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MEETING REPORT

13TH MEETING OF THE MEASLES / RUBELLA REGIONAL REFERENCE LABORATORIES

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COPENHAGEN

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Abbreviations

ASU	Annual Status Update
CRS	congenital rubella syndrome
CSF	cerebrospinal fluid
DBS	dried-blood spots
ELISA	enzyme linked immunosorbent assay
EQA	external quality assessment
EU	European Union
EVAP	European Vaccine Action Plan
GAPIII	WHO global action plan to minimize poliovirus facility associated risk
GMRLN	Global Measles/Rubella Laboratory Network
GSL	global specialized laboratory
IgG	immunoglobulin G
IgM	immunoglobulin M
IQC	internal quality control
IR	incidence rate
MeaNS	Measles Nucleotide Surveillance Database
mEQA	molecular EQA
MeV	measles virus
MR	measles and rubella
MR LabNet	network of measles/rubella laboratories in the WHO European Region
MRLDMS	measles and rubella laboratory data management system
N-450	measles virus genotyping region: 450 nucleotides C-terminus of nucleoprotein gene
N.E.W WG	Next Generation and Extended Genome Sequencing Working Group
NGS	next-generation sequencing
NIS	newly independent states
NRL	national reference laboratory
NVC	national verification committee for measles and rubella elimination
OF	oral fluids
PCR	polymerase chain reaction
PHE	Public Health England
PIMs	potentially infectious materials
PRNT	plaque reduction neutralization test
PT	proficiency test
RKI	Robert Koch Institute
RNA	ribonucleic acid
RRL	regional reference laboratory
RubeNS	Rubella Nucleotide Surveillance Database
RuV	rubella virus
RVC	Regional Verification Commission for Measles and Rubella Elimination
SIA	supplemental immunization activity

SNL	sub-national laboratory
CDC	United States Centers for Disease Control and Prevention
WGS	whole genome sequencing
WSLH	Wisconsin State Laboratory of Hygiene
WT	wild-type

Executive summary

The 13th meeting of the Measles/Rubella Regional Reference Laboratories of the WHO European Region took place in Copenhagen, Denmark on 15- 16 March 2018.

Representatives of the following institutions/laboratories attended the meeting:

- European Regional Reference Laboratories (RRLs): Gabrichevsky Institute (Moscow), Luxembourg Institute of Health (Luxembourg) and Robert Koch Institute (Berlin);
- Global specialized laboratories (GSLs): Public Health England (London) and United States Centers for Disease Control and Prevention (CDC) (Atlanta)
- Regional Verification Commission for Measles and Rubella Elimination (RVC)
- WHO Regional Office for Europe (Regional Office) and WHO headquarters

The participants were updated on the progress of measles and rubella (MR) elimination at the global and regional levels and discussed regional issues and future plans of the network of measles/rubella laboratories in the WHO European Region (MR LabNet) for training, verification of elimination and publications. Based on the presentations and discussions, the participants agreed on a set of recommendations, included in section 3 (Recommendations) of this report.

1. Introduction

The Regional Office the Region coordinates a laboratory network of specialized centres that conduct diagnosis and surveillance for measles and rubella (MR LabNet). The MR LabNet was set up in 2002 and comprises 73 laboratories distributed across 50 out of the 53 Member States of the WHO European Region (the Region). Three RRLs in Berlin, Luxembourg and Moscow and a GSL in London supervise and coordinate national reference laboratories (NRLs) and sub-national laboratories (SNLs) and conduct assay development and implementation across the Region.

Reliable diagnosis and effective surveillance of MR become increasingly critical as the Region nears MR elimination. The Region's GSL and RRLs meet annually to exchange information, address issues, share achievements and discuss future directions to facilitate MR elimination in the Region. This report summarizes their 13th meeting, which took place on 15-16 March 2018, and closes with the resulting recommendations.

2. Sessions

Dr Myriam Ben Mamou, the Regional Laboratory Coordinator, opened the meeting and thanked participants for their work towards MR elimination MR. This Region's laboratories have played an essential role in this process and collaboration with them and WHO headquarters has been invaluable for the Regional Office.

Mr Robb Butler, Programme Manager of the Vaccine-preventable Diseases and Immunization programme expressed his gratitude to the MR LabNet and its important role in progress towards the MR elimination goal. The contribution of the laboratories in the establishment of well-performing surveillance systems is essential in the context of the European Vaccine Action Plan (EVAP). Laboratory data have provided more enlightening reports of MR circulation and informed decisions in the European Region and other WHO regions.

Despite improvements in surveillance in the Region, MR elimination remains elusive, with a 5-fold increase in measles cases in 2017 after an all-time low in 2016. It is important to continue promoting the programme among political leaders and health care professionals so that MR remain at the fore of policy makers and populations. As countries approach elimination, laboratory results gain relevance, being essential to prove the interruption of endemic MR. For this, the LabNet is of critical value to the region. Mr Robb Butler concluded his opening remarks by thanking the participants for their ongoing contribution to the MR elimination programme, the LabNet for the essential role it has played towards the programme, the WHO HEADQUARTERS for collaboration and support and Dr Myriam Ben Mamou for her pivotal role in the coordination of the programme collaborators and in its promotion.

Session 1 – Global and regional updates

Chair: Dr Kevin Brown (United Kingdom GSL)

1.1. Regional update

Current measles and rubella situation

Dr Myriam Ben Mamou (WHO Regional Office for Europe)

The Region continues to focus on achieving the EVAP goals and objectives, including to implement and strengthen financially sustainable immunization programmes, meet vaccination coverage targets and eliminate MR in the region, with the ultimate goal of being a region free of vaccine-preventable diseases.

By the end of 2016, 32 countries had eliminated endemic measles (no continuous measles transmission chains for at least 36 months), 10 countries had interrupted measles (no continuous measles transmission chains for fewer than 36 months), and 9 still had endemic measles. Two countries submitted no reports on measles elimination. The same trend is observed for rubella, although more countries continued to have endemic transmission (n = 14), including countries whose submitted data was not of sufficient quality to prove rubella elimination. Two countries provided no reports on rubella elimination.

The number of measles cases in the Region has decreased drastically since the 1980s, reaching its lowest in 2016. However, there was a 5-fold increase in measles cases from 2016 to 2017. The countries with most measles cases were Romania, Italy and Ukraine, where 72% of the total 21 306 cases reported in the Region occurred. In terms of incidence rates (IRs), Romania led in 2017 with 95.2 cases/million habitants, followed by Tajikistan and Italy, both with IRs over 60 cases/million habitants. Four other countries had IRs over 10 cases/million habitants: Belgium, Bulgaria, Ukraine and Czech Republic. The vast majority of measles cases were reported in unvaccinated individuals.

The IR profiles vary from country to country, with mostly young children (<4 years old) affected in Italy and Romania, while in Ukraine the IR is higher among 1-9-year olds.

Pockets of under-vaccination can be due to inequitable access to immunization services, refusal to vaccinate or other reasons. Populations of concern with respect to suboptimal coverage rates include healthcare providers, specific religious groups, Roma, Traveller and anthroposophic communities. Educational and healthcare settings are important hubs of measles transmission, with over 8 countries reporting outbreaks in educational facilities and 12 recording nosocomial transmission in recent years. Healthcare providers have a 13-19-fold higher risk of acquiring a measles infection than the general population.

The number of rubella cases has declined by 99.8% since 2000. Poland reports the highest number of cases in the the Region, with432 cases in 2017, which represented 62% of all cases. This number is based on clinical confirmation of cases only.

The Regional Office is committed to helping Member States achieve high population immunity, enhanced training of healthcare providers and laboratory staff, and high-quality surveillance. These three pillars complement each other and will constitute the foundation required for MR elimination.

To improve vaccination coverage, it is necessary to address vaccination hesitancy and the limitations of immunization programmes. The investigation of causes for vaccine hesitancy would provide valuable insight and potentially indicate how to address them. The reasons that lead an individual or population to delay or refuse vaccination when it is offered are complex and context-specific, dependant on time, location and vaccine and will need to be identified and tackled in high-, middle- and low-income countries in different manners. Three major determinants of vaccine hesitancy are confidence (in the vaccine, system, authorities), convenience (geographical, timely and economical access) and complacency (when the risk of disease is perceived as low).

Limitations of immunization programmes include the lack of timely monitoring of immunization coverage, a limited ability to follow up unvaccinated individuals or groups, insufficient communication strategies, inadequate education of healthcare providers on vaccination, insufficient flexibility of vaccination services, issues with vaccine supply and delayed outbreak response. A number of activities is being implemented to address these limitations, such as implementation of vaccination registers with reminder systems, supplementary immunization activities (SIAs), tailoring of immunization programmes to meet the needs of susceptible populations, offering opportunity vaccination, including immunization in pre-school entry policies, promoting pre-travel vaccination and updating immunization policies for healthcare providers.

To achieve high-quality surveillance, there must be a focus on the reporting of suspected cases and carrying out epidemiological investigation of cases. Laboratory confirmation of cases must also be improved. Genotyping and sequencing data of circulating viruses must be improved, particularly for rubella. The guidelines for case investigation should be strengthened to promote the standardization of procedures.

