



MEETING REPORT

World Health Organization-coordinated Global Invasive Bacterial Vaccine-Preventable Disease (IB-VPD) and Rotavirus Surveillance Network Meetings

15th-18th November 2016

Geneva, Switzerland

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Global IB-VPD Surveillance Network Meeting, Day 1

Tuesday, 15th November 2016

Welcome and introductions

Presenter: Jean-Marie Okwo-Bele

Surveillance and showing impact from vaccines are core functions for all partners. IBV surveillance is being leveraged to monitor other VPDs. The mid-term review on the Decade of Vaccines found it compelling to see the impact of PCV in the Americas. Considering the cost of PCV, it is good to justify sustained use. We need to show impact from vaccines and a return on investment. For example, measles has shown an 80% reduction in mortality after prolonged and widespread vaccine use which shows the value of surveillance. Pneumonia and diarrhea are the leading causes of death among children <5 years of age globally, and we need sustained surveillance and improved coverage for PCV in order to show a similar decline. We face some challenges: countries that graduate from GAVI support and the winding down of polio funds. The countries that are lagging behind are not necessarily the most resource-poor countries. We need to encourage all countries to make surveillance a priority and help generate evidence to justify funding. Looking forward, what will be the epidemiology of VPDs after 2020? Will there be new vaccines developed? We need surveillance to be able to answer these questions.

Session I: Global Overview of IB-VPD surveillance network and 2016 progress

Presenters: Fatima Serhan and Adam Cohen

WHO recommends the introduction of pneumococcal conjugate vaccine in all countries. WHO's role in VPD surveillance is to generate and monitor VPD trends globally; to lead, coordinate, and advocate for surveillance activities with countries and partners, including EQA/QC ; to set global norms and standards for surveillance; to support countries with technical assistance and evidence-based policy decisions; and to support research that builds on surveillance platforms and informs immunization program monitoring and policy. WHO has coordinated two sentinel VPD surveillance networks since 2008: The Global Invasive Bacterial Vaccine-Preventable Disease (IB-VPD) Surveillance Network and the Global Rotavirus Surveillance Network. The objectives of the surveillance networks are evolving. We now focus on burden and vaccine impact in regions with data gaps, but also look at long-term impact after vaccine introduction and leveraging the surveillance platform to monitor other VPDs such as typhoid. Of the 52 countries that are part of the Global Surveillance Network, many meet the performance criteria, though they may not reflect the strength of the surveillance and whether the data is being used. Over 30,000 cases of meningitis and pneumonia were enrolled globally in 2015. Most regions, excepting EUR, has pneumococcus as the most common pathogen identified. Fourteen countries conduct pneumonia surveillance, for a total of nearly 12,000 cases; however, a pathogen was identified in only 1%, the majority pneumococcus. The surveillance data is being used for country decision making, publications, and global burden models.

The laboratory network is a critical component of surveillance. In 2015, 140 laboratories were part of the WHO coordinated laboratory network and participated in global quality assurance quality control programs that help assess laboratory capacities and monitor performance to diagnose and type the positive strains. Initial testing at the sentinel site include bacterial culture rapid diagnosis testing and serotyping/serogrouping is mainly done at the national or regional reference laboratories. In 2015, 98% of samples that were collected through meningitis and pneumonia surveillance had a laboratory test and 3% gave a positive result for one of the three pathogens, Spn, NM or HI of which 49% had been assigned a serotype/serogroup. The global external quality assessment program (EQA), coordinated by WHO and the Public Health England (PHE), consists in distributing proficiency testing panels to all participating laboratories. EQA results in 2015 showed a high level of performance where 84% of the labs did have a passing score. WHO in close collaboration with the CDC global reference laboratory conducted regional laboratory workshops to enhance PCR capacities in the national laboratories, contributing to sustainability of surveillance.

Session II: Using surveillance data for decision-making in countries

Chair: Jason Mwenda

PCV impact and effectiveness systematic review in Latin American countries

Presenter: Lúcia de Oliveira

The objective of the study was to summarize the evidence of impact and effectiveness of PCVs on hospitalizations and mortality in Latin American countries. The final analysis included 22 studies from 33 references; 16 used surveillance data, and 6 used secondary hospital data. This is the first review of the impact and effectiveness of PCVs in LAC countries. All studies showed reductions in the disease outcomes studied, which is consistent with the global literature. The sensitivity of pneumonia diagnosis and estimated vaccine effectiveness of PCV on pneumonia varied according to endpoint and case definitions and was higher when x-ray confirmed pneumonia was used as an endpoint. There was no evidence of superiority of one vaccine over other with regards to impact or effectiveness on hospitalization reduction in children <5 years.

