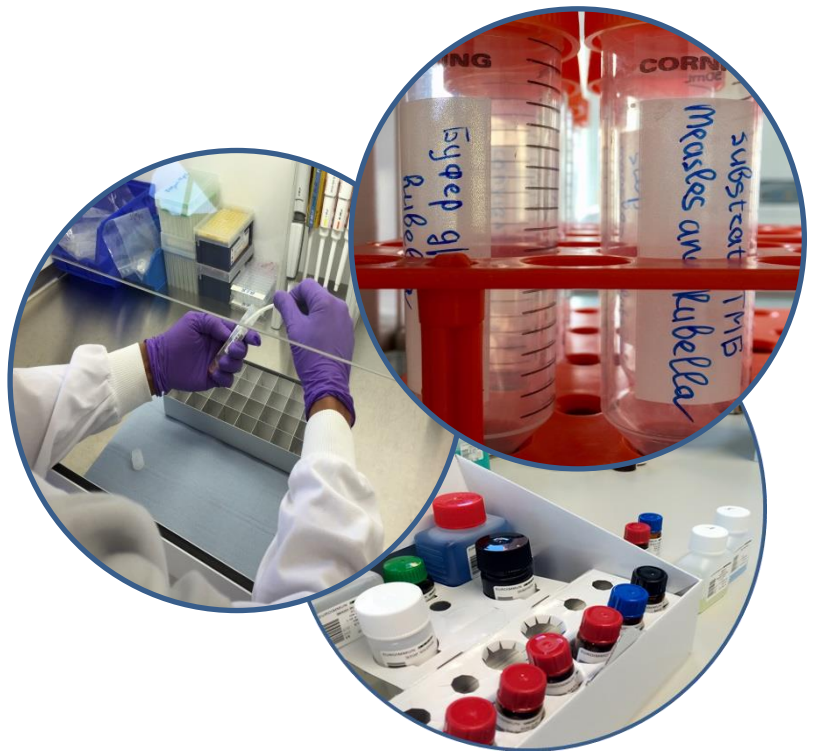


## MEETING REPORT

# 12<sup>TH</sup> MEETING OF THE MEASLES / RUBELLA REGIONAL REFERENCE LABORATORIES OF THE WHO EUROPEAN REGION

25-26 April 2017  
Moscow,  
Russian Federation



## Keywords

COMMUNICABLE DISEASE CONTROL

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## Abbreviations

B19V	Parvovirus B19
BLAST	Basic Local Alignment Search Tool
CDC	United States Centers for Disease Control and Prevention
CISID	Centralized Information System for Infectious Diseases
CRI	congenital rubella infection
CRS	congenital rubella syndrome
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
ELISA	enzyme linked immunosorbent assay
ES	enhanced (active) surveillance
EQA	external quality assessment
EVAP	European Vaccine Action Plan
EU	European Union
WHO/Europe	WHO Regional Office for Europe
GSL	global specialized laboratory
HH6	human herpesvirus type 6
IgG	Immunoglobulin G
IgM	Immunoglobulin M
LabNet	laboratory network
MCV	Measles-containing vaccine
MeaNS	Measles Nucleotide Surveillance database
MeV	Measles virus
MF-NCR	measles virus non-coding region between matrix and fusion genes
MR	Measles/Rubella
MRLDMS	measles and rubella laboratory data management system
N-450	measles virus genotyping region: 450 nucleotides C-terminus of nucleoprotein gene
NGS	Next Generation Sequencing
NIS	newly independent states
NL	national laboratory
NRL	national reference laboratory
NVC	national verification committee
OF	oral fluids
PAHO	WHO Region of the Americas/Pan-American Health Organization
PCR	polymerase chain reaction
PHE	Public Health England
PRN	plaque reduction neutralization
PP	proficiency panel
PT	proficiency test
RAGIDA	Risk assessment guidelines for infectious diseases transmitted on aircraft
RKI	Robert Koch Institute
RNA	ribonucleic acid
RRL	regional Reference Laboratory
RubeNS	Rubella Nucleotide Surveillance database

RVC	European Regional Verification Commission for Measles and Rubella Elimination
SAGE	Strategic Advisory Group of Experts on Immunization
SIA	supplemental immunization activity
Tessy	The European Surveillance System
UK	United Kingdom of Great Britain and Northern Ireland
USA	United States of America

## Executive summary

The 12<sup>th</sup> meeting of the Measles/Rubella Regional Reference Laboratories (RRLs) of the WHO European Region was held on 25–26 April 2017 in Moscow, Russian Federation.

The meeting was attended by representatives of the following institutions/laboratories:

- European RRLs: Gabrichevsky Institute (Moscow), Luxembourg Institute of Health (Luxembourg) and Robert Koch Institute (Berlin)
- GSLs at Public Health England (London) and US CDC (Atlanta)
- European Regional Verification Commission for Measles and Rubella Elimination (RVC)
- staff of the WHO Regional Office for Europe (WHO/Europe) and WHO headquarters

Updates were given on the progress of the Measles/Rubella programme worldwide and in the WHO European Region as well as on future plans of WHO/Europe in terms of training, elimination verification and publications. The recommendations from this meeting were agreed among the participants and are presented at the end of this report (section 3. Recommendations).

## 1. Introduction

The European network of WHO Measles/Rubella (MR) laboratories was set up in 2002. It is composed of 71 laboratories arranged in a tiered structure coordinated by WHO/Europe. The role of the LabNet is to ensure and coordinate a high-quality laboratory diagnosis service. The global specialized laboratory (GSL) in London and three regional reference laboratories (RRLs), in Berlin, Luxembourg and Moscow, supervise proficiency testing and assay implementation in national (NL) and sub-national laboratories.

As the European region of WHO progresses towards elimination of measles and rubella, good surveillance and effective testing of potential cases becomes increasingly important. The scope of this meeting of the European MR RRLs was to share recent information on MR LabNet's achievements, challenges and research in laboratory aspects of measles and rubella surveillance and on laboratory contribution to the verification process in the European Region.

This report consists of a summary of the presentations given by laboratory representatives and technical experts and lists the recommendations that resulted from the exchanges and discussions that took place during the meeting.

## 2. Sessions of the meeting

### Session 1 – Global and regional updates

*Chair: Prof Claude Muller*

#### 1.1. Regional Measles and Rubella programme update

*Dr Shahin Huseynov (WHO regional office for Europe)*

Apart from the WHO Region of the Americas (PAHO), where elimination of measles and rubella (MR) has been achieved, all other WHO regions have goals for elimination of measles. The WHO European Region also has a goal for rubella elimination. However, the Region was unable to achieve elimination of either measles or rubella in 2015 as intended.

There has been no change in the vaccination rates for measles-containing vaccine's first (MCV1) and second (MCV2) doses since 2013, with MCV1 rate stable at 94% and MCV2 at 89%. The number of measles cases fell by 98% between 1993 and 2007 in response to immunization campaigns, but the decrease was halted from 2010-15 due to lower vaccination rates, a pattern similar to that observed for rubella. 2016 was the year when the least number of MR cases were observed in the Region. A measles outbreak in Romania accounted for 47% of the total 5133 cases observed that year. Rubella cases in Poland composed 86% of the 1327 total reported. The picture is similar for 2017 so far, with continuing measles outbreaks in Tajikistan and Romania.

Together, Romania, Italy, United Kingdom (UK) and Germany registered 82% of the total number of cases in the European Region in 2016. There were 16 measles deaths reported in 2016: 15 in Romania and 1 in the UK. These deaths affected 6 infants non-eligible for vaccination, 7 children, 2 teenagers and 1 adult. Four countries had incidence rates (IRs) of measles over 10 per million of population: Romania (125.5/million), Italy (14.4/million), Bosnia and Herzegovina (11.8/million), and Belgium (10.5/million).

The majority of measles cases are observed in children under ten. Up to 2013, the second group most affected by measles were the 10-15 year olds. However, since then the 15-25 year old age group has overtaken the 10-15 in terms of measles prevalence. The age distribution of measles cases varies between countries: in Romania, 42% of cases occur in 1-4 year olds; in the UK measles is more prevalent in young adults; in Italy and Germany, measles cases peak in younger children and young adults. In terms of IR, Romania, Italy and Germany show higher IRs in children before 4 years of age, while in the UK both children younger than 5 years old and those older than 10 years old were equally affected.

Overall, the predominant age groups affected by measles in 2016 were those under 5 years of age (43%) and older than 20 (26%). 87% of cases occurred in unvaccinated populations. The populations most likely to be affected by measles and unvaccinated were Roma communities in Bulgaria, Anthroposophists in Germany, the Netherlands and Switzerland, Jewish ultra-orthodox communities in Belgium, Israel and United Kingdom, and Orthodox Protestants in the Netherlands. There were also outbreak foci in educational and healthcare settings.