To increase the level of knowledge about vaccination at all levels, medical and nursing curricula, as well as public education programmes should include more information on vaccination. Additionally,

healthcare providers should receive communication training and immunization should be incorporated into continuing professional development schemes.

In summary, significant progress has been made towards MR elimination, but some countries are still experiencing large nationwide outbreaks. A substantial number of countries is heading towards MR elimination but will need to improve surveillance and maintain immunization levels to reach the goal. This will require countries to take ownership, commit to closing immunity gaps and improve knowledge and training.

Brief MR LabNet update

Dr Myriam Ben Mamou (WHO Regional Office for Europe)

Routine activities undertaken by the Regional Office in 2017 included conducting the annual laboratory accreditation programme, supporting the regional verification process, capacity building, organization of meetings, supporting Member States with the procurement of reagents, advocating and promoting partnerships and contributing to the MR LabNet's activities. The Regional Office also conducted a review of the accreditation letter and checklist, organized external quality assessment (EQA) testing and conducted periodical and accreditation visits to laboratories in Belarus, Denmark, Italy, Serbia, Tajikistan, Turkmenistan and Ukraine. Late 2017, initial assessment visits were carried out in conjunction with WHO headquarters to laboratories in Montenegro and Switzerland, which officially joined the LabNet in 2018.

Of the 71 laboratories that participated in serology proficiency testing (PT) in 2017, all passed the assessment for both measles and rubella. All 56 laboratories that submitted samples for measles re-testing had good results. For rubella confirmatory testing 54 out of the 55 participating laboratories passed. However, not all laboratories are serology testing the required minimum of 50 specimens annually, with 10 out of 71 laboratories testing fewer samples. The results for the molecular EQA (mEQA) testing were less positive than for serology, with 21 out of 34 participating laboratories concluding the exercise successfully for all evaluated components, 12 failing in at least one component and 1 withdrawing from participation.

The timeliness and completeness of reporting are still suboptimal, with 77% of laboratories reporting surveillance results within 4 days, 42% reporting their results timely to WHO, and 62% doing so in a complete manner. Timeliness of reporting is an even bigger challenge in the communication of sequence data to the measles and rubella nucleotide surveillance databases (MeaNS and RubeNS, respectively), with less than half of laboratories doing so in the recommended 4 weeks. Overall, all 71 laboratories were accredited for serology testing, 33 of 34 laboratories for molecular detection and 23 of 34 for genotyping and sequencing.

Visits for capacity building and skills strengthening were carried out in Belgium (sequencing troubleshooting), Tajikistan (specimens collection in outbreaks for MR genotyping workshop) and Turkmenistan (refresher course on enzyme-linked immunosorbent assay (ELISA) and internal controls). Training was carried out at the London GSL for the Romanian and Spanish NRLs, at the Berlin RRL for the Polish NRL and at the Luxembourg RRL for the Turkish NRL. Inter-country workshops focusing on the verification of elimination were organized at the Regional Office in Copenhagen, Denmark, involving the national verification committees for measles and rubella

elimination (NVCs), epidemiologists and laboratories from the Balkans, Russia and newly independent states (NIS).

Procurement support from the Regional Office is essential to keep the MR LabNet supplied with ELISA reagents, FTA® cards and filter paper, EQA panels, United States Centers for Disease Control and Prevention (CDC) practice panels and molecular kits, and to contribute with sera for the Victorian Infectious Diseases Reference Laboratory's (VIDRL, Australia) production of proficiency panels. These activities are increasingly made difficult by cumbersome policies for cross-border shipment of specimens, reagents and EQA panels to some countries.

Dr Myriam Ben Mamou concluded her presentation by thanking all in the MR LabNet for their important contributions to MR elimination and WHO staff at its headquarters and Regional Office for their continuous support.

During the discussion that followed, it was suggested that there is increasing interest in Europe and worldwide for the issue of vaccine hesitancy, particularly the insufficient vaccination levels among healthcare providers, and greater collaboration among partners and stakeholders could benefit the elimination effort.

1.2. Update from Berlin RRL

Dr Sabine Santibanez (Berlin RRL)

In 2017, the Berlin RRL contributed to a special issue of the Journal of Clinical Microbiology and Infection in collaboration with the RRLs in London and Luxembourg and with the Regional Office. Professor Claude Muller and the journal's editor Professor Franz Allerberger contributed greatly to this publication.[1]

The Berlin RRL contributes to the Instand e.V. mEQA with viral material from its strain bank. The viruses are isolated, passaged, propagated and genotyped in the laboratory. Due to the recent outbreaks in Germany, many new strains are available for future mEQA rounds. Twelve rubella strains were provided by the CDC. The virus was passaged, propagated and the genotype and sequence data confirmed by the Berlin RRL. Three of these rubella strains were propagated for the current Instand e.V. panel.

The Berlin RRL performed measles virus (MeV) genotyping on behalf of the NRLs in Bulgaria, Czech Republic, Slovakia and Switzerland. Between 2003 and 2017, the Swiss laboratory submitted original specimen material, RNA or cDNA for genotyping. From 2018, genotyping is carried out by the University of Geneva. Bulgaria's NRL loads polymerase chain reaction (PCR) fragments generated using the CDC primers onto FTA® cards, allowing for successful genotyping in over 80% of samples. The NRLs of Czech Republic and Slovakia submit specimen material (throat or nasopharyngeal swabs) on FTA® cards. Approximately half of the PCR positive samples can be successfully genotyped. Since epidemiological and clinical case data were frequently incomplete for specimens submitted for genotyping, a new questionnaire was produced to distribute to NRLs and laboratories in other federal states of Germany.

[1] Santibanez S and al. Molecular surveillance of measles and rubella in the WHO European Region: new challenges in the elimination phase. Clin Microbiol Infect. 2017; 23:516-523.

A two-week training for NRL Poland staff was conducted at Berlin RRL on quantitative PCR and genotyping of MeV, and quantitative PCR of rubella virus (RuV). Although the laboratory conducts sequencing successfully, no real-time assay was available. Currently, rubella is the priority for the Poland NRL and the next step is implementation of real-time PCR for RuV.

Seven monoclonal antibodies were generated against the MeV Edmonston Zagreb vaccine strain and characterized by a former PhD student in the laboratory, Kerstin Beer, in her dissertation in 2012. Seven hybridomas-producing antibodies that neutralized all wild-type MeV (n=2) or discriminated between MV variants (n=5) were thawed in 2017 and cultivated for sequencing by Absolute Antibody in the United Kingdom. The variable domains of heavy and light chains were sequenced for each of the monoclonal antibodies. The generation of chimeric human IgG for two antibodies will be attempted next.

1.3. Update from Luxembourg RRL

Dr Judith Hübschen (Luxembourg RRL)

In 2017, there was a high measles incidence rate in Luxembourg, with four cases reported, three of which were imported and one import-related. The sequence data were essential in complementing epidemiology data. One imported and the import-related case were two brothers who were against vaccination.

After Montenegro joined the MR LabNet, the number of NRLs in RRL Luxembourg's constituency increased to 22.

Most retesting samples sent to the Luxembourg RRL are dry serum specimens, but liquid sera, dried blood spots (DBS) and oral fluids (OFs) are also received. Many reminders are required to get feedback on shipment date and sample selection. Three countries had major discrepancies due to incorrect result interpretation, issues with sample submission and repeated freeze-thawing of specimens.

The results for sera proficiency panel testing were good, with point deductions given only for single mistakes and failure to use in-house controls. During the exercise, feedback revealed that the possibility to copy and paste data from Excel for data submission would be useful. The shipment of mEQA panels directly to each NRL worked very well. It was suggested that the MeaNS EQA submission webpage could include a listing function and automatic WHO name assignation, given that the live website has these functions.

Approximately 370 samples were received from eight different NRLs for molecular detection, genotyping and sequencing of additional regions of the MeV genome. Accreditation visits were conducted to the NRLs in Belgium, Serbia and Ukraine. The former head of the NRL in Turkey was trained in Luxembourg in cell and MeV culture.

Other activities of the Luxembourg RRL included providing support to NRLs in its constituency. Laboratory material, cells and ELISA kits were provided to the NRLs of Bosnia and Herzegovina, France, Turkey and Ukraine. In 2018, two urgent requests for ELISA kits by Albania and the former Yugoslav Republic of Macedonia were answered. WHO sera, early 2017 molecular proficiency panels, CDC PCR, genotyping and panel practice kits, filter papers and FTA® elute micro cards were also shipped to other laboratories. The Luxembourg RRL published reports on the development and

validation of a TaqMan assay for RuV detection and on a mumps outbreak in Israel and contributed to two WHO Regional Office publications on MR molecular surveillance and laboratory diagnosis challenges in elimination settings. Other publications included a report on the immunization needs of newcomers to Luxembourg and two articles on basic measles virology. Professor Claude Muller was nominated as one of the ten members of the Mediterranean Regional Verification Commission for Measles and Rubella Elimination.

1.4. Update from Moscow RRL

Dr Tamara Mamaeva (Moscow RRL)

The Russian Federation laboratory network includes 20 laboratories supervised by the Moscow RRL: 9 national laboratories and 11 sub-national laboratories (10 in Russian Federation and one in Kyrgyzstan).