Discussion

- Results presented were not adjusted but rather summarized what was reported in the published literature.

Enhanced Hib surveillance in the Gambia

Presenter: Akram Zaman

The Gambia was the first African country to introduce routine immunisation with conjugate *Haemophilus influenzae* type b (Hib) vaccine in 1997, which resulted in virtual elimination of Hib disease by 2002. However, a low level of incidence of Hib disease continued until 2010. From 2011 to 2013 there was an upsurge of invasive Hib disease in eastern Gambia which was accompanied by several incidentally detected hospital cases in the Western Region (WR) of the country. This resurgence accompanied by evidence of waning antibody levels in older children in a fully vaccinated population raised the question of the need for a booster dose, and reinforced the need for continuing surveillance in this country. Hib meningitis surveillance was re-established in WR to

measure incidence of Hib disease, identify any emerging hyperinvasive clones of Hib, and to detect potential reservoirs for increased transmission by undertaking carriage studies. Enhanced surveillance was re-established at all health facilities WR that treat suspected meningitis cases. The same definitions and methods as used in the previous surveillance from 2007-2010 were followed for the sake of comparability and assessment of temporal trends. Interim results were presented. In the WR, sustained low levels of incidence of Hib meningitis have been maintained by high coverage of 3 primary series of Hib conjugate vaccine. In the eastern Gambia, the incidence is sustaining at low levels for the last three years. The prevalence of nasopharyngeal carriage in children has also been sustaining at low levels following introduction of Hib conjugate vaccine. These findings suggest that a booster dose may not be required to control invasive Hib disease in The Gambia and in other countries with similar settings. There is a need to continue surveillance of Hib invasive disease with carriage and sero-prevalence studies to monitor effective control.

Discussion

- United Kingdom and South Africa had similar experience of an increase in Hib disease after vaccine introduction. Factors for Hib resurgence in the United Kingdom may have included a catch-up campaign, which could have masked inadequate vaccine coverage, and changes in vaccine formulation. Later carriage studies showed 6-16 year olds were carriers, not adults. South Africa introduced a booster dose and saw a decline in disease.

Action Items

- Although this presentation was about Hib surveillance, meningococcal disease was also identified through IB-VPD surveillance. There was a suggestion that MRC share meningococcal disease data with national Ministry of Health to inform Gavi application for introduction of meningococcal vaccine.

Bangladesh Case Study

Presenters: Alvira Hasan and Senjuti Saha

In Bangladesh, surveillance data has played a key role in national vaccine policy decision making by showing the dramatic impact of *Haemophilus influenzae* type b (Hib) vaccine and demonstrating the burden of pneumococcal disease, which contributed to the decision to introduce pneumococcal conjugate vaccine in March 2015. While being a part of the Global IB-VPD Surveillance Network, Bangladesh improved laboratory capacity and performance, developed population-based surveillance site, has plans to use the existing IB-VPD surveillance platform to detect other vaccine-preventable diseases, such as typhoid fever and rotavirus, and has been monitoring antimicrobial resistance.

Discussion

- Countries in the Global Antimicrobial Resistance Surveillance System (GLASS) are encouraged to collect and document data on antimicrobial resistance

Session III: Leveraging IB-VPD surveillance network for other VPDs

Chair: Lúcia de Oliveira

Surveillance of other pathogens: Current WHO recommendations and EPI priorities

Presenter: Ben Satterfield

The current WHO recommendations and positions papers were presented for a number of other pathogens, including typhoid, pertussis, Group B Streptococcus, Japanese encephalitis, and RSV. One objective is to look at methods for adding additional diseases to the existing surveillance platforms. For example, RSV was added as a pilot component to global influenza surveillance with a modified severe acute respiratory illness (SARI) definition. When considering conducting surveillance for these other diseases, we need to consider which diseases are the next priorities? What resources are available for additional surveillance? And how do we adapt data systems to accommodate new diseases?