The RVC was established in 2011 and consists of a group of independent experts. Annual meetings are held to evaluate each of the 53 Member States (MS) progress towards MR elimination. The verification process is guided by the Regional Verification Framework and assessment based on reports submitted by each country's national verification committee (NVC). The above-mentioned reports contain data on epidemiology investigations, molecular analysis, population immunity, and surveillance status.

In 2016, 24 countries have been verified for MR elimination (36 months with no endemic cases). 14 and 16 countries have reported endemic measles and rubella, respectively. 2 countries failed to submit reports to the RVC.



The four main challenges for elimination of MR in the Region are: 1) reaching and maintaining high vaccination rates (address vaccine hesitancy and refusal, distrust in health authorities, missed vaccinations and issues with access to healthcare); 2) closing existing immunity gaps (reach low coverage communities, target susceptible age groups and professions); 3) achieving and maintaining high-quality surveillance (accurate reporting of suspected cases, increase laboratory testing rate, obtain genotyping data); 4) closing knowledge and communication gaps (address widespread misinformation and myths, lack of information on vaccination and disease, lack of education and training on vaccines in medical curricula, and anti-vaccine lobby).

## 1.2. Regional Measles and Rubella LabNet update

*Dr Myriam Ben Mamou (WHO Regional Office for Europe)*

Dr Myriam Ben Mamou, the regional coordinator of the Measles and Rubella Laboratory Network, reported on the main activities since the National Reference Laboratories meeting in Budva, Montenegro. The European Region comprises 1 Global Specialized Laboratory (GSL) in London, 3 Regional Reference Laboratories (RRLs) in Berlin, Luxembourg and Moscow, 48 National Reference Laboratories (NRLs), and 19 Subnational Laboratories (SNLs). These 71 laboratories are distributed between 48 MS. Of the 5 MS with no laboratories represented in the WHO LabNet, two, Montenegro and Switzerland, are in the process of establishing national reference laboratories. A new network of subnational public and private laboratories carrying out MR testing in Italy has been established. The network, MoRoNet, is coordinated by the NRL in Rome and its website can be found at <http://moronetlab.it/>.

Of all laboratory-tested measles cases, between 25% and 30% are confirmed positive. The return of positive results for rubella is lower, in part due to the submission of incorrect specimens. Since 2013, the majority of circulating measles virus (MeV) strains sequenced belong to genotypes B3 and D8.

The WHO/Europe LabNet are highly proficient in molecular and serological testing, with over 90% of laboratories meeting the criteria in number of specimens tested, confirmatory and proficiency testing, and molecular EQA. However, there are issues in the timeliness of reporting: only 19% of laboratories report IgM results within 4 days and 30% report genotyping results within 4 weeks. 47% of laboratories have deficient IQC procedures. Rubella genotyping is the major issue in the molecular EQA, with only 63% of laboratories meeting the accreditation criteria. 88% of laboratories report to CISID or MRLDMS, 74% doing so in a complete and 53% in a timely manner.

In 2016 all 71 MS laboratories achieved accreditation, though 3 did so provisionally. The first molecular EQA has been rolled out successfully to 34 laboratories. Members of WHO/Europe RRLs and GSL have conducted onsite accreditation visits to reference laboratories in Ireland, Sweden, Armenia, Denmark, Turkmenistan and Italy. All laboratories have passed the serology proficiency panel in 2017, except in Kyrgyzstan, which has not yet received the panel due to logistical issues. Retesting has been conducted successfully for all laboratories, with the exception of Rotterdam. The second round of the molecular EQA was initiated in January and the results will be available in May.

Several workshops and meetings have been organized since June 2016, including the 5<sup>th</sup> meeting of the RVC in October 2016, a NVC workshop for German-speaking countries and the WHO RLC / US CDC annual technical consultation in January 2017, the Ukraine national conference on MR

elimination and verification in February 2017, the 1<sup>st</sup> meeting of Italy's MoRoNet, in March 2017, and the current meetings of the Russian NRLs and the RRLs.

Serological and molecular training at country level was given by GSL and RRLs representatives in Armenia, Turkmenistan, Serbia and Georgia throughout 2016. Luxembourg's RRL conducted 2-week onsite capacity-building missions at Bosnia and Herzegovina, and Serbia. The NRL meeting in June 2016 also included training sessions on specific accreditation and verification issues.

In summary the European LabNet is a network of well-functioning, highly proficient laboratories, providing the programme with increasing amounts of epidemiological and laboratory data and fully integrated into the regional verification process. The molecular EQA exercise demonstrated an increasing capacity in terms of molecular testing, especially RT-PCR. Challenges are currently in addressing laboratory-specific issues, particularly in the implementation/improvement of internal quality control procedures, improvement in rubella genotyping and in the timeliness of result submission. In terms of rubella testing, rates of viral detection and investigation of the correct specimens need to be addressed.

The use of the NL listing functionality in MeaNS in conjunction with improved collaboration between laboratories, epidemiologists and their NVC will be essential to achieve better characterization of measles chains of transmission. Stringent data protection laws in some countries, issues with customs clearance for shipment of reagents and panels, increasing training needs due to staff turnover and the variety of requirements between laboratories, and a lower priority of measles and rubella in national health agendas constitute the major external challenges for the European MR LabNet.

In 2017, WHO/Europe will continue its collaboration with the laboratories in addressing identified problems and weaknesses and improving collaboration and sustainability across the LabNet. Several accreditation visits will be carried by the RRLs throughout the year to ensure high quality performance of the laboratories in the region. An assessment visit is also planned for the proposed reference laboratory in Montenegro. Workshops and meetings bringing together national laboratories, epidemiologists and verification committees will address issues related to the verification process. Finally, a meeting of the European Technical Advisory Group of Experts on Immunization (ETAGE) meeting will include immunization programme managers and laboratories. Throughout 2017, various training activities, including onsite and eTraining, will be carried out, encompassing diagnosis and research capabilities, the use of MRLDMS and procurement. Representatives of the Italian and Swiss NRLs will share their experience at the Global Measles and Rubella Laboratories Network Meeting, and the European Region will be represented at the WPR RVC meeting.

### **1.3. WHO global programme and LabNet update**

*Dr Mick Mulders (WHO headquarters)*

The global incidence of measles and rubella (MR) has steadily decreased until 2007. However, in the last decade the number of MR cases per year has stabilized. The uptake of MCV1 and 2 has also plateaued over the last 6 to 7 years. MCV1 coverage is over 90% in 61% of countries, falling below the 1<sup>st</sup> global milestone of achieving 90% or over MCV1 coverage. Despite having eliminated both measles and rubella, PAHO is at risk of re-introduction due to low vaccination coverage.

In 2015, measles incidence had decreased by 75%, reaching approximately 36 cases/million, still over the goal of the 2<sup>nd</sup> global milestone (fewer than 5 cases/million). Between February 2016 and January 2017, the IR for measles was over 50/million in Bhutan, Democratic Republic of the Congo, Equatorial Guinea, Gabon, Liberia, Mongolia, Nigeria, Congo, South Sudan, and Romania. The 3<sup>rd</sup> global milestone – a 95% reduction in measles deaths – is also yet to be achieved. In 2015, measles deaths had decreased by 79%. The WHO regions with the highest number of measles deaths are the African Region, the South-East Asia Region, and the Eastern Mediterranean Region.

Both PAHO and the European Region have achieved and maintained 95% coverage of the first dose of rubella-containing vaccine (RCV1). The Western Pacific Region has achieved a strong increase in vaccine coverage since 2010. The remaining regions (Eastern Mediterranean, South-East Asia and African) have lower vaccine coverage than the global average of 46%. RCV1 coverage will increase when 16 countries in the African and South-East Asia regions proceed to the introduction of a rubella vaccination programme between 2016 and 2018 as planned.

The Midterm Review of the Global Measles and Rubella Strategic Plan 2012-20 concluded that despite tremendous progress in measles and rubella control since 2001, neither is on track to achieve the ambitious goals leading to elimination. Although the basic strategies are sound, their full implementation is limited by insufficient resources due to lack of country ownership and global political will. As such, it is premature to set a timeframe for measles eradication at this point.

Improving surveillance data is essential to tackle outbreaks, and guide programme strategy and implementation. In order to achieve regional elimination goals, countries must shift from implementing immunization campaigns to strengthening their routine programmes so that they manage to deliver two vaccine doses.

To verify elimination, countries must document that they have interrupted endemic measles transmission for at least 36 consecutive months in the context of a high-quality surveillance system. The lines of evidence to be used should include data on epidemiology, genotyping, population immunity, quality of surveillance, and sustainability of the national immunization programme. Programme performance indicators include the fraction of cases with laboratory confirmation, proportion of chains of transmission with genotyping information, and turnaround time for laboratory results.

With 703 laboratories in 191 countries, the Global Measles and Rubella Laboratory Network (GMRLN) is the largest globally coordinated WHO laboratory network. It provides support and data in the progress towards elimination. The performance of the laboratories in the network is assessed on the basis of timeliness and completeness of reporting, quality assurance and control through proficiency and confirmatory testing, and accreditation visits to ensure that WHO performance indicators are met.