Nine national laboratories were involved in confirmatory testing in 2017. The majority of samples were dried serum samples. Of the measles specimens tested for IgM, 45 were positive, most of them (n=41) from Tajikistan due to an ongoing outbreak. Only 6 of the 406 specimens tested for rubella IgM were positive. There was 100% concordance in all confirmatory testing. The most commonly used test kit was the Siemens kit, with Kazakhstan and Uzbekistan using Vector Best.

Confirmatory testing for subnational laboratories also produced full concordance for most laboratories, with a single discordance for the SNL in Krasnoyarsk. All laboratories use the Vector Best for measles IgM testing, while the Ecolab kit was the preferred one for rubella IgM testing, with only the SNLs of Perm and Vladivostok using the Vector Best kit. Positive cases were mostly from regions that experienced outbreaks.

Twenty laboratories participated in proficiency testing, all obtaining fully correct results. However, 30% of laboratories made some mistakes in filling out the data at submission, particularly the validation criteria. The data input forms are not adapted for in-house controls. Fewer laboratories are having difficulties with cut-off values and positive in-house controls. A couple of laboratories used domestic test kits past the expiry date in 2017. Although these kits are quite stable, the results were rejected.

Given that there are different test kits used across Russian laboratories with different specificities and outputs, a comparison between Vector Best and Siemens kits was carried out using 58 serum specimens sent by Tajikistan in 2017. All eleven negative results obtained with Vector Best were also negative on Siemens. However, while there were 47 positive specimens with Vector Best, 44 were positive and 3 negative with Siemens. The 47 Vector Best positive samples were IgG avidity tested. 39 had low avidity, while 8 had high avidity. All patients were adults and considered to have a secondary immune response.

The measles IR has decreased since 2014, being at 0.49 cases per 100 000 of the population in 2017. The rubella incidence rate is currently very low, with only 5 cases reported last year. Despite the low IRs, a high number of cases are still being examined in laboratories as all exanthema cases are submitted for testing. Over 4000 specimens have been tested for measles and rubella, but the confirmation rate is close to 0% for both.

In summary, all 20 laboratories participating in ELISA proficiency testing scored at least 90%. The 3 laboratories participating in the measles and 2 in the rubella Instand e.V. molecular panel exercise passed. All 20 laboratories tested more than the 50 required specimens. One of the participating laboratories obtained 98.5% concordance in confirmatory testing, while the remaining 19 laboratories achieved 100% concordance. 1055 specimens were submitted for measles and 961 for rubella confirmatory testing; 81.1% measles samples and 98.0% rubella specimens were negative. 71.5% of specimens submitted for confirmatory testing were dried sera. All 20 laboratories are using positive in-house controls.

A joint on-site accreditation visit conducted in Turkmenistan in March 2017 included ELISA and positive in-house controls-use training. In 2018, joint accreditation visits with Moscow RRL representative(s) are planned to Kyrgyzstan's NRL in Bishkek and SNL in Osh as well as workshops for laboratory staff. Accreditation visits to the SNLs in Krasnoyarsk and Moscow are planned for August, with a workshop also planned for the laboratory staff of the first. Finally, the data from 2016–2017 is being collected to analyse and summarize the use of ELISA internal laboratory controls.

During the discussion following the presentation the participants talked about the fact that testing of a high number of negative samples is now assessing specificity rather than sensitivity. With an increasing number of countries achieving lower IRs, it will be relevant to discuss the objectives of proficiency testing in the context of elimination.

1.5. Update from London GSL

Dr Kevin Brown (United Kingdom GSL)

Wales, Scotland and Northern Ireland have their own systems, but report through Public Health England (PHE). However, it is sometimes difficult to obtain samples. Further restructuring is ongoing with the formation of the National Infection Service, which since 10 April 2018 has had a topic-specific structure, where the laboratories are commissioned to carry out the testing by the heads of division, who hold the budget. Currently, the MR laboratory is under renovation and has lost some key staff. It successfully obtained ISO 15689 after a very time-consuming process.

In response to an increase in the number of measles cases in 2013, an effective vaccine campaign was conducted. In 2016 measles IR was low, but there were some measles cases associated with festivals and young adults. Following three years of no endemic measles transmission in the UK, elimination was announced.

However, a new outbreak of measles started in the West Country in 2017, affecting patients of all ages and particularly those less than 4 years old. There have been 57 imported and 288 import-related cases so far. 24 of the 25 identified chains of transmission have been genotyped and most belong to the D8 genotype. Most importations were from Romania and came into different parts of the country. Given that they were of identical strains, it will be difficult to prove that cases were part of multiple chains of transmission. The United Kingdom GSL is currently looking into the use of the MeV MF-NCR sequences to distinguish importations. 359 MeV MF-NCR sequences have been obtained so far and an additional 40 Romanian samples have been sequenced with the collaboration of Romania NRL staff.

Three measles deaths occurred in 2017 in the United Kingdom. The first was a 28-year-old HIV-positive patient who presented with encephalitis of unknown aetiology with a history of travel to the Philippines. Patient samples were sent to PHE for intrathecal antibody testing and after some signal was detected for measles antibody, repeat samples were requested. The re-testing of samples that had been initially submitted for John Cunningham virus testing revealed that measles virus of the same strain that circulated in the Philippines 2-3 years prior was present in the CSF. Despite treatment with ribavirin, the patient subsequently died and a brain biopsy revealed measles inclusion body encephalitis was the cause of death.

The second case was of a 26-year-old female with encephalitis that had been diagnosed as acute disseminated encephalomyelitis (ADEM). The patient was a healthcare provider that had received the hepatitis B vaccine two days before becoming unwell. As her condition deteriorated, the patient was diagnosed as immunocompromised. After a cluster of measles cases was reported in the same hospital, a throat swab was PCR tested for measles and found positive. Following further deterioration, the patient perished. Post-mortem brain and CSF samples were sent to PHE and confirmed MeV PCR-positive. Further analysis revealed that the patient was the index case in the nosocomial transmission chain of MeV D8 genotype, although the source of the patient's infection is not clear.

The final 2017 measles death in the United Kingdom was of a 5-year-old patient. There was a three-month history of increasing mental deterioration. Specimens were tested for intrathecal antibodies, revealing a high index of measles antibodies. The patient had contracted measles at 9 months old during the 2013 outbreak in Wales, but there was no laboratory confirmation. The patient had received the MMR vaccine afterwards. SSPE was confirmed.

Since April 2016, the screening of all pregnant women's samples for rubella IgG was stopped and advice given to women on the reporting of rash illness. Additionally, there is a recommendation to vaccinate unvaccinated pregnant women post-partum. Training for midwives, screening and immunization leads, and virologists was conducted and the guidelines on rash and pregnancy are being re-written. There has been a slight increase in the number of IgM samples from pregnant women aged between 15 and 50 since the cessation of the programme. Six cases of rubella were detected in 2017, 4 of which were laboratory confirmed. Two occurred in pregnancy and resulted in foetal loss. There is no evidence of increased risk due to the cessation of the screening programme.

The new guidelines place the emphasis on the need for surveillance, using serology and not solely PCR and updating of the post-exposure prophylaxis. A measles and rubella elimination group (MAREG) has been formed to develop and write the United Kingdom's strategy document for elimination. It addresses the differential testing in devolved administration and targets under-vaccinated groups. Its purpose is to re-focus efforts on maintaining elimination goals and to renew the commitment from stakeholders across the United Kingdom.

The RRL in Ireland has underwent an accreditation visit in August 2016. Although accreditation was granted, some problems were identified. A significant number of 2015 samples sent in for retesting could not be confirmed at Colindale. All but one of the 23 measles serum samples sent for retesting from Ireland were confirmed at Colindale. All OF samples were confirmed. For rubella, 25 out of 26 retest rubella serum samples obtained concordant results at PHE. All rubella OF samples were confirmed at the GSL. No samples were received in 2017, but some were received in the two weeks

prior to the meeting. Further review of the SOP for OF processing indicated that the laboratory was not using the appropriate diluent. The diluent used with OFs must contain 3-10% fetal calf serum (FCS) and 0.2-0.5% Tween 20, otherwise testing may yield false positive results. The SOP will be reviewed and samples sent for retesting.

An issue has been identified with the MicroImmune IgM, specifically with the cut-off values used for serum and OF samples, which leads to false positive results for OFs. This has not been addressed yet, having only been corrected in the English version of the insert. Clin-tech have modified their English kit insert, but not flagged up the change. The method for elution described is not that used at PHE or that used for its validation. More recently, a significant decrease in the optical density (OD) of the internal quality control (IQC) used at PHE with the MicroImmune assay has been detected and flagged up to MicroImmune. It correlates to a change in the antigen used by the company. Further work is being carried out to understand the problem.

The main issues and concerns for the London GSL are in the receipt of samples for retesting from Ireland, dealing with increasing political wishes for devolution (both Scotland and Wales are now carrying out their own PCR testing). The roll-out of measles PCR raises concerns for the rash/fever surveillance service as laboratory and epidemiologists are not always informed. There are continuing concerns over the MicroImmune assay and the lack of progress in their resolution. Finally, the restructuring of the National Infection Service means it is still unclear how well the commissioning of the laboratory testing will work.