Discussion

- How do Demographic Surveillance Systems (DSS) play a role?
- In PAHO, some countries conduct IB-VPD and influenza surveillance in the same hospitals, but there are logistical challenges to think through.
- We should also think how to leverage polio surveillance resources.

Typhoid and enteric fever surveillance pilot study

Presenter: Mary Slack

An update of the typhoid and enteric fever surveillance pilot funded by the Bill & Melinda Gates Foundation was given. Hospital-based surveillance for typhoid is based on enrollment of case definition for suspected typhoid or paratyphoid fever and blood culture confirmation. There are four participating countries: Bangladesh (DSH, SSF, Kumudini), India (CMC Vellore), Ghana (Kumasi and Accra), and Uganda (Mulago). Data will be collected on case identification, clinical information, lab results, and patient outcome. In terms of implementation of the pilot, there has been no delay in lab supplies for Bangladesh and India; however, there were WHO procurement challenges and time delays for Uganda and Ghana. WHO has conducted trainings in the African sites that were not necessary in the Asian sites. Countries have taken ownership of studies. Lessons learned from the pilot thus far: Dedicated resources, time and support are required. There have been WHO procurement delays. Planning for a pilot requires more resources than ongoing, baseline IB-VPD support. A pilot can maximize capacities already built.

Discussion

- What will happen after the pilot? The purpose of pilot is to determine feasibility of this sort of surveillance for typhoid.
- There are additional 2 ongoing typhoid projects also funded by BMGF, 1 in Asia and 1 in Africa, to understand burden of disease.
- Findings from pilot and lessons learned should be documented

Congenital rubella syndrome (CRS) surveillance in Pakistan

Presenters: Kamal Fahmy

WHO recommends that countries leverage measles control and elimination activities for CRS. Pakistan has implemented CRS surveillance in Pakistan that leverages the IB-VPD surveillance hospitals. CRS surveillance requires facilities that will likely be able to diagnose CRS, such as children's hospitals and specialists for hearing, disabilities, cardiology, and ophthalmology. Pakistan decided to use two of the IB-VPD surveillance hospitals for CRS surveillance and have two additional, new sites. Next steps are development of protocol and training materials, training of focal points at sites planned for January 2017, and starting surveillance Q1 2017. Questions that remain include whether to use existing staff for train new staff and considering how to use current data collection and management.

Discussion

- This was conducted in DRC and was able to show impact on nurses and staff; showing impact on healthcare workers advocated for continued surveillance.
- Both measles and CRS have been eliminated in the Americas. PAHO representative invited the speaker to come to Americas and learn from their experiences.

Group B Streptococcus surveillance discussion

Presenter: Johan Vekemans

The development of a Group B Streptococcus (GBS) vaccine for maternal immunization and prevention of early life GBS invasive disease and stillbirth constitute a medical need of high priority, especially for low and middle countries where the disease burden is high and no effective preventive strategy is available. Technical feasibility is estimated to be high. Better epidemiological documentation of the GBS disease burden including stillbirth constitute one of the priority activities on the technical vaccine development roadmap. Introduction of GBS invasive disease surveillance in existing networks of invasive bacterial disease surveillance would have high public health value.

Discussion

- We should think about GBS surveillance in the context of other ongoing surveillance projects (e.g., CHAMPS), what the existing diagnostics are, and what would need to be added.

Session IV: Leveraging IB-VPD surveillance network for outbreak control

Chair: Olivier Ronveaux

Panel discussion

Panel members: Jason Mwenda, Martin Antonio, Fernanda Lessa, Mahamoudou Outtarra

The sentinel IB-VPD network has not been designed to detect meningitis outbreaks and its current functioning and timeliness do not make it operational for that purpose. In Africa, the current yield – in terms of detected pathogens- is very low when compared to the burden caused by meningitis outbreaks, but in other regions, data from the IB-VPD may be the only ones available and therefore useful. Current strengths of the IB-VPD, including National and Regional Reference Laboratories and technical expertise may be useful to support rapid confirmation, strain identification, EQA/QC, and

operational research. The support provided by MRC Gambia to the 2016 pneumococcal outbreak in Ghana is a good example of a useful utilization of the IB-VPD technical expertise. Global IB-VPD Surveillance Network is not designed for outbreak response: country level capacity for rapid confirmation is lacking in some countries; it is a sentinel system, it has limited age groups under surveillance; there are scarce meningococcal serogroup confirmation capacity in country, and reporting is not timely enough for outbreak detection and response.