To improve results, countries should standardize criteria across multiple data sources, link cases and specimens through unique case identifiers, improve the sensitivity of surveillance systems, improve data quality, address lack of genotyping data, and mobilize resources and ownership. One of the major concerns regarding the quality of surveillance in the MR network is the underreporting of cases. It is estimated that only 3% of the estimated measles cases are reported. Improved timeliness of result reporting is also necessary. For example, a discrepancy is found between the number

measles IgM tests carried out on serum specimens reported to GMRLN monthly and annually, with the latter being higher. This is not the case for rubella, for which good concordance is observed between monthly and annualized data, possibly due to the public health focus on rubella due to congenital rubella syndrome (CRS).

Current molecular epidemiology data indicates that the main genotypes of measles circulating worldwide are D8 and B3, with H1 being the prevalent genotype in some Western Pacific Region countries. For rubella, the prevalent circulating genotype is 2B, but there are major gaps in the reporting of rubella virus (RuV) sequences.

A number of workgroups are in place addressing various aspects and issues related to the MR elimination programme, such as genotyping, testing, vaccination failure, and surveillance. The workgroup working on the third revision of the Measles Rubella Laboratory Manual will release a first draft of the revised manual by June 2017. SOPs for all relevant laboratory procedures will be included as annexes to this new manual. A new workgroup entitled Informal Executive Steering Committee GMRLN has recently been established.

Some of the challenges for the GMRLN are in maintaining expertise, managing competing expectancies, upholding levels of staff and training, attracting funding, and dealing with the transition of resources from the polio programme. Other challenges include achieving or maintaining high test rates, integrating laboratory and surveillance systems, promoting collaboration, and dealing with issues with shipment of specimens and reagents across borders.

#### **1.4. RRL Moscow update**

*Dr Sergey Shulga / Dr Tamara Mamaeva (RRL Moscow)*

The RRL Moscow coordinates 22 other laboratories, of which 10 are NRLs and 12 are sub-national laboratories (SNLs) in the Russian Federation and neighbouring countries. All 23 laboratories participated in proficiency and confirmatory testing in 2016 and were fully accredited by the WHO. Every laboratory achieved a score over 90% in the PT panel, with 17 laboratories obtaining a full score. Four and two laboratories participated in the molecular external quality assurance (mEQA) panels provided by Instand for measles and rubella, respectively. No laboratories tested fewer than 50 serum samples in 2016.

The fraction of positive IgM sera has decreased for both measles (20.2%) and rubella (3.5%), reflecting a lower IR. Most laboratories use the Siemens kits provided by WHO/Europe. In some cases, Vector Best and Ecolab test kits are used. Some laboratories experienced difficulties in purchasing test kits and used kits that were not approved by the test centre. The result agreement is 100%, independently of the kit used. Four laboratories are now using dried serum spots.

The fraction of positive IgM tests for both measles and rubella has significantly decreased, with 32.4% of IgM assays carried out for measles-suspected cases and 7% for rubella in rubella-suspected cases being positive.

Moscow's RRL has promoted joint meetings between epidemiologists, clinicians, and laboratories in the Russian Federation and newly independent states (NIS) on October and November 2016. These meetings aimed to address countries' issues related with the elimination of measles and rubella.

Workshops on the implementation of EQA in MR ELISA IgM assays have been held in Armenia and Turkmenistan, on the collection and genotyping of samples in Tajikistan, and on the implementation of molecular testing in Tajikistan and Kazakhstan.

The RRL in Moscow has led the implementation of a database to which laboratories should submit all data on every measles- or rubella-suspected case, including discarded cases. It includes serology, molecular, genotyping, and epidemiology data, outbreak information and case classification. The database aims to be a tool routinely used by laboratories, and all data can be exported, for example to WHO databases.

The genotyping of measles and rubella is carried out in accordance to the WHO's criteria for verification of elimination. The IR for measles is decreasing, with the majority of measles cases belonging to a single genotype, D8, with one to two variants (predominantly Frankfurt, MVs/Frankfurt Main.DEU/17.11, and Hulu Langat, MVi/Hulu Langat.MYS/26.11). The measles IR has been strongly impacted by importations from other countries in the Region (D8 Frankfurt), Indonesia and Thailand (D8 Hulu Langat).

Of the 178 measles cases in the Russian Federation, 44% were associated with an outbreak in Ekaterinburg. 123 cases of measles strain D8 Frankfurt were detected in Belarus, although only 10 were in citizens. The vast majority of cases (95.9%) were of unvaccinated young children. Outbreaks of measles genotype H1 were detected during 2016 in several countries, associated with multiple importations. No endemic transmission was detected for longer than seven months.

The challenges faced by the RRL Moscow include the high staff turnover and the associated need for training, the exchange of data in real-time between laboratory and epidemiology (which will hopefully be aided by the new database), and the lack of experience in outbreak response and investigation. In the context of low IR, the monitoring of measles transmission and classification of endemic/sporadic cases on the basis of genotype poses a challenge. This is particularly true at local level, where the collection of incorrect samples or difficulties in sample transport lead to negative PCR results and impossibility of genotyping.

The laboratories in this area of the European Region demonstrate high levels of proficiency. The majority of cases are associated with multiple importations followed by spread in pockets of susceptible populations, such as unvaccinated children and adults, Roma communities and religious groups. The increase of trans-border transmission upholds measles circulation in the European Region and introduces new strains of the virus. One such case is the importation of measles strains of genotype H1 from China, which had not been reported until 7 years ago and has now spread from healthcare settings to unimmunized populations.

Dr Sergey Shulga's update on the RRL Moscow's activities was completed by Dr Tamara Mamaeva's report on rubella genotyping. Overall the IR of rubella in this part of the European Region is low and shows a downward trend. However, the number of rubella cases increased from 25 in 2015 to 38 in 2016. No cases have been reported in 2017 thus far. Due to the low number of cases in the RRL Moscow constituency, only the Russian Federation is carrying out genotyping for this part of the EUR network.

The three clusters of rubella cases detected in 2016 occurred in Russia. The first cluster was caused by RuV strains related to those circulating in the South-East Asia Region. It subdivided into two sub-clusters and was associated with one case of congenital rubella syndrome (CRS). A second cluster was caused by RuV strains related to those circulating in India. The third cluster started in a military unit and was imported through recruits from the AFR. The RRL Moscow carries out repeat testing of IgM negative sera received from non-WHO-accredited laboratories. Although one sample from a pregnant woman was IgM positive, this did not result in CRS.

The available data on the variability of RuV strains in the NIS region is limited and hinders identification of sources of the virus (e.g., no genotype 1H strains had been reported since 2010). All RuV strains of 2B genotype were linked to importation from different endemic regions (African and South-east Asian).

### **1.5. RRL Berlin update**

*Prof Annette Mankertz / Dr Sabine Santibanez (RRL Berlin)*

Since 2007, yearly outbreaks of measles have been occurring in the area of the Region coordinated by the RRL Berlin. Although last year's IR has been lower following a large outbreak in 2015, it is anticipated that it will be higher again in 2017. Outbreaks are being seen in regions where few or none had been reported before, while clusters of cases remain small in Berlin due to higher immunity levels.

Many measles cases have been reported in younger children due to the waning in immunity of mothers. The majority of cases have been clinically diagnosed, with 2 cases in every 50 laboratory-confirmed. There has been a reduction in the influx of migrants from Syria, Romania and Poland. A vaccination campaign has been targeted for the migrant population in Berlin, as thousands of children initiate school.

Of the children with no migration background, 92.8% have two doses of MCV. Having a one- or two-sided migrant background had no impact on vaccination levels. The lowest vaccination rates are observed in migrants with Eastern and Western European backgrounds. Despite relatively high levels of vaccination overall, only approximately 59-76% of individuals in each group have received the MCV2 in time.

In 2016 there were 326 notified measles cases. Of the 391 measles submissions, only 40% were confirmed. For rubella, there were 95 notified cases, and only 4% of the 45 submissions for rubella were confirmed. The majority of the 148 measles samples sequenced belonged to genotype D8 (55.4%) and B3 (40.5%). 2.7% of the sequences obtained belonged to strains of genotype H1. Measles transmission chains were mainly seeded from strains originating from other countries in the European Region and worldwide and re-initiated upon re-import from other countries, evidencing the role of trans-border transmission in sustaining measles transmission in the European Region.

The measles B3 Harare strain was associated with an outbreak in Berlin, which was interrupted, but progressed on to other regions and countries. Current cases of the same strain have been sporadically detected in Munich after importations from Romania. The measles D8 strain of Rostov on Don started circulating during the summer of 2015 and is now endemic.