1.6. Update from Atlanta GSL

Dr Paul Rota (Atlanta GSL)

There were 120 measles cases in the United States in 2017, most in individuals that were unvaccinated or with unknown vaccination records with a history of travel abroad; 97% of cases were import-associated. 13 of the 19 imported measles cases were United States residents. 55 cases were genotyped as B3, 23 as D8 and 2 as H1.

Seven outbreaks were identified, the largest in a Somali community in Minnesota with vaccination coverage between 30 and 40% due to concerns about a link between measles vaccine and autism. In response to the outbreak, 50 000 additional vaccine doses were administered to the community. As a result, many post-vaccination samples have been submitted for ruling out wild-type (WT) measles infection. Most specimens were associated with reactions to the first MMR dose.

N-450 sequence analysis revealed that measles B3 genotype cases were related to the named strains MVs/Dublin.IRL/8.16/, MVs/Kabul.AFG/20.14/3 and MVs/Kansas.USA/1.12/. Measles D8 cases derived from MVi/Hulu Langat.MYS/26.11/, MVs/Osaka.JPN/29.15/ and MVs/Victoria.AUS/6.11/. The genotype H1 cases shared the MVs/Hong Kong.CHN/49.12/ sequence. Sequences are identical to others reported in Afghanistan, Bangladesh, Cambodia, Dubai, Germany, India, Italy, Myanmar, Romania, Somalia and Thailand.

A measles outbreak has been ongoing in Venezuela for a few months. A poor medical assistance system leads patients to travel abroad to seek medical attention, raising concerns over neighbouring countries' maintenance of elimination status. The term elimination is sometimes misinterpreted, leading efforts towards control and vaccination to be lowered in some regions. Emphasis should be

put on elimination of endemic measles instead, as physicians are questioning why they should be looking for measles if it has been eliminated.

The laboratory has been working on the validation of the measles vaccine real-time PCR assay (MeVA). This assay is specific for MeV vaccine strains, but its sensitivity is lower than the PCR used for WT strains by 2 to 3 Ct values. Specimens must be tested using both assays: vaccine strains will be positive on both assays, while WT strains will only be detected in the standard PCR. The MeVA test does not work with the Invitrogen kit. In order to validate the assay, a panel of specimens was shared across laboratories. The results and interpretation were compared across laboratories and the report format was agreed on.

Of the 21 specimens composing the panel, 16-17 were previously tested diagnostic samples and 4-5 were lysates of cell culture isolates. The specimens were throat and nasopharyngeal (NP) swabs and urine samples. They included 8 MeV WT strains, 10 MeV vaccine samples and 3 negative samples. Due to volume limitations, not all laboratories could test each sample, but all specimens were tested by at least two laboratories.

In general, the assay performs very well. Two workflows for initial roll-out are being considered so that guidance can be provided to the states:

1) MeV and MeVA assays should be carried out in parallel and, in the initial phase, all MeVA positive specimens are sequenced.
2) Only the standard MeV PCR is routinely performed. The MeVA assay is carried out when a vaccine reaction is suspected. All positive samples in the latter are sequenced in the initial phase.

A potential consequence of the availability of the MeVA assay is that specimens that would not have otherwise been considered for testing due to the absence of circulating measles may now be submitted, which would increase workload and expense.

Dr Joe Icenogle (United States GSL)

There is a paucity of information on the burden of congenital rubella syndrome (CRS). It was recognized in 2015 that there is a 30% mortality rate associated with CRS in the first two years of life. The expected lifetime costs from adverse health outcomes per CRS case in high-income countries is now estimated at over US$ 930 000.

Although endemic CRS has been eliminated in the Americas Region of the WHO (AMR), efforts continue on the maintenance of elimination. Understanding persistent RuV replication in CRS cases and the association of Fuch's uveitis and granuloma in primary immune deficient patients in the United States with RuV vaccine strains, characterisation of the genetic diversity of circulating RuV and facilitating detection and sequencing of RuV in other laboratories in the WHO MR LabNet are other continuing activities in the United States GSL.

Of the six sequences obtained for RuV in the United States in 2017, four were obtained from imported CRS cases and one from a persistent infection of the eye in a patient with Fuch's uveitis syndrome. Three strains belonged to genotype 2B, two to 1G and one to 1E. Half of these cases had been exported from Nigeria. The number of CRS cases reported is very close to the number of rubella imported cases, suggesting that the surveillance system is effective for CRS.

In November 2017, an unvaccinated asymptomatic American returned to the United States from India. His unvaccinated pregnant sister had contact with him and developed a rash and fever two weeks later. Serum samples from both siblings were taken and serology testing indicated recent rubella infection. The samples were taken too late for PCR testing. Given that the mother was infected in the second trimester of pregnancy, it was continued and samples will be collected at birth.

A study into maternal immunologic correlates for CRS was carried out in Uganda. The study included mothers birthing healthy and mothers birthing CRS babies and initially looked into RuV-specific IgG antibody titres and avidity, neutralizing antibody levels, RuV protein-specific IgG (by western blot) and anti-capsid IgG antibody titres (by C-ELISA). The initial results were published in the Journal of Infectious Diseases in 2015 and indicated that the western blot and C-ELISA assays were good in separating CRS cases and controls. Women who delivered CRS babies were observed to have higher IgG, neutralization antibody and anti-capsid IgG titres and lower IgG avidity. The laboratory is currently working on an ELISA to replace the western blot assay.

Dr Bettina Bankamp (United States GSL)

In 2017, the United States GSL supervized the production and shipment (by the Wisconsin State Laboratory of Hygiene (WSLH) of 49 mEQA proficiency panels that were distributed to participating laboratories in all WHO regions, except the European Region (panels provided by Instand e.V.). Shipments to the African Region and the Region of the Americas were delivered directly to the laboratories, while the Eastern Mediterranean, South-East Asia and Western Pacific regions received bulk shipments to the WHO regional offices. Report forms were e-mailed by the CDC to the laboratories after receipt of shipment information from the WSLH.

The reporting of sequencing results was done through MeaNS and RubeNS mEQA sites, which required all laboratories to have access to the sites. Laboratories were requested to upload chromatograms and text files with the sequences obtained and fill out onset date and WHO name. The genotype can be generated by MeaNS or RubeNS. 100% accuracy in the results reported is expected, with individual nucleotide errors leading to a retest score.

So far, 42 results have been received for the 49 panels shipped and more responses are still expected. Two laboratories in the Western Pacific Region, one in the Eastern Mediterranean and one in the African Region were required to retest. One laboratory in the Eastern Mediterranean Region failed in genotyping proficiency. Further information or the upload to MeaNS is still being awaited from 5 laboratories. Nine of the 33 laboratories that submitted results through MeaNS had issues with the submission process.

Forty-two of the participating laboratories have already submitted their RuV mEQA results. Two laboratories in the Western Pacific Region, two in the South-East Asia Region and one in Region of the Americas have to retest. One laboratory in the Eastern Mediterranean Region failed in RuV genotyping. Fourteen of the 33 laboratories that submitted their results through RubeNS reported issues with the process. Some laboratories used both real-time and end-point diagnostic assays, making it unclear whether they understand how each assay should be used.

To obtain a pass in the mEQA exercise, laboratories must satisfy all the following criteria:

- correct detection of MeV or RuV RNA (or negative reaction) in all samples;
- no false positive/negative results;
- adequate positive and negative controls;
- genotype correctly identified for each positive sample;
- sequence covers the entire sequencing windows for measles (N-450) and rubella (739nt);
- no nucleotide errors.

When identified issues can be solved by repeating the test and without further training (e.g., one sample with low sequence quality), laboratories are issued a retest result. When the problem identified requires training or a change in workflow (e.g., invalid real-time assay), laboratories are issued a fail result. Issues with WHO names or with MeaNS/RubeNS reporting will not lead to retests but will be mentioned in the comments section.

There were issues with the stability of the RuV panel sample 4 in FTA® cards, which meant that some assays were unable to amplify it. In response to this, a statement was sent out identifying this sample as optional this year. In the future, FTA® samples will be submitted to stability testing at two temperatures for one and two weeks prior to shipment. This will require an earlier selection of the panel samples (i.e., April or May rather than July or August).

The CDC proposes to provide and assess the mEQA panel and results to all WHO regions, including the European Region, in order to harmonize the process. This would relieve the workload of the Robert Koch Institute (RKI) and provide equal evaluation criteria to all participating laboratories. Instand e.V. and the RKI would continue to provide panels and evaluation for non-WHO mEQA ring trials.

During the discussion that followed, it was agreed that the standardization of panels and evaluation were important for the harmonization of proficiency testing and accreditation across the MR LabNet. As such, the US GSL will coordinate with WSLH in the provision of panels for all WHO regions in future mEQA exercises.

1.7. Brief update from WHO headquarters, including laboratory manual and serosurveys guidelines

Dr Mick Mulders (WHO headquarters)

Approximately the same number of Member States reported 20% fewer measles cases to the WHO from 2016 to 2017. The region reporting the most measles cases throughout 2017 was the South-East Asia Region, which is still trying to achieve elimination of endemic transmission. In 2018 the number of cases reported in the European Region has increased. Since 2014 there has been a marked decrease in the number of measles cases reported by the Western Pacific Region, which is mainly attributed to the interruption of endemic measles transmission in China, an impressive achievement. Some cases have been reported in the Region of the Americas, mostly associated with an outbreak in Venezuela.

