmation: A proposal for MR-endemic countries.

(5) Session 3 – Updates on MR serology and molecular EQAS:
- Reporting of MR molecular EQAS panel results: Lessons in filling format;
- Submission and tracking orders through IRR platform;
- Journey for achieving ISO 17043 certification: MR serology PT provider;
- Experience of rolling out the national serology PT scheme in India; and
- Importance and common practices for document control in laboratory settings.

(6) Session 4 – Strengthening measles and rubella molecular surveillance in the SE Asia Region:
- Importance of molecular surveillance for verification status of measles and rubella elimination and overview of submissions in MeaNS and RubeNS;
- Report on MR sequencing from RRL, Thailand and report on MR sequencing from RRL, Mumbai;
- Sharing laboratory results: Revision in molecular test reporting formats;
- Discussion: Responsibilities and frequency of communication of MR sequence analysis information to the programme and the SE Asia Region;
- Measles virus extended sequencing (MF-NCR): Report from US CDC; and
- Discussion: Implementing MR-NCR sequence window for measles virus in RRLs and NLs.

(7) Session 5 – Country presentations:
- Bangladesh
- Bhutan
- DPR Korea
- India
- Indonesia
- Maldives
- Nepal
- Sri Lanka
- Thailand
- Timor-Leste.

(8) Session 6 – Other updates:
- Storage policy for precious material in MR laboratories;
- Sharing examples of measles and rubella genetic interpretation of the surveillance programme;
- Update on measles RDT, field trial in India and a neq MR-RDT research project.

(9) Meeting recommendations

(10) Closing remarks.
Annex 4

List of participants

Laboratory experts
Mr David Featherstone
Formal Global Coordinator
WHO Vaccine Preventable Disease Laboratory Network
Dr Eveline Irawan
Member
National Expert Committee on Diphtheria
Ministry of Health
Indonesia
Dr Patravee Soisangwan
Director
Bureau of Laboratory Quality Standards
Ministry of Public Health
Thailand
Dr Nalini Ramamurty
Consultant
Sri Ramachandra Institute of Health Education & Research and
Former Scientist IVD WHO SEARO
Dr Atchariya Lukebua
Head
MR Regional Laboratory
National Institute of Health
Ministry of Public Health
Thailand
Dr Patcha Incomserb
Medical Scientist
MR Regional Laboratory
National Institute of Health
Ministry of Public Health
Thailand
Dr Uma Nalavade
Technical Officer
National Institute of Virology, ICMR
Mumbai, India
Dr Kaveri Krishnasamy
Deputy Director
King Institute of Preventive Medicine and Research
Chennai, India

US CDC
Dr Bettina Bankamp
Team Lead, Measles
Division of Viral Diseases
United States Centers for Disease Control and Prevention
Atlanta, USA
Ms Raydel Anderson
Microbiologist
Measles Team
Division of Viral Diseases
United States Centers for Disease Control and Prevention
Atlanta, GA, USA

Laboratory country participants

Bangladesh
Dr Rasheda Sultana
Director
Institute of Public Health
Ministry of Health & Family Welfare
Dhaka, Bangladesh
Dr Khondoker Mahbuba Jamil
Virologist
Institute of Public Health
Ministry of Health & Family Welfare
Dhaka, Bangladesh

Bhutan
Ms Sangay Zangmo
Deputy Chief Laboratory Officer
Royal Centre for Disease Control
Ministry of Foreign Affairs
Thimphu, Bhutan
Mr Tenzin Dorji
Senior Laboratory Technician
Royal Centre for Disease Control
Ministry of Foreign Affairs
Thimphu, Bhutan

India
Shri Amit Mohan Prasad
Addl. Chief Secretary (H&FW)
Ministry of Health & Family Welfare
Uttar Pradesh
Lucknow, India

Special invitees
Dr Shailesh Pawar
Scientist & Officer-in-Charge
National Institute of Virology, ICMR
Ministry of Health & Family Welfare
Government of India
Mumbai, India
Ms M.K. Ismath Jahan  
Measles Rubella Laboratory Supervisor  
Government Mohan Kumaramangalam Medical College Hospital  
Ministry of Health & Family Welfare  
Government of India  
Salem, India  

Dr Sima Bhatt  
Professor Microbiology  
B J Medical College (BJMC)  
Ministry of Health & Family Welfare  
Government of India  
Ahmedabad, India  

Dr Purva Pankaj Sarkate  
Deputy Director  
National Centre for Disease Control (NCDC)  
Ministry of Health & Family Welfare  
Government of India  
Delhi, India  

Dr Ujjala Ghoshal  
Prof & Head Dept of Microbiology  
Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGI)  
Ministry of Health & Family Welfare  
Government of India  
Lucknow, India  

Ms Sneha Ghildyal  
Senior Research Fellow  
Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGI)  
Ministry of Health & Family Welfare  
Government of India  
Lucknow, India  

Ms Suman Yadav  
Senior Research Fellow  
Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGI)  
Ministry of Health & Family Welfare  
Government of India  
Lucknow, India  