An outbreak of measles genotype B3 occurred in Eichsfeld between October and December 2016, affecting individuals of all ages (median age of 22 years old). The index case was a seasonal worker from Romania working in a fun fair. The outbreak followed nosocomial transmission events from healthcare workers. Of the 23 cases, all laboratory-confirmed, 20 had two doses of MMR, raising concerns over vaccine protection against this strain. Further investigation revealed low IgG avidity in some of the cases, indicating low immunity following vaccination. All of these had been vaccinated in the same practice between 1990 and 2014 with different vaccines and lot numbers. No obvious mismanagement was identified.

The RRL Berlin has implemented a PCR assay that distinguishes between wild-type and vaccine strains, providing a quick answer to the question of whether a case results from a vaccine reaction or vaccine failure as the time between sample reception and identification of a wild-type measles case is reduced from two weeks to less than 24 hours. This enables the implementation of control measures early on in response to real cases.

A master student has developed a multiplex bead assay (MBA) for the detection of measles IgG in human sera, optimizing antigen preparation and starting concentration as well as the concentration of the detection antibody. He also developed an in-house standard and tested mock controls, which show the assay is specific for measles virus IgGs. The comparison of this assay with the Luminex ELISA on a limited set of samples shows moderate correlation. Another master thesis aiming to establish further correlation to ELISA and to define a cut-off value will ensue.

The laboratory is cooperating with the NVC in order to harmonize epidemiology and laboratory data for the reporting of genotype results and endemic circulation, and to make the evaluation system of the RVC more transparent. This collaboration aims to address challenges such as the difficulty in matching epidemiology and laboratory data, the fact that laboratory confirmation of cases is not mandatory, the lack of reporting of negative cases, issues in dealing with the Federal system, and the lack of resources.

The RRL Berlin was accredited by the WHO in March 2016, and received ISO17025 and ISO15189 accreditation from DAKKS (the German accreditation body) in November with a single (uncritical) deviation. The laboratory also obtained a full score in the serology proficiency test panel 01602 for measles and rubella IgM. In its role as a reference laboratory, the RRL Berlin carried out confirmatory testing/retesting for the laboratories in its constituency, and is currently evaluating the results for a ring trial PCR for MR detection. There are concerns with the new EQA system as some laboratories find it too complex, making reporting difficult.

In summary, there are two main measles virus genotypes circulating in this area of the Region, B3 and D8. The longest transmission chain of measles lasted 5 months, and thus endemic transmission was interrupted in 2016, but it is anticipated that the number of cases will increase again in 2017. There are too few submissions for rubella (n=45, 2 positive samples), and no molecular surveillance is in place for RuV.

During the question and answer session after the talk, Professor Annette Mankertz explained that the reporting of measles is time consuming due to the need to obtain data approval and

epidemiology data from public health officers, and the difficulty in consolidating that data with that available in MeaNS.

The MBA antigen is isolated from MeV-infected cells and then centrifuged, but not purified.

## 1.6. RRL Luxembourg update

*Dr Judith Hübschen (RRL Luxembourg)*

Luxembourg's RRL distributed 26 serology PT panels and 22 molecular panels to laboratories in its constituency. Reagents and kits were also distributed, namely CDC kits for real-time PCR and genotyping, filter papers, and Microelute cards. Ten countries have participated in Instand's mEQA scheme.

The results for the measles serology PT panel were very good, with all countries attaining a score over 96%. Although all countries met the kit validation criteria, there were issues with the completeness of reporting of kit information, and with the lack of in-house controls. Similarly, all countries performed well in the rubella serology PT panel, scoring over 96%, with no problems with expiry date, kit data and validation. The main issues were related with the lack of in-house controls.

The number of laboratories participating in confirmatory testing has remained stable since 2015, with one laboratory stopping (Rotterdam) and another starting to participate (Ukraine). The number of samples retested has decreased last year due to the occurrence of fewer cases. The specimens sent for confirmatory testing are predominantly non-liquid: dried serum spots (46%), dried blood spots (9%) and oral fluids (OFs; 6%). Liquid sera now constitute 39% of the submitted samples.

Most laboratories had 100% concordance in the samples retested for measles, with only two showing a major discrepancy, but still over 96% concordance. Discrepancies were confirmed by avidity testing. Six laboratories sent fewer than ten specimens for confirmatory testing. For rubella, all laboratories had full concordance of results for the specimens submitted. However, four laboratories did not submit any samples and five NRLs sent fewer than ten specimens for retesting.

The RRL Luxembourg has received specimens for genotyping from several countries in its constituency: Georgia, Serbia, Bosnia and Herzegovina, and Ukraine. The measles D8 Frankfurt Main strain that led to a large outbreak in 2014-15 is no longer detected. Two different D8 genotype strains now dominate chains of transmission in this part of the Region: Rostov on Don and Villupuram. Other measles strains detected belong to genotypes D8, Cambridge and Hulu Langat variants, and B3, Dublin named strain.

Other reference activities carried out by RRL Luxembourg's representatives during 2016/17 included a capacity building mission to the Serbian NRL, the accreditation of RRL Berlin, training of Bosnia and Herzegovina's, and Serbia's NRLs staff at the RRL, expedition of reagents, panels and samples to countries in the constituency, providing advice to the WHO South-East Asia Regional Office in the development of a vision and mission for the Royal Centre of Disease Control in Bhutan, and accreditation visits to the Ukraine's NRL.

Additionally, the RRL Luxembourg collaborated with Serbia, Bosnia and Herzegovina, and Romania in publications characterizing local outbreaks. Other publications were on a novel TaqMan assay for



RuV, the etiology of MR-negative rash/fever patients, and a review on MR laboratory diagnosis in the elimination era.

The RRL is also collaborating with the Institut Pasteur du Laos in studies aiming to address topics such as MR seroprevalence, seroconversion after vaccination, waning of maternal antibodies, and rash/fever disease investigations. Measles and rubella IgG test results obtained between 2006 and 2015 by six diagnostic laboratories in Luxembourg are being analyzed to identify gaps in MR immunization. Finally, RRL Luxembourg is collaborating with its partners to assess MMR seroprevalence among children and health care workers from Sudan and investigate rash/fever disease in Cuba and Myanmar.

During the question and answer session that followed the presentation, it was pointed out that when preparing dry spot specimens, it should be ensured that the circle marked in the paper is fully covered in blood (instead of the blood being delimited by the circle). Additionally the dilution factor of dry spot samples is important to ensure reliable results and should be done according to WHO instructions.

Dr Judith Hübschen also referred that a global epidemic of parvovirus B19 appears to be underway, with increased numbers of cases in various countries. These epidemics occur 4 to 5 years, and parvovirus B19 should be considered as a possible cause of rash illness cases.

During the discussion, it was raised that a study addressing the impact of supplementary immunization activities (SIAs) on routine vaccination programmes and whether each approach contributed differently to MR elimination efforts would potentially be useful in assessing best approaches for attracting funding and controlling MR.

## **1.7. PHE GSL update**

*Dr Kevin Brown (GSL United Kingdom)*

Following concerns, since proven unfounded, on the safety of the MMR vaccine almost 20 years ago, vaccine coverage in the UK dropped to its lowest in decades (below 80%) in 2002. A large outbreak of measles occurred in England and Wales in 2012-13, affecting many of the children left unvaccinated in the early 2000s. SIAs followed, targeting the affected areas in Wales and unvaccinated children in England. Both campaigns lead to a significant reduction in measles cases in the following months.

There were 708 suspected measles cases in the UK in 2016, the majority of which was laboratory-confirmed or discarded. Most cases occurred in 15-19 year olds, who should have been vaccinated in the years when MCV1 coverage was lowest. A campaign was undertaken to remind doctors and healthcare practitioners to suspect measles in rash illness cases in older children and young adults as a large cluster of cases was initiated in London after an importation from Italy followed by transmission at an airport and then at hospitals.

Of the 52 cases measles cases that occurred in England and Wales between mid-June and mid-October 2016, almost half affected 15-19 year olds. It was found that several individuals had acquired measles at one summer arts festival and then gone on to attend other festivals while infectious. This resulted in multiple interlinked outbreaks geographically spread both in and out of

the UK. As such, summer festivals were identified as challenging to the control of measles transmission in Europe. In 2017, vaccine clinics will be present at the sites of these gatherings, targeting unvaccinated young adults in attendance. An outbreak of measles virus (MeV) genotype D8 is ongoing, with the circulating strains being Cambridge and Torquay. The latter strain differs from the Cambridge strain by a single nucleotide.

The screening of all booked samples for rubella IgG has been stopped. Non-vaccinated women are now advised to be vaccinated post-partum. Health professionals such as midwives, screening and immunization leads/virologists are being re-trained in the new guidelines for rash illness in pregnancy. So far, no increase has been detected in the number of IgM samples from women aged 15 to 50 years old.

There have been two rubella cases in the UK in 2016. One of these cases was in a cabin crew member of a flight that stopped in the USA. PCR and sequencing were carried out in the USA and the oral fluid (OF) was confirmed as rubella-positive in the UK, where the patient resides. The second case occurred in a 21-week pregnant lady who was re-infected during pregnancy. She had no history of travel, but had most likely been infected at her work setting in childcare. The baby was born healthy, with no congenital rubella infection (CRI).