The three countries with most measles cases (to date in 2018 at the time of the meeting) were India (n = 53 836), Nigeria (n = 10 571) and Ukraine (n = 7 772). The three top countries in terms of IR (in cases/100 000 population) were Gabon (IR = 400.55), Liberia (IR = 187.70) and Serbia (IR = 181.74). After a large measles outbreak in 2014, the Philippines is again seeing an increased number of cases in 2018.

The Global Measles and Rubella Laboratory Network (GMRLN) is expanding, with the Chinese Center for Disease Control and Prevention to become a new GSL, 39 new laboratories joining in the WHO Southeast Asia Region, 2 joining in the European Region and the possibility of expansion of subnational networks in the Democratic Republic of the Congo and Pakistan. Conversely, there are now 2 fewer SNLs in Colombia.

There are still discrepancies in the monthly and yearly reporting of IgM testing for measles, but there are fewer differences in the reporting of rubella IgM testing. The number of MeV and RuV sequences reported to MeaNS and RubeNS respectively has seen an increasing trend, with approximately 3500 measles and 150 rubella sequences reported in 2017. B3, D4, D8, D9 and H1 are the only circulating measles genotypes. Although genotype G3 has not been reported since 2015, it is not clear if it has been eliminated from Indonesia. In the Region, B3 and D8 are the dominating genotypes, with a few import cases of other genotypes reported.

The surveillance data for rubella is lower in quality than for measles. The same number of Member States reported 16 000 rubella cases in 2017, a decrease of 28% from 2016. Encouragingly, the number of laboratory-confirmed cases increased by 43% from 2016 to 2017 (n = 12 758). The South-east Asia Region (n = 7539), followed by the African Region (n = 4562) and Western Pacific Region (n = 2282) reported the most rubella cases in 2017, with the Western Pacific Region having seen a drastic reduction in cases since 2015.

The number of rubella cases that have been clinically diagnosed, epi-linked or laboratory confirmed has declined from approximately 150 a month in early 2016 to approximately 50 a month currently. The predominant WT RuV strains in circulation worldwide belong to genotype 2B.

The GMRLN continues working on programme strategy, sequence reporting (MeaNS and RubeNS), assay development, investigating vaccine failure, assessing the usefulness of extended sequencing windows for MR, proficiency assessment and accreditation, and training, with 10 working groups looking into the multiple facets of the LabNet work. A strategy working group is looking into the streamlining and prioritization of responses to requests, a new measles point of care test (POCT) is being trialled in the African Region, new sero-surveillance guidelines are almost completed and a new laboratory manual is completed and will go live once feedback is received from the GSLs and RRLs.

The new format of the laboratory manual makes it possible for laboratories to download and print the desired chapters and will facilitate regular updates and corrections. The date of the last revision will be displayed at the bottom of the screen so that laboratories can verify whether they are in possession of the latest version.

Continuing challenges include high staff turnover both at the WHO and laboratory level, which raises difficulties with training and expertise and impacts laboratories' performance; the provision of kits to priority laboratories is funded by a single donor and delayed by WHO procurement procedures; the shipment of proficiency panels and samples across borders presents complications associated with bureaucracy and cross-border controls and policies.

Further commitment to training via workshops, e-learning and the appointment of laboratory coordinators for the Eastern Mediterranean and African regions aims to ensure high levels of

technical expertise throughout the network. Serology and mEQA proficiency testing (PT), as well as accreditation aim to maintain high levels of proficiency.

1.8. Update on polio containment

Dr Maria Iakovenko (WHO polio programme)

The 2013–2018 strategic plan for polio eradication comprises four dimensions: 1) eliminate the risk of WT poliovirus (PV) transmission; 2) effective epidemiological surveillance of PV; 3) cessation of oral polio vaccine (OPV) to eliminate the risks of vaccine-associated paralytic poliomyelitis (VAPP) and vaccine-derived PV (VDPV); 4) implement PV safe-handling and containment measures.

The current PV containment efforts are based on the World Health Assembly (WHA) 68.3 resolution on poliomyelitis of May 2015, a report to the SAGE meeting in December 2015, the WHO global action plan to minimize PV facility-associated risk (GAPIII) and the containment certification scheme (CCS). Phase I of GAPIII is the preparation for PV type 2 (PV2) containment and has been accelerated since PV2 eradication in 2015. Phase II will be in place until types 1 and 3 are eradicated and consists of PV2 containment. Once the other polio types are eradicated, phase III will be implemented to ensure containment of all polioviruses.

To complete phase I, each Member State must conduct a PV inventory, destroy non-needed PV2 materials, designate a PV-essential facility (PEF) if PV2 materials are still held, transfer PV2 materials into a PEF, establish a National Authority for Containment (NAC) to provide accreditation, certification and confirm that PEFs meet requirements of containment, and prepare for PEF certification.

Currently, 28 countries globally plan to retain PV materials in 91 designated PEFs. This number of PEFs is too high and WHO is trying to restrict them to those that serve essential functions such as vaccine production or storage. The majority of PV vaccine producers are located in the European Region, where 12 countries intend to designate 39 PEFs. Of these, 6 countries host 12 manufacturing sites.

Some challenges must be overcome prior to the initiation of GAPIII certification. These include the absence of appropriate legislation in some PEF countries (including those hosting manufacturing sites), lack of understanding of the NAC role, insufficient expertise of CCS auditors in many countries, and lack of understanding of PEF requirements.

In order to identify and isolate potentially infectious materials (PIMs), laboratories must be made aware of the potential presence of PVs in some types of clinical materials and Member States should make a decision on whether they need additional containment to be implemented.

Once PV eradication is complete, laboratories will be the only PV reservoirs. The risk of PEFs is addressed in GAPIII in 2015 and WHO has published guidance on PIM materials. All faecal, environmental, respiratory secretion samples and products of PV-permissive cell lines are PIMs and, as such, laboratories working with agents such as rotavirus, hepatitis A and E virus, influenza, MeV or other enteric and respiratory agents must conduct an inventory of their PIMs. Guidance for non-PV facilities to minimize risk of sample collections containing PIMs has been issued.

PV risk is defined as the chance or possibility of transmitting PV to the laboratory worker and/or the community. It is a factor of multiple elements such as the nature of PIM collections (when and where they were collected, and sample type), the characteristics of potential PV (minimum infectious dose, transmissibility, route of infection and stability), laboratory hazards present (inoculation of PV-permissive cells and aerosol-producing procedures) and susceptibility of laboratory workers or community (non-immune, inactivated polio vaccine (IPV) or OPV recipient, population immunity levels).

Collections with potential for WT PV and/or circulating vaccine-derived poliovirus are considered high risk and will need to be kept in a PEF. When there is potential for OPV/Sabin vaccine PV, samples will be classified in moderate (faecal or concentrated sewage samples amplified in PV-permissive cells; extracted nucleic acid transfected into permissive cells), low (samples as the previous with no use of permissive cells) or lowest (throat samples with no use of permissive cells and non-transfected nucleic acid). CSF, blood and serum or inactivated PIMs are classified as non-PIM.

To mitigate risk, laboratories will need to declare PIMs and limit access to them, follow good laboratory practices, conduct risk assessments for specific processes in use, immunize staff against PV, submit to accreditation at a national or international quality standard and ensure that staff understand the risk associated with work with PIMs.

During the discussion that followed, participants voiced concerns over the fact that there is no accepted method to prove that samples do not contain PV and that given the extreme rarity of laboratory-acquired polio infections it would maybe be preferable to simply immunize laboratory workers.

Session 2 – Accreditation issues

Chair: Prof Claude Muller (Luxembourg RRL)

2.1. Revised accreditation checklist

Dr Mick Mulders (WHO headquarters)

The checklist used for accreditation of WHO laboratories has been updated to better reflect the needs of assessors and laboratories. The new checklist is now divided into four sections, the first of which is “General review and overall findings” and must be completed for all laboratories. Sections 2, 3 and 4 are completed only if the laboratory carries out serology, molecular or virus isolation, respectively. Each section is composed of two parts: the first is “Profile or performance” and should be completed by the laboratory prior to the accreditation visit. The second is “Laboratory operating procedures and work practices” and will be completed by the assessors during the accreditation visit.

These major changes aim to cut redundancy by eliminating questions that were asked in both parts and capture the main capacity, performance indicators and needs of the laboratory in part I (required for desk review). By splitting the accreditation checklist into four sections, laboratories and assessors are encouraged to focus only on the activities conducted in the laboratory. If the latter solely carries out serology testing, only sections 1 and 2 must be completed, for instance. Finally, the scoring methodology on part II has been harmonized so that there are 100 points attributed in each

section. If all sections are filled out, the laboratory can score up to 400 points. The criteria evaluated for accreditation remain the same.

Following Dr Mulders' overview of the new document the participants agreed that splitting the checklist into 4 sections is helpful and suggested further modifications, such as taking into consideration space for each dimension of work as, for example, there might be enough storage space for molecular but not serology samples; and using consistent terminology so that the information required is clear. It was pointed out that the digital track of results between instrument and reporting system will also need to be taken into account. It was also suggested that part II should be filled in with yes/no by the laboratory prior to the visit so that all necessary documentation is prepared prior to the accreditation visit.