Ms Nibedita Das  
Specialist (Microbiology)  
Institute of Serology (IOS)  
Ministry of Health & Family Welfare  
Government of India  
Kolkata, India  

Dr Binod Kumari Pati  
Associate Professor  
All India Institute of Medical Science  
Ministry of Health & Family Welfare  
Government of India  
Patna, India  

Dr Mini P. Singh  
Professor  
Post Graduate Institute of Medical Education & Research (PGIMER)  
Ministry of Health & Family Welfare  
Government of India  
Chandigarh, India  

Mr M.A. Azeem  
Assistant Director  
Institute of Preventive Medicine (IPM)  
Ministry of Health & Family Welfare  
Government of India  
Hyderabad, India  

Dr Ajanta Sharma  
Professor of Microbiology and Incharge, Gauhati Medical College (GMC)  
Ministry of Health & Family Welfare  
Government of India  
Guwahati, India  

Dr Jaya Lohani  
Associate Professor  
Gandhi Medical College (GMC)  
Ministry of Health & Family Welfare  
Government of India  
Bhopal, India  

Dr Pushpendra Singh  
Scientist  
National Institute of Research in Tribal Health, ICMR  
Ministry of Health & Family Welfare  
Government of India  
Jabalpur, India  

Dr Bharti Malhotra  
Senior Professor  
Sawai Man Singh Medical College (SMSMC), Ministry of Health & Family Welfare  
Government of India  
Jaipur, India  

Dr S. Lakshmikanth  
Scientist  
Regional Medical Research Centre, ICMR  
Ministry of Health & Family Welfare  
Government of India  
Port Blair, India
Dr Manoj Kumar  
Professor & PI (VRDL)  
Rajendra Institute of Medical Sciences (RIMS), Ministry of Health & Family Welfare  
Government of India  
Ranchi, India

Ms Sana Irfan  
Scientist  
Mahata Gandhi Memorial Medical College  
Ministry of Health & Family Welfare  
Government of India  
Jamshedpur, India

Dr Ira Praharaj  
Scientist and In-Charge  
Regional Medical Research Centre, ICMR  
Ministry of Health & Family Welfare  
Government of India  
Bhubaneswar, India

Dr B. Anukumar  
Scientist  
National Institute of Virology, ICMR Kerala  
Ministry of Health & Family Welfare  
Government of India  
Kerala, India

Dr Jaichand J.  
Scientific Officer & Officer in Charge  
State Public Health Laboratory (SPHL), Ministry of Health & Family Welfare  
Government of India  
Trivandrum, India

Dr P. Madhusudhan  
Research Scientist  
Siddhartha Medical College, Vijayawada  
Ministry of Health & Family Welfare  
Government of India  
Vijayawada, India

Dr Usha Kalawat  
Professor  
Sri Venkateswara Institute of Medical Sciences, Tirupati  
Ministry of Health & Family Welfare  
Government of India  
Tirupati, India

Ms Ankita Sharma  
Scientist  
Dr Rajendra Prasad Government Medical College & Hospital  
Ministry of Health & Family Welfare  
Government of India  
Tanda, India

Dr Ankur Saxena  
Research Scientist  
Government Medical College  
Ministry of Health & Family Welfare  
Government of India  
Haldwani, India

Mr Bashir Ahmad Fomda  
Professor and Head  
Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Soura  
Ministry of Health & Family Welfare  
Government of India  
Srinagar, India

Indonesia

Ms Evi Dwiwanti  
Health Laboratory Administrator  
Centre for Health Laboratory  
Ministry of Health  
Republic of Indonesia  
Surabaya, Indonesia

Ms Maulida Ulfa  
Health Laboratory Administrator  
Centre for Health Laboratory  
Ministry of Health  
Republic of Indonesia  
Makassar, Indonesia

Ms Catur Adiariyani  
Health Laboratory Administrator  
Centre for Health Laboratory  
Ministry of Health  
Republic of Indonesia  
Palembang, Indonesia

Ms Dyah Widhiastuti  
Chief of Surveillance and Epidemiology  
PT Bio Farma  
Ministry of Health  
Republic of Indonesia  
Jakarta, Indonesia

Ms Rita Triwulan  
Health Laboratory Administrator  
Centre for Health Laboratory  
Ministry of Health  
Republic of Indonesia  
Yogyakarta, Indonesia

Dr Bie Novierenallia Uumar  
Health Epidemiologist  
Directorate for Immunization Management  
Ministry of Health  
Republic of Indonesia  
Jakarta, Indonesia

Dr Mursinah Sp.MK  
Researcher  
Centre for Health Resilience System and Health Resources Policy  
Ministry of Health  
Republic of Indonesia  
Jakarta, Indonesia

Mr Juwita Kurniawati A Md  
Research and Engineering Technician  
Centre for Health Resilience System and Health Resources Policy  
Ministry of Health  
Republic of Indonesia  
Jakarta, Indonesia
### Maldives
- **Ms Juweyriya Saleem**  
  Senior Scientific Officer  
  Indira Gandhi Memorial Hospital Lab  
  Ministry of Health  
  Malé, Maldives
- **Ms Soafy Mohamed**  
  Laboratory Technologist  
  Indira Gandhi Memorial Hospital  
  Ministry of Health  
  Malé, Maldives