The PHE guidelines for measles investigation and post-exposure prophylaxis have been updated. A Measles and Rubella Elimination Group (MAREG) was also established with the aim of developing the UK strategy for elimination, addressing differences in testing algorithms in the devolved administrations and targeting under-vaccinated groups. The majority of measles cases in England in 2016 affected children under 8 and between 13 and 20 years old.

The GSL conducted an accreditation visit to the Irish laboratory in August 2016. Although accreditation was granted, issues were identified in confirmatory testing and processing of OF samples. A problem has been identified with the Microimmune measles IgM assay that is specific to OF specimens. It was found that the use of foetal calve serum (FCS) as part of the diluent for OFs is critical and that Tween 20 may also have a role. The Clin-Tech kit's insert has been updated, but it does not reflect the changes in the kit or the procedure used at the London GSL.

In the question and answer session that followed his presentation, Dr Kevin Brown was asked how the SIAs were conducted in England and Wales following the 2012-2013 measles outbreak. He explained that in Wales vaccination clinics targeted mainly school-aged children, while in England all those unvaccinated or lacking a complete vaccination record were either called to their GPs or offered vaccination when attending their practice for any other reason.

### **1.8a. CDC GSL update – Rubella**

*Dr Joseph Icenogle / Dr Bettina Bankamp (GSL USA)*

The heavy burden of congenital rubella syndrome (CRS) was quantified in 2015. It was determined that there is a 30% mortality rate among CRS cases. The mortality and disability-adjusted life years associated with CRS account for significant expected lifetime costs from adverse health outcomes per CRS case. These were estimated at over \$930 000 in countries defined as high income by the World Bank. In the same year, rubella and CRS were declared eliminated in the AMR.

In recent years, roughly the same number of acute rubella and CRS cases has been reported to CDC. The ratio of CRS to rubella cases varies with epidemic years, but is generally higher than would be expected. This could be due to pregnant women seeking advanced health care in the USA or to missed acute rubella cases.

The molecular surveillance of rubella is impaired due to the lack of a complete dataset of rubella genotypes and sequences. However, even the small amount of information available can be helpful in some cases. Recently, RuV associated with Fuchs uveitis in a patient suffering from persistent rubella infection has been sequenced and identified as identical to a viral sequence from Stuttgart, where the patient grew up.

Vaccine-associated RuV has been found in skin lesions in immune-deficient patients with ataxia telangiectasia (AT). This disorder is due to a mutation in a gene involved in cellular stress-responses. In some cases, granulomas may become necrotic and the virus can be found in multiple sites, including the skin, liver and kidney. The RuV found in these patients are divergent, but can be related to the vaccine virus. In 2016, the CDC sequenced the RuV associated with an encephalitis case from PHE. In testing virus isolated from a granuloma case, it was found that although some sera from healthy vaccinated individuals were negative for neutralizing antibodies against the granuloma virus, sera from the granuloma patient was neutralizing.

Of the 13 RuV genotypes previously described, only 5 are currently circulating. 3 of these are infrequently detected: 1J, predominantly in the Philippines and rarely seen elsewhere; 1G, endemic in central Africa and sporadically seen in other regions; 1H, previously thought to be eliminated, but seen in the Russian Federation in 2008 and then in Turkey in 2016. The majority of rubella cases are associated with two genotypes: 1E and 2B, both widely distributed. Although sequences submitted to the rubella nucleotide surveillance database (RubeNS; who-rubella.org) are associated with the submitting country, it is possible to determine the virus provenance based on four main lineages associated with genotype 2B. Countries such as China, Vietnam, Thailand and Indonesia appear to be the main source for RuV reported elsewhere.

In 2016, Atlanta's GSL continued to perform validation and distribution of kits for rubella testing (166 kits) and genotyping (148 kits) globally. Molecular EQA evaluations were also carried out for approximately 50 laboratories. Research-wise, the CDC continues to analyse transcriptomes of rubella-infected cells and to use NGS methods (both pathogen-dependent and independent) to produce whole genome sequences (WGS) of RuV. A new RuV detection system and control RNA have been developed that detect all genotypes with identical sensitivity, making use of simpler primer/probe system that has higher sensitivity.

Good serology markers have been identified for CRS in school-aged children using western blot. However, due to limitations associated to exporting this method, a C protein ELISA is being developed to mirror the western blot results. This assay is ready to use in research serology studies. The plates for the assay are stable for a year.

Dr Bettina Bankamp updated the participants on CDC's activities on measles. 2016 was relatively calm year for measles in the USA. 69 cases were reported in 15 states, associated with 4 outbreaks (3 or more linked cases). 23% of cases lead to the hospitalization of the patient. All 50 sequenced MeV belonged to genotypes D8 (n=37) or B3 (n=13). D8 viruses were imported from India, Spain,

Ukraine, Indonesia and Mexico, while B3 strains originated from Jordan, Saudi Arabia, Pakistan, India and Europe. While no exact source of the virus was found for the outbreak in California (4 nucleotides difference from the virus circulating in India), the strains detected in Arizona are an exact match to those circulating in New Zealand, Australia and India. The outbreak reported in Illinois and Florida appears to be associated with an importation from either Malaysia or Thailand. Finally, MeV sequences from the Tennessee outbreak match those found in Romania, Serbia, Ireland, Italy and Austria.

In 2016, the mEQA panel was prepared and shipped by the Wisconsin State Laboratory of Hygiene and included backup samples for retesting. The report was redesigned to separate detection and genotyping and included a detailed description of the required supporting information and acceptable file formats. An example of a completed report was also included. 100% accuracy in sequence reporting is required this year and nucleotide errors will lead to a “retest” score.

The majority of panels have been shipped, except those destined to Argentina, Brazil and Mexico. There have also been issues with the distribution of panels by the RRL of Oman to the WHO Eastern Mediterranean Region laboratories. Of the 37 laboratories that have received mEQA panels, 8 have been asked to re-test for measles and 1 for rubella. 32 laboratories have passed the measles panel and 35 the rubella panel.

There are plans to assess sensitivity of detection, with future panels to reflect the typical specimens received by the laboratories. The need for RT-PCR positive controls to assess the sensitivity of the detection assay will be emphasized. Additional activities under consideration include submission to the MeaNS or RubeNS databases, and web-based reporting of results.

The CDC has changed the primers used for MeV sequencing, adding an M13 sequence to the forward and reverse primers that is then used for the sequencing reaction. This does not affect PCR sensitivity and improves sequence quality as the distance to the end of the sequencing region is increased.

So far, the primary samples used for molecular detection of measles have been throat swabs. However, cold-chain transportation is required for these samples, and can be challenging when samples need to be moved long distances, sometimes across borders, to laboratories that can perform the required assays. In 2014, a study was carried out in collaboration with the INRB in Kinshasa, DR Congo where samples were collected in throat swabs (TS) and shipped as swabs or applied to FTA cards (FTS) in order to assess the sensitivity of molecular assays when performed on these two types of specimen.

The tests and data analysis were performed at CDC Atlanta and a manuscript is in preparation to report the results. It was found that in general the use of FTA cards to transport throat swab samples yields good results. 18.1% of PCR-positive TS samples are negative when applied to an FTA card. For genotyping, the cut-off for obtaining MeV sequences is  $1 \times 10^4$  copies. Hence, due to the lower likelihood of obtaining a sequence (40.3% for FTS samples and 77.7% for TS samples), this method of transport is not advised for sporadic cases. However, this method would be appropriate in outbreak situations, where many samples are available for sequencing. FTA cards may also be applicable to the transport of samples from CRS cases, but not from acute rubella cases. The use of OF samples

collected using an Oracol device is also an alternative to throat swabs, with 71% of samples collected in this manner being amenable to MeV sequencing.

A multiplex immunity assay (MIA) that can be used in IgG quantification for measles, rubella and mumps can be used to reduce the costs and labour required for carrying out immunity studies in populations, such as seroprevalence and seroprotection studies, and verification of herd immunity for elimination. This assay also requires smaller sample volumes and can be used for dried blood spots (DBS) specimens. It could be used by RRLs to support laboratories in their region. The MIA using whole measles virus compared favourably to a variation of it using the N protein as an antigen. It has good correlation coefficients with EIA and plaque reduction neutralization assays. Efforts are underway to address issues with antigen supply and to standardize bead production.

Vaccination is often carried out in response to outbreaks and approximately 5% of vaccine recipients develop rash and fever. So far, vaccine and wild-type measles cases are identified in the laboratory by genotyping. A new RTqPCR for detection of vaccine strains has been developed and its sensitivity is higher than for the assays available so far. The method has been published in 2017 by Roy et al. in the Journal of Clinical Microbiology.