There were also some concerns about the timing of accreditation visits given that many laboratories will not have all the data available at the time that the visits are conducted. However, WHO headquarters and the Regional Office pointed out that this timing is necessary due to the additional workload that would come from separating accreditation and verification of elimination procedures.

2.2. Accreditation review for 2019: preliminary outcomes and planned accreditation visits

Dr Myriam Ben Mamou (WHO Regional Office for Europe)

Seventy-two laboratories participated in the serology proficiency-testing scheme in 2017. Two of these are new to the MR LabNet: the NRLs in Montenegro and Switzerland. The results from the NRL in the Yugoslav Republic of Macedonia were still pending. One SNL failed the first panel, due to data entry issues, but passed when a new panel was sent out. Sixty-five out of the 71 laboratories that have submitted their results had a full score on the first part of the proficiency panel. Fifty-seven of 71 had a full score in the second part. All laboratories passed the proficiency test, 50 of them with full scores. For the rubella proficiency panel, 70 out of 71 laboratories obtained a full score in the first part and 53 in the second part. All laboratories passed the rubella proficiency testing, 52 of which with full scores.

The data collection for IgM retesting was almost concluded, with data from only a couple of laboratories pending. A recurrent issue is that some laboratories are still testing a very limited number of suspected cases, below the 50 specimens per year recommended by WHO. Another concern is that in some Member States rubella testing is carried out in the country, but not at the NRL.

Fifty-three completed accreditation checklists were received from the 73 laboratories in the Region and they were being reviewed. EQA results will be carefully revised and laboratories that had problems in the exercise will be offered support and training. Between July and August, accreditation letters were to be sent to ministries of health, including a summary of the findings and recommendations. Accreditation visits planned for 2019 include France (Caen, Villejuif) and Montenegro. Visits to Kyrgyzstan (Bishkek, Osh), Greece, Hungary, Norway, Turkey (Ankara and Gaziantep) and the Moscow RRL were also being arranged or considered.

2.3. Outcomes of mEQA round 3

Preliminary results

Dr Myriam Ben Mamou (WHO Regional Office for Europe)

Thirty-six laboratories participated in the mEQA scheme in 2017, up by 3 from 2016. For measles, 34 laboratories signed up for the detection and 30 for the sequencing exercise. For rubella, 32 underwent detection and 17 sequencing proficiency testing.

The fraction of laboratories that passed all the components they signed up for was 75%, up by more than ten percentage points from 2016. Nine laboratories failed on one or more components of the test. 97.1% of the laboratories passed the measles detection, 86.7% the measles sequencing, 90.6% the rubella detection and 76.5% the rubella sequencing component.

Some laboratories appeared to have improved in this third round of the mEQA exercise, obtaining pass scores where they had previously failed, while others performed worse than in the two previous mEQA rounds. Laboratories that had trouble in this year's proficiency test will be offered support and training by the respective RRL and the Regional Office.

The collaboration between the Regional Office and Instand e.V. had been productive, but also challenging. The lack of flexibility in the timeline for the distribution of panels and publication of results caused issues; the need for the genotyping and sequence analysis to be carried out by the MR LabNet substantially increased the workload of PHE and RKI and the lack of standardization and harmoniation between Instand e.V. and the CDC proficiency panels complicates the proficiency scheme procedure.

Performance of mEQA websites

Dr Kevin Brown (United Kingdom GSL)

David Williams is now the Virus Reference Department bioinformatician in charge of MeaNS and RubeNS. Due to the introduction of many modifications to MeaNS since its introduction, the code is increasingly difficult to manage. Additionally, there are issues with the automatic import of GenBank sequences due to WHO names not being harmonized in the two databases leading to duplicate entries in MeaNS.

To address these problems, both nucleotide surveillance sites will be rebuilt in the form of a modular platform using the python language and documented code. The mEQA websites used for MeV and RuV sequences served as a pilot for some of the ideas for the new databases. However, other local priorities such as UKAS accreditation took precedence to this work. Additionally, continuing changes in IT protocols and a lack of commitment from senior staff to the LabNet have delayed further progress.

Thirty-one laboratories in the Region and 64 worldwide made their measles mEQA results submission through the trial website, with 237 and 518 chromatograms uploaded by the Regional Office and in total, respectively. For the RuV mEQA there were 19 submissions in the Region and 52 worldwide, corresponding to 220 and 690 chromatograms, respectively.

An issue that was identified with the websites is that if the WHO name format is incorrect, the database automatically produces a name and this is sometimes too distant from the intended name. Some laboratories submitted good-quality chromatograms, but incorrect sequences (e.g., antisense sequence, unedited trace analyser output). Laboratories that had this type of issue in their results will be re-trained in sequence analyses and all laboratories were reminded that they need to look at their sequences prior to submission.

The 2017 mEQA exercise provided a very good opportunity to test the future MeaNS and RubeNS databases and delivered useful learning outcomes for their future development. Given that many laboratories used these websites to submit their mEQA results, the user lists for MeaNS and RubeNS are now more exhaustive and will be transferred to the rebuilt databases when they are completed. Some changes will be introduced to the websites prior to the next mEQA round: entries will no longer be indexed by WHO name, and new download and naming conventions will be introduced to facilitate data analysis.

Categorizing training needs and modalities

Group discussion

Following the presentation on the mEQA exercise of 2017, the participants discussed training needs and how to address them. It was agreed that laboratories that had issues in sequence editing and interpretation could be helped remotely, either by their RRL or remote/online training. When the issues were in the quality of the chromatograms obtained, PCR amplicons could be sent to the relevant RRL so that issues can be identified and solutions proposed. If issues are in the procedure prior to sequencing, on-site training will have to be conducted. A session on molecular techniques could be offered coupled with the accreditation visit.

Finally, it was pointed out that when laboratories are obtaining false positive or false negative results, this must be considered a serious problem. Mistakes in the editing and submission of data reflect a lack of sufficient quality controls at the laboratory level and often reflect other quality problems.

2.4. Lessons learned from Instand-WHO collaboration and future directions for mEQA round 4

Group discussion

This discussion focused on the collaboration with Instand e.V. in the production and distribution of mEQA panels to the Regional Office. Although WHO is very grateful to Instand e.V. for the investment in this process, there have been issues as well that need to be considered.

Several factors add a layer of complexity to the scheme's coordination. The constant evolution of the scheme will also complicate standardization across all WHO regions if more than one entity is responsible for panel production and shipment.

The participants agreed that CDC should supervise the production and shipment of mEQA panels across all regions, including the European Region in order to standardize and simplify the process. The panels could be shipped to RRLs and then distributed at annual NRL meetings to decrease shipment costs; and the workload of sequence analysis and assessment could be distributed between RRLs and GSLs.

Session 3 – Regional verification process

Chair: Dr Paul Rota (United States GSL)

3.1. RVC update

Dr Irja Davidkin (RVC member)

The verification of elimination starts at the national level, with data on immunization and surveillance being compiled into the Annual Status Update (ASU) report. The NVC accepts and reviews the data and submits it to the RVC. An RVC meeting follows where it is decided whether to accept the NVC evaluation. The laboratories are the most important contributor to many of the indicators used by the RVC for their decision. These indicators include the rates of laboratory investigations, of discarded cases, of viral detection and the ability to identify the origin of infection.

Since 2012, modifications have been frequently introduced to the ASU form to clarify what is required. This is particularly challenging as the document must be employed by all Member States, which have very different systems in place, and include all the relevant information while being sufficiently flexible to adapt to each country's approach.

The first part of the 2017 ASU included the report of the NVC's conclusions and its response to the previous year's comments from the RVC. The second part dealt with crucial information of the core annual data and information discussed by the NVC and its secretariat. There are four sections to this second part: 1) the country's measles and rubella profiles for 2017; 2) an update on general programme activities; 3) the activities of the NVC and its secretariat and 4) additional data on measles, rubella and CRS.

Section 1 included all critical information on diseases epidemiology, surveillance and laboratory-related component of surveillance and was based on the existing routinely collected data (surveillance, laboratory testing, immunization monitoring) and any information from additional activities and/or additional data that countries can provide. The second section consisted of a list of all activities and events in the country in the year of reporting that have an impact on MR elimination. Section 3 focused on the work of the NVC, best practices and concerns, as well as an updated list of the relevant contacts. The final section included all additional information on measles, rubella and CRS, such as case distribution maps, genotype/lineage/sequence variant information, and the form for outbreak and SIA activities report.

The RVC is concerned with the still present immunity gaps and with insufficiently sensitive surveillance systems. It recognizes the necessity to optimize national operating procedures for epidemiological and laboratory information and to raise awareness to the importance of genetic information for the achievement of high-quality surveillance.

3.2. Preliminary feedback on using the revised ASU template

Group discussion

The revised ASU integrated feedback from the regional verification rounds, RVC, RRLs, GSLs and the 17th GMRLN meeting. The revised form grouped all laboratory performance information requested into one section and aimed to simplify laboratory data collection and ensure that no cases were missed due to discrepancies in the data reported at the NVC level. A fourth category was created for

those laboratories which have obtained accreditation at the ISO15189 national level and support tools added to MeaNS for the better visualization of the chains of transmission reported.

Following the walk through the new ASU form, participants suggested that concepts such as outbreak and chain of transmission should be defined in an annex and that countries should specify the definitions used at the national level.