Main discussion points:

- Data from EMRO unavailable due to difficulties in receiving reagents and samples in a timely manner.
- Must be careful while interpreting serotype distributions because it seems like 19A serotype is still prevalent in PAHO countries despite the introduction of PCV13 in most countries in the region.
- When presenting serotype distributions by region, it would be good to have a list of countries that have introduced and not introduced the specific vaccine.
- Monitoring antimicrobial resistance in surveillance network.
- Consider surveillance of *Haemophilus influenzae* among neonates.
- Consider integration of surveillance networks.
- How best to use global network surveillance data to detect outbreaks:
 - Leveraging existing systems and platforms to detect outbreaks, while recognizing that existing sentinel surveillance platforms aren't able to act quickly in outbreak situations because the specimen processing takes time.

Global IB-VPD Surveillance Network Meeting, Day 2

Wednesday, 16th November 2016

Laboratory Technical Working Group for IB-VPD

Meeting Objectives

- Discuss Quality Assurance/Quality Control (QA/QC) systems including the External Quality Assessment (UK NEQAS/PHE) and regional updates from AFR, AMR, and WPR
- Optimization of laboratory procedures in the IBVPD laboratory network including the introduction of direct real-time PCR and utilization of the International Reagents Resources
- Improving data quality and management in the IBVPD global surveillance network by standardizing data analysis and interpretation

Session I: Quality Assurance/Quality control systems

Chair: Mary Slack

Presenters: Shila Seaton, David Litt, Linda de Gouveia, Gloria Rey and Karolina Mercoulia

EQA review

Presenter: Shila Seaton

United Kingdom National External Quality Assessment Service (UK NEQAS) is an external quality assessment (EQA), also known as proficiency testing, service provider to over 1800 clinical laboratories worldwide. The primary objective of UK NEQAS is educational and this is delivered through a variety of EQA schemes from all clinical disciplines. UK NEQAS prepared and distributed two EQA panels for the WHO IBVPD surveillance network, one to Regional Reference Laboratories (RRLs) and the other to National Laboratories (NLs) and Sentinel Site Laboratories (SSLs) in 60 countries. Results were collated and analyzed to compare the performance of the laboratories in specimen identification and strain characterization when applicable.

EQA Summary of Results from 2016

Presenter: David Litt

Two versions of an EQA panel were sent to the RRLs, NLs, and SSLs in the network during the summer of 2016 using the services of UK NEQAS for Microbiology. The simpler panel for SSLs contained 4 simulated CSF smears to Gram stain and describe, plus 7 live bacterial cultures to identify, serotype/serogroup (optional) and carry antimicrobial sensitivity testing on (optional). The SSLs were scored on the results of their Gram staining and culture identification only. Preliminary analysis showed 76/89 (85%) SSLs passed the 75% pass mark. Of the 13 that failed, only 6 had analysed enough samples to have given them the potential to have passed. RRLs, plus any National labs (NL) and SSLs that requested to take part, were sent an extended panel that contained the samples described above plus 7 (non-viable) simulated CSF samples for PCR detection and serotyping/grouping. These labs were scored on the results of their Gram staining, culture identification and typing, and simulated CSF detection and typing (antimicrobial sensitivity testing

was not scored). Preliminary analysis showed that 6/9 (67%) RRLs passed the 90% pass mark (although 2 labs narrowly failed, with 89% scores). Similarly, 7/16 (44%) NL/SSLs that took part passed the exercise; of the 9 NL/SSLs that failed, only 1 had analysed enough samples to have given them the potential to have passed. One sample in the panel, the simulated CSF smear of *E. coli* for Gram staining, was consistently misidentified by RRLs, NLs and SSLs and the results for this sample were excluded from the EQA scoring.