## Session 2 – Quality assurance

*Chair: Dr Sabine Santibanez*

### 2.1. Serology EQA

*Dr Judith Hübschen (RRL Luxembourg) / Dr Tamara Mamaeva (RRL Moscow) / Professor Annette Mankertz (RRL Berlin)*

In the RRL Luxembourg's constituency, the measles IgM EQA panel results are good. However, there are still issues with incompleteness of the data submitted. Commonly missed were the kit data, kit expiry date, and in-house control. There were also problems with the timeliness of submissions. The laboratories performance was worse than in the previous EQA exercise, with 18 out of 20 laboratories achieving accreditation. Half obtained a perfect score, which is up from last year's panel.

For the rubella serology EQA, this year's performance was better than for the last panel. There are 5 different kits in use, most countries use an in-house control and provided complete information. Only a single laboratory failed to submit results on time. Half of the laboratories obtained a perfect score for the EQA exercise, which is improved since the last EQA panel.

In terms of confirmatory testing, there was very high concordance for both measles and rubella, with few major discrepancies. Although all laboratories met the accreditation criteria, the number of samples submitted is very low. The Macedonian laboratory did not submit samples for measles confirmatory testing and the Greek laboratory failed to do so for rubella.

All laboratories in the Moscow RRL's constituency participate in the WHO EQA panel and repeat testing for external proficiency control. In-house laboratory controls are in place for internal quality control. For the first time in 2016, all laboratories have tested over 50 samples. Over 80% of the laboratories report IgM results within 4 to 8 days, over 90% report results to WHO, and conduct proficiency testing and repeat testing for measles and rubella IgM.

The laboratories had issues with online submission of proficiency testing results. Although there was 100% concordance with panel results, six laboratories still failed to include or take into account validation criteria such as the cut-off value. Some laboratories also used expired kits for their testing. The test kits used are mainly Vector-Best, Ekolab and Siemens. In 2016, 17 out of the 23 laboratories in the constituency achieved a perfect score in the EQA panel, improved from 11 out of 23 in 2015.

The result form for repeat testing reporting to the WHO is now available in Russian. The first page is for Siemens kits and the second for Russian kits. The reproducibility of ILC testing between 10 Russian sub-national laboratories using the Vector kit for measles IgM testing was assessed using paired sera samples. The results indicate the necessity of accounting for modifications in the utilized kits when calculating the cut-off value for the test. The dilution of IgM-containing ILC samples is recommended to prevent cross-reaction with non-target markers (IgG) and to obtain the goal cut-off value of 2-3.

Only one laboratory in Berlin RRL's constituency failed in the proficiency testing. However, laboratories frequently do not use in-house controls or use expired kits, and report control values divergent from the mean. In terms of confirmatory testing, all countries except one achieved perfect result concordance. The single incorrect sample was due to a single mistake that was not related to the test. The major issue in confirmatory testing is that countries are testing very few samples, a trend that may be aggravated as countries approach elimination. The picture is similar for measles and rubella.

## **2.2. Molecular EQA**

*Dr Sabine Santibanez (RRL Berlin)*

A new form was used for the molecular EQA panel in 2016. It requires more kit and primer information and explains how the laboratory should dilute the samples obtained from FTA cards. The results are still being analysed and will be completed before this year's global meeting in May.

The results for the countries that participated solely on the detection proficiency panel are with Instand e.V.. A preliminary analysis of the results from countries that participated in both the detection and sequencing exercises shows that many countries submitted incorrect length sequences. Some of the sequences submitted had errors, and, in some cases, there were many mistakes. Incorrect primer sequences were also reported. The very low incidence of MR in Scandinavian countries constitutes a challenge for maintaining good molecular surveillance. It was agreed to ask for the chromatograms to be submitted from countries who had sequence errors for further analysis. PHE agreed to review the chromatograms as needed.

In the discussion that followed this presentation, participants discussed the procedure to deal with countries that submitted sequences with errors or incorrect length. It was agreed that these countries would not be accredited for sequencing this year. The procedure decided on for following years is outlined in the recommendations from the meeting in section 3 of this document: Recommendations.

## **Session 3 – Trainings**

*Chair: Dr Judith Hübschen (RRL Lusembourg)*

*Dr Myriam Ben Mamou (WHO regional office for Europe)*

The third session of the meeting was dedicated to identifying training needs and modes of addressing them. Dr Ben Mamou made a brief presentation on the current gaps in training to prompt the discussion.

Training is essential to maintaining the LabNet's high level of proficiency and performance. Two components of this are that staff knowledge and competencies are kept up-to-date and that more targeted training required for capacity building and skill strengthening is carried out periodically. The annual accreditation programme and the mechanism of supervision by the RRLs are crucial in identifying training needs.

In the European Region, training has been conducted in various manners: laboratory workshops (organized by the WHO, the USA CDC GSL and the Moscow RRL); individual-tailored training at the UK GSL and the RRLs' premises; capacity building and on-site training missions (conducted by the RRLs). Despite being very useful, these approaches are insufficient as cost, time and logistic issues limit their comprehensiveness, both in topics and staff covered. These limitations are compounded by staff turnover and the absence of a structured training plan/programme.

The WHO aims to create an interactive e-Learning course to address these limitations and complement the existing training structures. This would be a platform available to all laboratory workers of the WHO European LabNet, where they could update their knowledge on MR laboratory investigation, learn the requirements for compliance with LabNet standards, and stay connected.

As the production of training materials is time- and cost-intensive, training materials already available (published materials and meeting training sessions for example) should be brought together to address identified gaps in expertise. For this, a small committee, which would include laboratory representatives, should be created. This workgroup would identify training needs, review available materials, design the training package required, and develop the content of the first WHO online training for the European MR LabNet. The first phase of the project is underway and is dedicated to content development. The second phase will involve transferring the content created to an online learning platform.

During the brainstorming session that followed, various alternative training approaches were suggested, including video conferencing, meeting slide sharing, more technical modules addressing specific techniques. Video conferencing, webinars, on-call troubleshooting and forums could complement more static modes of training.

## **Session 4 – Verification of measles – rubella elimination**

*Chair: Dr Kevin Brown*

### **4.1. Update from the RVC**

*Dr Irja Davidkin (WHO EUR RVC representative)*

All six regions of the WHO have set elimination goals for measles elimination. PAHO has achieved elimination of measles and rubella. The Eastern Mediterranean and European Regions missed their elimination targets of 2015, Western Pacific Region of 2012. The African and South-East Asian

regions aim to eliminate measles by 2020, with the same date being set for rubella/CRS control in the South-east Asia Region.

2016 was the year with the fewest measles cases ever reported in the European Region. Romania was the major contributor for measles circulation, with 2 432 measles cases reported. The incidence of rubella has also been declining, with a 99.8% reduction in cases reported between 2000 and 2016. Poland reported 86% of the rubella cases registered in the Region.

The RVC was established in 2012 with the aim of evaluating and providing feedback on each country's annual status for elimination. The verification process has been modified and the annual report form updated. Messaging and communication have been crucial and improved in response to countries' issues and response.

The verification of elimination is an on-going process that must be evidence-based, measurable and independent. The laboratories have a pivotal role in the process of elimination, as confirmation of cases and a well-performing reliable surveillance system are required for early identification of outbreaks and susceptible populations. Genotyping information is also essential in confirming endemic cases.

Indicators used to assess the efficiency of surveillance systems include timeliness and completeness of reporting, rate of laboratory investigations, rate of discarded cases, viral detection, origin of infection, and timeliness of investigation.

In 2015, the RVC evaluated 51 countries for measles and rubella elimination. 24 countries achieved elimination of measles and rubella, while 2 failed to submit a report to the RVC. 14 countries still have endemic measles and 16 have endemic rubella. The remaining countries have interrupted endemic transmission for fewer than 3 years. Since 2014, all assessments have been conclusive, a significant improvement since the establishment of the RVC in 2012, due to better structured systems and reporting.

The challenges to the verification process are in incomplete and/or low sensitive surveillance systems, the insufficient vaccination coverage in many countries and diverse national operating procedures for epidemiological and laboratory investigations in some countries. The importance of genomic sequence data will continue to increase as the elimination requires high-quality surveillance to confirm the origin of every case and chain of virus transmission.

Actions that will be essential to achieve measles and rubella elimination in Europe are achieving high vaccination coverage, establishing high-quality surveillance systems, closing immunity gaps and improving knowledge and training within the LabNet.

## **4.2. Update from the WHO Secretariat**

*Dr Myriam Ben Mamou (WHO regional office for Europe)*

The WHO secretariat has collaborated with the RVC in the revision of the annual status report, and in assessing the 51 annual country updates submitted to the RVC. The priority of the WHO/Europe is on the countries endemic for measles and/or rubella.