### Nepal
- **Dr Runa Jha**  
  Director  
  National Public Health Laboratory  
  Ministry of Health and Population  
  Kathmandu, Nepal
- **Mr Bal Krishna Awal**  
  Deputy Chief Medical Technologist  
  National Public Health Laboratory  
  Ministry of Health and Population  
  Kathmandu, Nepal
- **Dr Ratna Baral**  
  Additional Professor & Microbiologist  
  B.P. Koirala Institute of Health Sciences  
  Ministry of Health and Population  
  Kathmandu, Nepal

### Sri Lanka
- **Dr Janaki Abeynayake**  
  Consultant Virologist  
  Medical Research Institute  
  Ministry of Health  
  Colombo, Sri Lanka
- **Dr Rohitha Muthugala**  
  Consultant Virologist  
  National Hospital Kandy  
  Ministry of Health  
  Colombo, Sri Lanka

### Thailand
- **Ms Kannikar Kwanchum**  
  Medical Scientist  
  National Institute of Health  
  Ministry of Public Health  
  Nonthaburi, Thailand
- **Mr Thanapol Preamkamon**  
  Medical Scientist  
  National Institute of Health  
  Ministry of Public Health  
  Nonthaburi, Thailand
- **Ms Sawalee Saosathan**  
  Medical Technologist  
  Regional Medical Sciences Center 1  
  Chiang Mai  
  Ministry of Public Health  
  Nonthaburi, Thailand
- **Ms Sasikarn Namwong**  
  Medical Technologist  
  Regional Medical Sciences Centre 1/1  
  Chiang Rai  
  Ministry of Public Health  
  Nonthaburi, Thailand
- **Ms Monlica Rattanamuang**  
  Medical Technologist  
  Regional Medical Sciences Centre 2  
  Phitsanulok  
  Ministry of Public Health  
  Nonthaburi, Thailand
- **Ms Pornnapa Khampam**  
  Medical Technologist  
  Regional Medical Sciences Centre 3  
  Nakhon Sawan  
  Ministry of Public Health  
  Nonthaburi, Thailand
- **Ms Sirilada Suphankong**  
  Medical Technologist  
  Regional Medical Sciences Centre 5  
  Samut Songkhram  
  Ministry of Public Health  
  Nonthaburi, Thailand
- **Ms Walailuck Talue**  
  Medical Technologist  
  Regional Medical Sciences Centre 6  
  Chonburi  
  Ministry of Public Health  
  Nonthaburi, Thailand
- **Ms Sutthikan Sombattheera**  
  Medical Technologist  
  Regional Medical Sciences Centre 7  
  Khon Kaen  
  Ministry of Public Health  
  Nonthaburi, Thailand
- **Ms Khwanjai Wangkahat**  
  Medical Technologist  
  Regional Medical Sciences Centre 8  
  Ubon Ratchathani  
  Ministry of Public Health  
  Nonthaburi, Thailand
- **Ms Boonyaorn Yuttayong**  
  Medical Technologist  
  Regional Medical Sciences Centre 9  
  Nakhon Ratchasima  
  Ministry of Public Health  
  Nonthaburi, Thailand
Ms Wattanee Sunghirun
Medical Technologist
Regional Medical Sciences Centre 12
Songkhla
Ministry of Public Health
Nonthaburi, Thailand

Ms Suwandee Sapcharoen
Medical Technologist
Regional Medical Sciences Centre 12/1
Trang
Ministry of Public Health
Nonthaburi, Thailand

Timor-Leste
Ms Endang Soares da Silva
Executive Director
National Health Laboratory
Ministry of Health
Dili, Timor-Leste
Ms Alberina do Carmo Viera
Technician
National Health Laboratory
Ministry of Health
Dili, Timor-Leste

WHO

WHO Headquarters
Dr Mick Mulders
Scientist
Global VPD Laboratory Networks
WHO-HQ
Geneva Switzerland

WHO SE Asia Regional Office (SEARO)
Dr Sunil Bahl
Coordinator (COVAX, IVD)
Immunization and Vaccine Development (IVD)
WHO-SEARO
New Delhi, India

Dr Lucky Sangal
Virologist/immunologist
Immunization and Vaccine Development
WHO-SEARO
New Delhi, India

Mr Aditya Prasad Pai
Team Assistant
Immunization and Vaccine Development
WHO-SEARO
New Delhi, India

WCO India
Dr Roderico Ofrin
WHO Representative to India
WHO Country Office
New Delhi, India
Dr Deepa Sharma
National Professional Officer
VPD Lab Network
National Public Health Support Network
WHO Country Office
New Delhi, India

WCO Indonesia
Dr Tina Kusumaningrum
National Professional Officer
Laboratory Network
WHO Country Office
Jakarta, Indonesia
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Theme of the meeting: Expanding the scope with commitment to excellence