Global and regional QC: updates from AFR, AMR, and WPR External Quality Control Exchange between Laboratories in AFR

Presenter: Linda de Gouveia

The external quality control exchange started in 2010 with 3 participating laboratories AFR with an objective to improve the laboratory surveillance systems. Isolates have been exchanged to be tested for concordance between the participating laboratories and the RRL (NICD) to test for identification, serotyping/serogrouping, and antimicrobial susceptibility. In 2015, a total of 4 AFR laboratories, including 2 RRLs and 2 NLs, participated in this activity that tested isolates and spiked samples for PCR. No major problems were identified and there was generally high concordance (at least above 75%) among all laboratories in phenotypic isolation, identification, and serotyping of specimens. In 2016, there has been a significant amount of progress and improvement in molecular diagnostics among the participating AFR laboratories. This external quality control exchange is a good networking opportunity where they can share methods, identify problems, and initiate discussions about methodologies being used. As a future direction, new participating laboratories can be added and/or continue with this exercise twice a year. Spiked samples and isolates should be continued to be used for the QC, but the process of preparing, distribution, and evaluation may need to be rotated between the participating laboratories.

Regional EQA/QC in the IBVPD Surveillance Network in AMR/PAHO

Presenter: Gloria Rey-Benito

In PAHO, since 2004, there has been an extensive surveillance network associated with detecting bacterial pneumonia and meningitis called SIREVA-II. It functions separately from the WHO IBVPD global surveillance network, but there have been efforts in data sharing with WHO. One of the main activities done to improve SIREVA-II has been the EQA/QC program that is conducted among the South American countries. The main objective of the EQA/QC program is to check the concordance between NLs and RRLs based on pathogen identification, serotype/serogroup, and antimicrobial susceptibility. Generally, NLs refer specimens to RRLs that cannot complete serotyping in their laboratories due to lack of antisera or non-typeable strains. These non-typeable strains have their ST/SG confirmed at RRLs by Quellung and by PCR. Only a few AMR countries have introduced PCR for serotyping because conventional PCR is very time and labor intensive and multiplex real time PCR is very expensive (due to imported supplies). The next steps in improving the IBVPD surveillance network in AMR include molecular diagnostic workshops for detection and serotyping of Spn, Hi, and Nm, WHO to continue supporting SSLs, NLs and RRLs by providing supplies and reagents, and a regional meeting of SIREVA II is planned to be held in March 2017.

Regional QC between RRL and NL – Western Pacific Region

Presenter: Karolina Mercoulia

Each year, national laboratories in the western pacific region send all positive, equivocal and a subset of negative CSF samples and any cultures they may have for quality control testing to the regional reference laboratory in Melbourne, Australia. This allows NLs together with WHO and the GRL to track the progress of the NLS and also detection and typing to be completed for samples where NLs do not have molecular capacity for testing CSFs. Overall, we saw good concordance (92%) between NLs and the RRL in 2015/2016 with the exception of one laboratory where concordance was down at 75%. Further investigation found there were contamination issues and transcription errors however participation in the QC program allowed for errors to be detected quickly and managed with little disruption to the final dataset for the region.

Session II: Optimization of laboratory procedures in the IB-VPD network

Chair: Stephanie Schwartz

Serotyping of *S. pneumoniae* directly from CSF without DNA extraction

Presenter: Mahamoudou Ouattara

Several limitations have been encountered with the traditional RT-PCR: DNA polymerase enzymes used in traditional RT-PCR are sensitive to inhibitors present in clinical specimens, it is time-consuming, extensive manipulation can introduce cross-contamination, and there is some DNA loss during extraction. A direct PCR method was developed to overcome these limitations. Direct RT-PCR assay is comparable to our current traditional RT-PCR assay and uses 5-times less specimen than the traditional RT-PCR (2 µl vs 10 µl). Elimination of the extraction process reduces processing time, decreases risk of cross-contamination, and it is more cost-effective. Direct RT-PCR is beneficial for laboratories that have high volume of testing. A triplex direct RT-PCR for the detection of Spn, Nm, and Hi was also developed. It uses only 2 µl of specimens for all 3 pathogens vs 6 µl for monoplex detection of each of the bacteria. Up to 80 specimens can be tested for the 3 major meningitis pathogens in a single plate run.