The LabNet is essential for the elimination verification process as three essential indicators rely on proficient WHO laboratories (WHO accredited and/or with established quality assurance programme with oversight by a WHO accredited laboratory):

1. Rate of laboratory investigations – percentage of cases suspected for measles or rubella for which adequate specimens were collected and tested in a proficient laboratory;
2. Rate of viral detection – percentage of laboratory-confirmed chains of transmission of measles or rubella with suitable samples collected for viral detection in an accredited laboratory;
3. Rate of discarded cases – fraction of suspected measles or rubella cases investigated and discarded as non-measles or non-rubella cases using laboratory testing in a proficient laboratory and/or epidemiological linkage to another confirmed case.

The WHO secretariat is increasingly interacting with the RVC to bring verification to the fore at the level of accreditation, training and meetings. The reporting of MeaNS and RubeNS sequence identifiers is now required in the annual status update (ASU). The secretariat and the RVC also share databases for accreditation and verification, with the secretariat providing crucial information to the RVC's assessment such as background information and graphical representations of genotyping data. Dr Irja Davidkin, the only virologist in the RVC concentrates on the analysis of the laboratory data, while the remaining members of the commission look into the epidemiological data.

The rate of laboratory investigations is in general higher for measles than for rubella. Four countries report the vast majority of rubella cases in the European Region, with 86% of cases being reported by a single country (Poland). 16% of the 37 laboratories reporting measles cases failed to provide measles genotyping data, while 71% of 24 countries recording rubella cases do not report rubella genotyping information in their ASU. Thirty MS reported measles cases and genotype information in their ASU. Of these, 12 used the NL listing functionality in MeaNS correctly, while 18 either did not use this tool or provided incorrect MeaNS distinct sequence IDs.

Many countries have detected a low number of measles cases and have low rates of viral detection. 18 out of 37 countries document more than 80% chains of transmission, which is an improvement from previous years. For rubella, the picture is more concerning, with very few countries having a good rate of viral detection. Only 2 of the 24 MS with rubella cases have over 80% of chains of transmission documented.

Of the 53 MS, 50 have tested measles suspected cases. Of these, 37 reported that all of their laboratory results originated from WHO-accredited or proficient laboratories, although the evidence to support proficiency is sometimes insufficiently documented in the ASU. 3 MS reported that they do not control proficiency of the laboratories where most or all their results originated and 9 do not know what proportion of the results reported originated in proficient laboratories.

7 of the 53 MS did not test rubella suspected cases. Of the 46 MS that reported rubella cases, 10 do not know what proportion of their results are provided by proficient laboratories. In 32 MS, the majority of the results reported were obtained in WHO-accredited or proficient laboratories. For rubella, a significant fraction of the tests reported are related with systematic screening rather than suspected case testing.

### **4.3. Revision of EUR ASU form for 2018 round**

*Dr Myriam Ben Mamou (WHO Regional Office for Europe)*

The sixth round of annual status updates took place in 2017. As the data for these reports results from the contributions of both laboratory and epidemiology, frequent discordances are found in the data submitted. Based on lessons learnt from 2017 and previous rounds, the report form is being updated for 2018 in order to facilitate the reporting, analysis and decision-making process, and to incorporate any missing data. The participants were guided through the current report form and asked for feedback. The new report form and corresponding instructions will be made available to the laboratories when completed.

### **4.4. Guidance to NRLs to establish national oversight / 4.5. Laboratory strategy for case classification**

*Dr Myriam Ben Mamou (WHO Regional Office for Europe)*

The participants discussed issues with national oversight and case classification. Concerns were raised over data included in the ASU that was obtained by laboratories over which no WHO laboratory has oversight, and the lack of clear WHO guidelines on case discard per sample type timing and testing. The outcomes of this discussion are included in the recommendations of the meeting (section 3 of this report, Recommendations).

## **Session 5 – Molecular epidemiology and data sharing**

*Chair: Dr Sergey Shulga*

### **5.1. Update on molecular epidemiology in EUR**

*Dr Kevin Brown (GSL United Kingdom)*

Dr Kevin Brown updated the participants on the molecular epidemiology in the EUR based on the data of MeaNS ([who-measles.org](http://who-measles.org)) and RubeNS ([who-rubella.org](http://who-rubella.org)). A new senior bioinformatician is in post, Dr David Williams. Interviews have been conducted for another bioinformatics post and the selected candidate will start during the month of August.

The website for the MeaNS database will run correctly in most browsers, except for Internet Explorer 9, where sub-menus are not displayed correctly. Issues have been found with the RubeNS website as it appears to have been attacked with malicious intent. The domain [qws.who.rubella.org](http://qws.who.rubella.org) has been purchased triggering alerts in Google Chrome and Firefox. Up to now, no problems are found with displaying the website in Internet Explorer. So long as the user inputs the website address correctly ([who-rubella.org](http://who-rubella.org), no [www](http://www)), the page displays and runs correctly.

There are currently 33 441 sample records and 34 355 viral sequences in MeaNS. An overall upwards trend in the number of submissions has been observed since 2000. The two main contributors of sequences to MeaNS are the Western Pacific and European regions. The measles genotypes of measles still circulating are B3, D4, D8, D9 and H1, with other genotypes having not been detected for several years. Of the no longer circulating genotypes, G3 was the most recently recorded in 2014.

The Eastern Mediterranean and PAHO regions are the leading WHO regions in laboratory confirmation of measles suspected cases with 81 and 66%, respectively. The regions with the fewest laboratory confirmed cases are the African (0.6%) and the South-East Asian (3%) regions. This means that the data submitted to MeaNS is biased towards the genotypes circulating in regions where laboratory confirmation of cases and genotyping is carried out. Another caveat in the analysis of MeaNS data is that many countries do not submit their sequences to the database in real time. Some do so almost a year after sample testing, limiting the usefulness of those sequences.

In the European Region, D4 was the prevalent measles genotype between 2007 and 2012, having since been supplanted by D8 and, to a lesser extent, B3. The majority of the sequences submitted by the EUR countries were D8 (65%) and B3 (31%). There were 5 different B3 named strains reported throughout 2016 in the European Region, with the most N-450 sequences reported being identical to the MVs/Niger.NGA/8.13/ strain. The country from which most importations of measles genotype B3 strains were reported was Romania. D8 sequences submitted matched 6 different named strains, with 57% of sequences matching MVs/Cambridge.GBR/5.16/. Summer arts festivals in the UK were found to seed multiple outbreaks of the Cambridge strain European Region-wide. Indonesia is the country from which most D8 importations were reported by European Region countries.

There were few RubeNS submissions in 2016 from the European Region. The majority of submissions of RuV sequences were from countries in the Western Pacific Region. The top submitter in the European Region was the Russian Federation. Turkey confirmed several rubella cases, but submitted only a sequence of genotype 1H, not frequently seen in the region. The vast majority of RuV sequences reported were of genotype 2B and 1E.

MeaNS and RubeNS are becoming increasingly important in the process of verification of elimination and provide valuable tools for reporting, monitoring transmissions and documenting importations. MeaNS reveals European Region-wide patterns of measles circulation and that the number of circulating MeV genotypes is decreasing. It remains to be ascertained whether this reduction is real or a product of sampling and submission biases.

## 5.2. Update on MF-NCR research / NGS studies

*Dr Bettina Bankamp (GSL USA) / Dr Kevin Brown (GSL United Kingdom)*

The CDC obtained the N-450 and MF-NCR (non-coding region between the matrix and fusion genes) sequences for the samples collected during a 12 week measles genotype D9 outbreak in an Amish community in Ohio during 2014. No changes were observed in either the N-450 or the MF-NCR for the 37 samples sequenced. When attempting to sequence samples from an H1 measles outbreak in Mongolia, it was found that although it was possible to amplify 75 out of the 80 samples received and genotype 70 out of the 75 successfully amplified specimens, the success rate for sequencing the MF-NCR for these samples was much lower, with only 26 complete MF-NCR sequences obtained. This could be due to RNA degradation associated with sample shipment on FTA cards. The most divergent MF-NCR sequences differed by 11 nucleotides.

Whole genome sequencing (WGS) of MeV is being carried using a PCR-based approach using the primers published by the GSL in London adapted to include additional degeneracy. In order to shorten the process, amplification is being carried out in a real-time machine, using SYBR green to assess product concentration, thus obviating the need for running gels and measuring ODs. This

methodology provides good results and is higher throughput, more efficient and cost-effective. The addition of carrier RNA during the RNA extraction was found to improve coverage.

Two different enrichment methods have been attempted for WGS by metagenomics. The first was the use of enrichment probes on MeV isolates. This was successful, resulting in a 20 to 40-fold increase in mapped reads. However, the first attempt on clinical samples led to no enrichment and is now being repeated. The limitations with the methodology are that the coverage was not uniform (potentially more probes needed) and that it is very costly (an additional USD 200 per sample). An alternative enrichment method tried was the use of duplex-specific nuclease (DSN), which works by removing dsDNA from a partially hybridized library. It is inexpensive and is not template specific, and so would work on any genotype. The preliminary results are mixed, with little to no enrichment found in first experiment carried out and up to 23-fold enrichment observed in the second.