3.3. Measles molecular epidemiology, Russian Federation and neighbouring countries

Dr Sergey Shulga (Moscow RRL)

The number of measles cases in the Russian Federation had risen from 178 in 2016 to 721 in 2017. The same trend was observed in the remaining countries of the Moscow RRL constituency, with Ukraine (n=4767), the Russian Federation (n=721) and Tajikistan (n=649) registering the highest numbers of cases in 2017. Most cases were caused by strains belonging to the B3 and D8 genotypes. Transmission chains were long and prevailed for most of the year. A new outbreak was caused by the MeV Dublin B3 strain and was ongoing.

The MeV Frankfurt D8 strain had not been observed in the Moscow RRL's constituency since 2015/early 2016 but was detected again in June 2016 and has been circulating since, having caused an outbreak of 123 cases in Belarus in 2016, which affected mostly unvaccinated children. This marks the resurgence of endemic measles in the region supervised by Moscow's RRL. The second most common D8 strain was Hulu Langat. It was reported in 2016 and 2017, being frequently linked to importations. Cases associated with measles genotype H1 have been reported throughout the same period in Kazakhstan, the Russian Federation, Tajikistan and Kazakhstan. Sporadic cases of other strains were associated with importations from Bangladesh, India, Indonesia and Italy.

The main concerns observed by the Moscow RRL were that some long transmission chains were being observed of the D8 Frankfurt strain, with outbreaks occurring in 2016 and 2017 in several countries. This was especially worrying as it coincided with the football world cup in the summer of 2018, which was to be held in Russia and would provide ample opportunity for import and export of MeV.

In response to the issue raised during the presentation of whether the detection of long transmission chains, despite the relatively low MeV IR, could indicate failings in the surveillance system, the participants pointed out that multiple genotypes and strains were being reported, which indicates good-quality surveillance.

3.4. Measles molecular epidemiology, central and northern European sub-regions

Dr Sabine Santibanez (Berlin RRL)

The most frequent MeV genotypes found in the Berlin RRL's constituency were B3 and D8. The most frequent B3 strains reported matched the MVs/Dublin.IRL/8.16 strain N-450 sequence, but there was also continuous circulation of MVs/Niger.NGA/8.13. B3 strains MVs/Kansas.USA/1.12 and MVs/Kabul.AFG/20.14 were identified sporadically. MVs/Osaka.JPN/29.15 was the most frequently identified MeV genotype D8 strain. The MeV strain MVs/Hulu Langat.MYS/26.11[D8] had been seen repeatedly but was not endemic in the area. Other D8 strains reported on a less frequent basis in the constituency included MVs/Cambridge.GBR/5.16, MVs/Frankfurt Main.DEU/17.11 and MVs/Rostov

on Don.RUS/47.13. The latter was associated with repeated importations from Bosnia and Herzegovina.

The Berlin RRL submits sequence data to MeaNS from the countries for which it carries out sequencing, such as Bulgaria, the Czech Republic, Slovakia and Switzerland. There were three main strains circulating in Italy, two of genotype B3 (Niger and Dublin) and one of genotype D8 (Osaka). In Romania, there had been long-lasting transmission of the B3 Niger strain, which stopped in July 2017 and was superseded by the B3 Dublin strain. Germany had seen importations of the B3 Dublin strain from both Balkan countries and Italy. Several groups were affected by measles, such as unvaccinated individuals in the general population and in mobile groups, but determining which cases were associated with each group was made difficult by Germany's data protection act.

3.5. Measles molecular epidemiology, western and southern European sub-regions

Dr Judith Hübschen (Luxembourg RRL)

Fifteen of 23 Member States in the constituency of the Luxembourg RRL had sequences from 2017 on MeaNS, with France (n=172), Ukraine (n=83) and Spain (n=80) contributing most sequences. The B3 Dublin and some of its variants were the most frequently identified strains in Albania, Serbia and the former Yugoslav Republic of Macedonia, as well as in Kosovo (in accordance with United Nations Security Council Resolution 1244 [1999]), while Kabul was the predominant B3 variant in Ukraine. D8 Cambridge was the overall dominant sequence variant identified in Ukraine, but a few Hulu Langat and other D8 variants were also detected. In Georgia, a derivative of the D8 Frankfurt Main strain was found in different locations.

3.6. Rubella congenital surveillance in Russia and molecular epidemiology

Dr Tatiana Chekhliaeva (Moscow RRL)

Rubella is not endemic in Russia and incidence has been low for the past four years. In 2017, only five cases of rubella were reported in Russia in the context of exanthema diseases surveillance. RuV genotype 2B had global prevalence between 2014 and 2016. Variants of a genotype 2B strain with various origins were identified in 2016.

The last report of RuV 1H genotype in the Russian Federation and the NIS was in 2010, and it was thought that this genotype was no longer prevalent in the area. However, reports in 2016 demonstrated there was an outbreak of this genotype in Turkey and in 2017 it was associated with a case in Orenburg. This affected a male 27-year-old unvaccinated healthcare provider who might have been exposed to medical students from India.

In the context of CRS surveillance, pregnant women who have been in contact with an index case are examined and registered at antenatal clinics. Newborn babies are also examined for suspected CRS. Although many sera are tested for CRS and four were found to be IgM-positive, after further examination these cases were shown not to be rubella. No CRS cases were detected in 2017.

Session 4 – Procurement of ELISA reagents

Chair: Dr Sergey Shulga (Moscow RRL)

4.1. Update from WHO work group KitComp / Pre-qualification

Dr Mick Mulders (WHO headquarters)

Siemens plans to stop updating its manual serology kits by no later than 2020, possibly with the intent of moving into the high-throughput market. However, many MR LabNet laboratories do not test a high enough number of samples to justify automation. Given that the distribution of the manual kits is not assured in the future, several WHO GSL and RRL laboratories will be testing other commercially available manual serology kits. The serology work group is organizing this testing with the objective of determining the sensitivity and specificity of commercial kits for IgM and IgG detection of measles and rubella, and evaluating the operational characteristics of the kits tested in this inter-kit comparison study.

Four to five IgG and IgM kits will be assessed at the Public Health Agency for Canada for both measles and rubella. So far, the kits under consideration are Euroimmun, Virion Serion, NovaTec and Vector Best. Four panels of well-characterized sera collected during routine testing and surveillance will be tested in two rounds, the first for IgM (two panels with 300 sera in total) and the second for IgG (also two panels with a total of 300 sera) kits. The sera collection will include well-documented specimens with different reactivity strengths, vaccination status, potential cross-reactive samples and negatives. Some sera may be used across different panels.

Further dialogue is ongoing to draft a protocol and define the panels to be used. A second laboratory will carry out the estimation of uncertainty of measurement. The goal is to provide laboratories with the information gathered to help them decide which kits best meet their needs.

A discussion followed of relevant samples and appropriate controls to include. Participants agreed that it is essential that sera from acute, convalescent, vaccinated and unvaccinated cases are included and that the main manufacturer kits used across the MR LabNet should be tested. It was also suggested that Siemens should be included as a control; negative sera should be put through to plaque reduction neutralization test (PRNT); and samples missed by Siemens should be tested.

4.2. Regional Office procurement update and planning validation studies for Euroimmun Measles IgM for use with DBS

Dr Myriam Ben Mamou and Robert Jensen (WHO Region Office for Europe)

The Regional Office spends increasing amounts of time and resources in the procurement and distribution of kits. Robert Jensen, WHO Procurement Assistant has been looking into the issues with cross-border shipment of reagents, particularly the Euroimmun, Vector Best and Ekolab kits. Although Euroimmun is available in NIS countries through normal distributors, this is not the case everywhere. The situation is also complex for the other kits and the regulations are changeable, meaning that kits may be registered in some countries but distribution to neighbouring states is limited.

Additionally, the WHO procurement system leads to delays. Shipment is now further complicated by the employment of a new shipping company with fewer offices than the previous distributor. In some Member States shipping must be done through locally approved distributors, further complicating the process.

In order to cope with delays in sample shipment across borders, many laboratories are relying on the use of DBS, but the testing of this type of sample with Euroimmun kits is yet to be validated. To validate the use of DBS, Member States are asking the Regional Office for a validation protocol.

During the discussion that followed, participants pointed out that in some countries, the shipment of DBS samples is limited by regulations. It was suggested that positive sera could be used to spike blood to assess DBS use. It was also commented that although procedures for emergency shipping are in place for polio, this is not the case for MR.

Session 5 – Future plans, research and recommendations

Chair: Dr Sergey Shulga (Moscow RRL)

5.1. Experience of using MeV vaccine-specific reverse transcription PCR (RT-PCR) in the European Region and MR LabNet position on routine use by NRLs

group discussion

Participants discussed the use of the measles vaccine-specific real-time PCR test in the Region. Some of the Region's RRLs had issues with sensitivity and strict reagent requirements. They were also concerned that in a pre-elimination setting the assay may increase rather than reduce workload. The assay is already successfully employed in Canada and the United States and is moving towards national roll-out in the first. However, the Region's GSL and RRLs feel that further evaluation must be carried out in the Region due to differing elimination status among countries and types of samples used.