The CDC bioinformatics pipeline revealed a double infection with MeV and respiratory syncytial virus (RSV) in a 8 year old patient hospitalized after visiting Disneyland in January 2015. The measles strains had 99.8% identity with MVs/Luton.GBR/4.14/[B3], while the RSV strain detected strain was identical to a strain circulating in the United States in 2013.

The UK GSL is also further optimizing the methodologies for WGS and MF-NCR sequencing of MeV. After a first promising experiment with metagenomics in cell culture isolates, the assay is being optimized and used to obtain the sequences of the WHO strain bank isolates kept at PHE. The required starting material has been reduced from 5 to 1 ng of RNA and a single experiment with an oral fluid specimen yielded promising results. Two visitors from WHO NRLs will arrive later in the year for training in the sequencing of the MF-NCR. The sequencing step of this procedure is still under optimization. Currently, sequences can be obtained for 72% of the genotyped specimens.

### **5.3. Publishing molecular epidemiology data in EpiBrief/EpiData**

*Dr Myriam Ben Mamou (WHO Regional Office for Europe)*

A new EpiBrief report was first published in 2016 by WHO/Europe, covering measles and rubella molecular epidemiology data. The report highlights current circulating strains and the caveats associated with the use of sequence data and will be published quarterly. The EpiData report is published monthly and has been updated to show more useful information, while leaving out less-used data. Both the EpiBrief and EpiData reports are available on the public domain of the WHO website.

In order to answer increasing interest in molecular data and limitations of MeaNS and RubeNS terms and conditions, a new Measles-Rubella bulletin will be published by WHO. It will include genotype data with indication of the number of reported cases (upon country authorization), circulating lineages, and regional maps depicting genotypes and named strains.

## **Session 6 – Future plans & recommendations**

### **6.1. Agenda and format of NVC-NRL meeting, Belgrade, Nov 2017**

*Group discussion*

WHO/Europe is organizing meetings to bring together laboratories, epidemiologists and policy makers of the Balkan countries to discuss issues found during the ASU preparation. The goal is to improve collaboration at the various levels for better reporting and to promote exchange of experiences and approaches between laboratories. The RVC and relevant RRLs will be present to address problems and answer questions. Topics should include mEQA, logistics, IQC, serology PT, and reporting. If the format proves helpful, more meetings will be organized for other country groups.

## 6.2. Update on publications

### *Group discussion*

A paper on the circulating MeV genotypes in the European is being planned. The scope of the publication must be addressed and countries asked for authorization.

## 3. Recommendations

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

### SURVEILLANCE

1. The recent mid-term review of the Measles and Rubella Global Strategic Plan<sup>1</sup> is a useful tool to advocate for strengthening laboratory-supported surveillance and was recently endorsed by SAGE<sup>2,3</sup>. The WHO Regional Office to disseminate the Russian translation of the report to WHO European MR Labnet.

### LAB TECHNIQUES – PROTOCOLS

2. FTA cards have been shown to lead to a decrease of approximately 4 fold in viral titres and are thus not advisable for sporadic measles/rubella case testing when other sample types can be shipped/forwarded to the lab. When laboratories have logistic issues receiving samples of acceptable quality for testing, FTA cards can be used. FTA cards remain valid for outbreak situations.
3. An ELISA test for older children with CRS has been developed by the CDC and is available to other laboratories for studies. Plates and reagents are stable for over a year.
4. Dried Blood Spots (DBS) are successfully used in the European Region for IgM retesting contrasting with lower performance in other regions like the South-East Asia Region. Take the opportunity of the upcoming GMRLNM in Geneva (June 2017) for the European/South-East Asia Region to share experiences.
5. Careful attention should be paid to the protocol for OFs elution: need to use FCS and Tween to avoid false positives (PHE SOP available on request).

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<sup>1</sup>[http://www.who.int/immunization/sage/meetings/2016/october/1\\_MTR\\_Report\\_Final\\_Color\\_Sept\\_20\\_v2.pdf?ua=1](http://www.who.int/immunization/sage/meetings/2016/october/1_MTR_Report_Final_Color_Sept_20_v2.pdf?ua=1)

<sup>2</sup><http://apps.who.int/iris/bitstream/10665/251810/1/WER9148.pdf?ua=1>

<sup>3</sup>[http://www.who.int/immunization/sage/meetings/2016/october/October\\_2016\\_SAGE\\_report\\_RU.pdf?ua=1](http://www.who.int/immunization/sage/meetings/2016/october/October_2016_SAGE_report_RU.pdf?ua=1)

6. Adding M13 to sequencing primers improves the quality of sequences (CDC SOP available on request).
7. Data were presented on progress of WGS and Luminex studies. Further evaluation is needed before potential routine use for the programme.

#### QUALITY ASSURANCE - ACCREDITATION

8. VIDRL might consider modification of the PT online submission form for non-Siemens kits as several laboratories find it non-intuitive.
9. RRLs to follow up on in-house control issues and kits expiry dates with non-compliant NRLs.
10. PCR detection and genotyping constitute different sub-categories of molecular EQA. Laboratories that succeed in the PCR detection section of the mEQA are accredited for PCR testing, but they will only be accredited for genotyping if successful in the sequencing section of the test. Laboratories should be informed of the general issue with their sequence(s), but encouraged to carry out problem solving themselves with the help of their RRL if required. As previously announced, the outcome of 2016 mEQA will be integrated into 2018 accreditation. RLC to inform MeaNS/RubeNS administrator about the NRLs that failed genotyping component of mEQA.
11. Additional resources are needed for mEQA evaluation. WHO headquarters considers soliciting additional budget from donors.
12. Next round of mEQA to request chromatograms to allow automated pre-screening of the sequences.

#### TRAININGS

13. Distinguish between the categories of mEQA issues to adjust capacity building accordingly with targeted interventions.
14. WHO/Europe developed draft terms of reference for an e-learning project, including the constitution of an e-Learning Advisory Committee (e-LAC). The project will gather available training resources and considering implementing new training resources to address gaps in training. The project was endorsed by RRLs/GSLs and RLC requested to proceed with the call for applications during the second half of 2017.
15. Important features that the e-learning should integrate: low cost options video conferencing, dynamic adjustment to training needs, interactivity and quick answers (forum, troubleshooting), Q&A, modular structure.

#### REGIONAL VERIFICATION PROCESS

16. The laboratories have voiced concerns over the need and clarity of the information requested in the ASU. RVC to clarify specific questions answered by tables in section 3 and how labs should fill them in. Some definitions (e.g., chains of transmission length, sporadic cases, definition of suspected cases, discarded cases –how to discard, proficient laboratories) in the ASU report need clarification and possible adaptation to European Region specificities.
17. ASU to be revised and draft shared for the European MR LabNet's comments and suggestions, to be piloted during November meeting (see below meetings section).
18. PCR is acceptable for case-confirmation, but criteria for discarding cases are not established. This should be made clear in WHO guidelines for testing/laboratory manual as well as in the

ASU report form (indicator of rate of discarded cases to mention “by serology” and lab strategy to specify that exclusion only by negative PCR is not recommended).

19. Provide further instructions on accredited laboratories: how WHO reference laboratories should deal with their data, given the lack of a supervision role. Consider having an additional category in the ASU like laboratory accredited by a national accrediting body (not by WHO) and expanding the meaning of proficient.
20. Currently there are two different tables for “outbreaks” and “sporadic cases” that might need to be merged, upon RVC’s recommendation.
21. To global level: consider reviewing the criteria for rubella elimination (rate of viral detection) to reflect particular challenges of rubella surveillance. Currently the European Region is working with countries to assess availability and reliability of other sources of rubella data that could document / support rubella verification.

## MEETINGS

The Regional Office is organizing a joint workshop on 20-24 November 2017 bringing together country delegations of NVC, epidemiological surveillance representatives and laboratory experts from NIS and Balkan countries. The focus will be the verification process and testing the revised ASU to finalize the revision for 2018 round (2017 data).

22. The programme and the format of the meeting to be designed based on the expected results of the meeting.
23. The brainstorming provided useful suggestions for the agenda and the format. RLC to discuss within ADC, consolidate and share a draft agenda with RRLs/GSLs for additional comments.
24. It is advised to organize mock exercises for country delegations to collaborate on filling out new ASU forms using their actual surveillance data. Separate sessions to be organized for laboratory issues (accreditation, EQA).
25. It is also recommended to set up bilateral meetings between NRLs/ RRLs as organized in Budva meeting – June 2016, to address specific issues.

## PUBLICATIONS

26. Modifications of laboratory tables in WHO EpiBrief/EpiData are approved and can include additionally the data disseminated by VPD surveillance (MeaNS RubeNS maps and genotypes per country). Specific mention of variants distribution requires MeaNS submitters’ prior authorization.
27. Several papers have been published by RRLs / GSLs in 2016/2017. Leading authors to share them with RLC for dissemination among European MR LabNet and GMRLN.
28. Other articles that have been initiated to be finalized.

## Annex 1: List of participants

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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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