The possibility of testing at the RRL level was discussed, but it was agreed that this would lead to the loss of any time-saving advantages of employing the assay. It was proposed that the RRLs and GSL of the Region address the Region-specific concerns prior to roll-out to NRLs and that, until then, advice would be provided to interested laboratories on request.

5.2. N.E.W. Working Group developments

Dr Bettina Bankamp (United States GSL)

Whole genome sequencing (WGS) of RuV allows for better phylogenetic resolution, particularly when tracking rubella outbreaks. Two methods are available for WGS of RuV, one based on a metagenomics approach and the other using targeted sequencing. Full genome sequences can only be obtained from high titre specimens or isolates by the metagenomics method, with only 0.1% of reads mapping back to RuV, meaning that fewer than 18 samples can be multiplexed in the same next-generation sequencing (NGS) run. Using the targeted sequencing approach, up to 68 specimens with Ct values under 28 can be multiplexed and sequenced, but the risk of cross-contamination is increased.

A project aiming to evaluate the utility of sequencing the non-coding region between the matrix and fusion genes (MF-NCR) for analyses of measles transmissions and sources during outbreaks in countries with low measles incidence is ongoing at CDC. The aim is to sequence well-characterized samples and assess the likelihood of transmission. Samples should be collected in an elimination setting and result from a clear source and a single importation. Laboratories can either be financed to do in loco sequencing or send the samples to CDC for sequencing there.

To improve efficiency of NGS sequencing of clinical samples, a real-time assay has been designed to detect human 18S and bacterial 23S RNA in clinical samples. This allows for determining the types of contaminant present in the sample and for their removal prior to sequencing. So far, the coverage obtained was not uniform. The CDC is also collaborating with the Broad Institute to develop measles-

, mumps- and rubella-specific enrichment probes. Although this approach is costly, its cost can be partly recouped by multiplexing higher numbers of samples.

5.3. MR LabNet plans for 2018 including MRLDMS and e-learning update

Dr Myriam Ben Mamou (WHO Regional Office for Europe)

In 2018, many initiatives are planned in the MR LabNet to promote and provide training and better data access. These include accreditation reviews and on-site visits, the regional verification process, meetings, capacity building and skills strengthening activities, updates to procurement and the finalization of the measles and rubella laboratory data management system 2 (MRLDMS2).

The deadline for submission of ASU reports by the NVCs was 15 April. The review process would follow and provide the background documents to the RVC. The 7th RVC meeting was to be held in June 2018 and results letters and reports would be sent to Member States during the summer.

Planned regional meetings included integrated workshops between epidemiologists, NRLs and NVCs of European Union and non-European Union Member States on 13-16 November (to be confirmed), the RVC meeting and meeting of the European Technical Advisory Group of Experts on Immunization.

Capacity building and skills strengthening activities included Euroimmun and sequence management webinars, support to NRLs having issues with mEQA exercises, refresher MeaNS and RubeNS at NRL meetings, individual laboratories training carried out on-site or at RRLs and the production of an e-training course targeted at the MR LabNet.

The Regional Office and associated reference laboratories recognized the value for an e-learning platform that can provide training for new and existing members of staff whenever required. Fifty thousand US dollars had been assigned to the project and initial steps taken to identify a provider and platform. The Agora and openWHO platforms were being considered. Work was expected to start in early summer and be completed by October, for presention and rolled-out to the LabNet in November 2018.

By 14 April 2018 there were 34 772 specimens submitted to MRLDMS by 25 contributing Member States. The pilot MRLDMS2 had been developed and was only awaiting some tools to be finalized. The final stage was already open to online request proposals, with 5 applications received so far. A meeting for the evaluation and selection of bidders was to be held atn the beginning of April.

3. Recommendations

The following recommendations were agreed by the participants following the exchanges and discussions during the meeting.

Proficiency testing / EQA

1. The aims of confirmatory testing of IgM in the context of elimination must be well defined and the use of confirmatory testing and proficiency panels adapted to the requirements and to the new epidemiological situation (country-specific). It was recommended to extend the discussion to GMRLNM participants in June 2018.

2. Laboratories should be looking at the chromatograms of their measles/rubella sequences prior to submission of molecular EQA (and routine sequencing) results to ensure they are of reasonable quality and match the expected region. Failure to do so reflects weak quality control/management.
3. RRLs should follow up with NRLs that failed to submit correct sequences. Where the mistakes occurred after obtaining high-quality chromatograms, training might be done remotely. When the chromatograms are of low quality, the laboratory could be asked to submit PCR products to identify whether the issue is at the sequencing level or prior to sequencing. Mistakes earlier in the process may need on-site training. It was recommended to include training on sequence analyses and management as part of the annual MR LabNet meeting in November 2018.
4. The Regional Office expressed gratitude to Instand e.V. for a fruitful collaboration in the production and distribution of mEQA panels for laboratories in the European Region. However, in the interest of harmonizing the mEQA process across all WHO regions as for serology proficiency testing, in future panels will be produced by the CDC and distributed to each regional laboratory coordinator, who will arrange further distribution, for example at annual meetings. Sequence assessment will be distributed between RRLs and GSLs.

Measles and rubella elimination

5. The use of the phrase "measles elimination" can prove counter-productive as it may lead to the disengagement of policy-makers and make physicians less aware when measles/rubella cases are observed. "Elimination of endemic measles" should be preferred.
6. Laboratories may subscribe to regular e-mails of measles and rubella surveillance updates including maps and incidence rates worldwide by sending an email to listserv@who.int with the following text in the body of the email: subscribe GLOBAL_MR_UPDATE
7. The updated laboratory manual is available online at www.who.int/immunization/monitoring_surveillance/burden/laboratory/manual/en/. RRLs and GSLs were asked to peruse the current draft version of the document and return comments and suggestions by mid-April 2018 before the website goes live.
8. The WHO polio programme was to release guidelines on PIMs in the coming weeks. Laboratories were encouraged to review the guidelines as they will affect any laboratory holding respiratory specimens or cell culture isolates.
9. Rubella surveillance in Poland: During a recent WHO mission to Poland, the surveillance system suggested to switch to oral fluids specimen collection instead of blood to overcome the lack of specimens from rubella suspected cases reaching the NRL. The MR LabNet can provide guidance on the different types of specimens at any time. However the surveillance system in Poland should first enquire to understand the reasons for lack of specimens from rubella suspected cases before changing the policy.

Verification of elimination

10. As already indicated in the ASU template, countries are encouraged to specify their case definitions in the ASU form so that different methods of case classification are taken into account.
11. Countries should be reporting all cases diagnosed in country, including foreign residents, commuters, tourists, etc. There should be communication between surveillance systems to ensure all cross-border cases are being followed up and accounted for without duplications.

Accreditation

12. For the next year's accreditation process, laboratories will be asked to fully complete part 2 of accreditation checklists with their self-assessment as part of the annual review. This is to

ensure that laboratories are aware of the requirements on which they will be evaluated and can prepare the relevant documentation.

13. The terminology in the revised accreditation checklists must be reviewed to address inconsistencies and improve the clarity of inputs expected from laboratories. RRLs and GSLs were requested to share their comments with WHO headquarters by end of March 2018. In particular, the terminology of testing (e.g. number of assays, tests, specimens, cases, results) to be included in part 1 of sections 1-4 of the accreditation checklist should be made clearer.
14. To ensure consistency and harmonization of on-site accreditation visits by different assessors, WHO was to consider setting up assessors training.

Procurement of ELISA reagents

15. In the current context of comparing kits to provide alternative options to Siemens, the following issues were provided for consideration by the serology work group setting up the inter-kit comparison study:
    - Sera from acute and convalescent patients should be included.
    - Goals of the assays should be defined and samples to test chosen accordingly (acute infection, reinfection, serosurveys).
    - Time between onset of symptoms and serum collection should be noted and used to evaluate the results.
    - Positives missed by Siemens kits should be included.
    - Ideally more than one recommended kit should be available for each assay to allow for result confirmation and choice by the laboratories. High sensitivity should be prioritized relative to specificity in IgM kits in an elimination setting. If a reduced budget does not allow to also have kits with high specificity, samples for which a false positive reaction is suspected can be forwarded to the RRL or GSL for further investigations.
    - Sera with low IgM and high IgG should be included to reflect the type of sample that will be most commonly seen after elimination.
    - IgG negatives should be checked by PRNT.
16. The Regional Office made the decision to switch to Euroimmun kits for 2018 procurement. The Office will share positive sera with Euroimmun so that blood can be spiked and used to test DBS with Euroimmun kits and validate the use of DBS for measles IgM detection.
    Multiple issues with ordering and shipment of Euroimmun kits were being addressed by the Regional Office in collaboration with Euroimmun and WHO headquarters: It is recommended to use rapid post mail as a short-term solution for distribution of kits to the NRLs. In the meantime, WHO headquarters and its administrative office in Kuala Lumpur were to negotiate centralized procurement.
17. Explore options to use emergency procurement procedures in countries.

Future plans and research

18. The MeV-VA RT-PCR is currently not recommended for general use in the Region. The assay will become more useful in the post-elimination scenario, but currently would lead to increased workloads and be limited in the circumstances it should be employed. Specific guidance to be provided to NRLs on request.
19. Facilitate sample-sharing with CDC for MF-NCR studies (Regional Office to follow-up with, Georgia, Germany and Italy).

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The WHO Regional Office for Europe

The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

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