Direct PCR Validation at RRL South Africa (NICD)

Presenter: Mignon du Plessis

The direct real-time PCR assay was validated at NICD using current primers and probes by testing with various sample types. The aim was to achieve the same level of sensitivity of detection for pathogen identification and serotyping/serogrouping as the traditional real-time PCR assays. A total of 369 specimens from AFR were tested including CSF, whole blood, blood culture broth, non-viable culture broth (Dorset transport medium and Brain Heart Infusion (BHI)), and pericardial fluid. The master mix used for direct real-time PCR was from Quanta. As a result, high concordance was seen between the two real-time PCR methods when CSF and blood culture specimens were tested. There was also good concordance when serotyping/serogrouping was tested on CSF specimens. However, direct real-time PCR failed to detect positive specimens when whole blood specimens were tested, indicating that direct real-time PCR may not be the best option with whole blood. Performance on non-viable BHI specimens is still uncertain since some positive specimens were not detected by

direct real-time PCR. RNase P has yet to be evaluated by direct real-time PCR. A total of 10 different serotypes were tested, and thus, more samples must be tested to assess the performance of direct serotyping. As the next step forward, NICD will be planning to do a head to head comparison with the two different real-time PCR methods by using a new batch of AFR specimens. Interestingly the results obtained by direct PCR on samples collected through the South African network (national surveillance) were more concordant with the results obtained by conventional real-time PCR than the AFR samples. More analysis will be needed for the validation process.

Improving IBVPD laboratory capacity in the Western Pacific Region

Presenter: Varja Grabovac

One of the methods to build and improve the laboratory capacity in the WHO Global IB-VPD Surveillance Network is to facilitate regional training workshops for detection and molecular characterization of IBVPD pathogens. One of the hands-on training that was done recently in WPR was at the Research Institute for Tropical Medicine in the Philippines where WPR RRLs (Korea CDC and MDU Australia) and GRL CDC assisted in facilitating. All participants were very eager to learn as they learned basic laboratory test management skills, how to perform molecular testing with real-time PCR, and troubleshooting. Mongolia is a prime example in WPR where molecular capacity, EQA/QC results, and overall laboratory performance significantly improved in 2016 after trainings in collaboration with the RRL in South Korea. Regional training should occur every 2-3 years either at a NL or RRL which will provide an opportunity for the participants to see a different laboratory set up. Follow-up visits are recommended at each site for on-site review, especially among the laboratories that have introduced new methodologies.

International Reagent Resource and Global Health Securities Agenda

Presenter: Stephanie Schwartz

The International Reagent Resource (IRR) was formerly the reagent resource funded by CDC that was allocated for influenza, but now it has been rebranded as an international reagent resource. CDC initially contracted with ATCC immediately after the influenza pandemic in 2009 to establish a robust distribution system for hard to obtain reagents (e.g., PCR reagents) as well as off-the-shelf and CDC-derived reagents. Now, the IRR has received funding to accelerate the Global Health Securities Agenda (GHSA) and thus, the Global Health Security (GHS) Phase 1 and high-risk, non-Ebola affected (HRNA) countries can participate in receiving reagents through IRR for other pathogens including non-flu viral and bacterial diseases. The GHS Phase 1 countries include Bangladesh, Burkina Faso, Cameroon, Cote d'Ivoire, Ethiopia, Guinea, India, Indonesia, Kenya, Liberia, Mali, Pakistan, Senegal Sierra Leone, Tanzania, Uganda, and Vietnam. It is still under discussion on how to make IRR sustainable beyond GHSA and possibly expanding to other RRLs and NLs that are not necessarily GHS or HRNA countries to build the laboratory capacity of the WHO IBVPD global surveillance network.

Session III: Improving data quality and management in the network

Chair: Danni Daniels

Global IB-VPD Surveillance Network Laboratory Analysis and Interpretation

Presenter: Tomoka Nakamura

Preliminary laboratory surveillance data from 2015 were presented including the overall number of suspected cases reported and the global distribution of pathogens identified by culture, rapid diagnostics tests (RDTs), and/or PCR, stratified by each WHO region. There were difficulties in determining the final pathogen results in some cases because laboratory results tested by different methods or at different levels were discordant. When discordant results are first seen at the HQ level during data processing or analysis, the first protocol is to send these back to the regional level where it should be followed-up with the SSL, NL or RRL. When the discordant results cannot be resolved, an algorithm can be followed as an option. An algorithm was introduced to define the final pathogen and has been refined based on continuing discussions:

1. A specimen is considered positive if it is positive by any test performed: culture, PCR, or rapid diagnostic test (RDT) such as latex agglutination kit and Binax.
2. In the instance that more than one pathogen is identified by different tests (i.e., discordance in positive tests)
 - a. If a serogroup or serotype is identified, that takes precedence over a results without serogroup or serotype. For example, if culture identified Spn 19A and PCR identified Nm without a serogroup, that specimen would be classified as Spn 19A.
 - b. If no serotype or serogroup is assigned for a discordant result by both culture and PCR, then the case will be dropped from analysis and the case will not be considered positive.
 - c. If RDT and either culture or PCR are positive, then culture and PCR results take precedence over RDT.
 - d. If there are results from culture, RDT, and PCR, the specimen will be classified as whatever pathogen was identified by more than one test.
 - e. If the above guidelines cannot determine the pathogen, then no pathogen should be identified and it should not be considered positive. It will be retained in the dataset as a negative case.
3. In the instance that there are discordant serotype or serogroups, the results from the following tests will be taken in order of precedence, and may need to be confirmed by the RRL
 - a. Quellung/slide agglutination on an isolate (i.e., positive by culture)
 - b. PCR results (whether on isolate or clinical sample)
 - c. Rapid diagnostic latex agglutination kit result (some kits provide ST/SG of HI and Nm)

For those that had an ST/SG reported, it was emphasized that the drop down options need to be selected in order to distinguish between a vaccine vs. non-vaccine serotype. It is also important to note that some samples had been serotyped, but they were unable to be typed due to PCR limitations, and this needs to be noted when results are entered in the database.

The ST/SG distribution of Spn, Nm and Hi stratified by region from 2015 were presented, but the data continue to show difficulties in clearly understanding the global distribution for various reasons. Some of the issues include not specifying the ST/SG when the case is classified as non-PCV 13 ST, incomplete data reported from certain regions, and inability to report back the data at a timely

manner. Because surveillance data are constantly changing and laboratory capacities are improving each year, there may be limits to how much data we can use to do further in-depth analyses such as comparing ST distributions during pre- vs. post-PCV introduction. Standardized reporting and continued feedback between the regional and HQ level are crucial to leverage the IBVPD global surveillance network.

Discussion

- The discussion highlighted some of the issues with the reference lab data in some Regions including the reporting of data from different levels (e.g. national or regional) in the same fields without the possibility to know where the results came from or the type of specimen tested missing.
- It was agreed that these issues should be dealt with before the data analysis stage. This raised the importance of linking surveillance and laboratory data as early as possible (and preferably before the data reach HQ) so that consistency checks can be performed.
- Although there was a general agreement regarding the importance of gram stain testing in the clinical setting, its usefulness in the context of the Network was discussed but it was agreed to keep gram stain results in the current data dictionary.
- The serotype/serogroup distributions were also discussed. It was mentioned that some countries report non-PCV13 types without further details (i.e. not using the drop down list from the Excel file provided by HQ). This makes the results difficult to interpret. It was mentioned though that samples may be typable but because of the low amount of DNA available, identifying the serotype after testing for vaccine-types may not be possible. It was also suggested to change the wording from untypeable to “not able to type”.
- The use of data pre- and post- vaccine introduction was also discussed. Topics included the usefulness of sentinel sites data to look at vaccine impact and whether it was possible to use country data to do so. Overall the feeling was that using global level data was difficult but that Regional data could be used to counterbalance the small amount of data in a single country.

Action items

- Continue the EQA/QC programme at all levels; Gram staining will continue to be included in the future surveys.
- WHO will assist in facilitating the procurement process of the reagents (primers/enzymes) necessary to perform direct real-time PCR.
- WHO, GRL and RRLs will continue to provide technical support to countries to reinforce national laboratory capacities in PCR; direct PCR is a great tool to implement at national level for both diagnosis and serotyping/serogrouping.

Regional example of current data quality and management activities

Presenter: Reggis Katsande

The modular data management system used in AFRO, as well as the recent updates applied to the system, were presented (e.g., changes of variables, data consistency checks). Data from the sentinel sites and reference labs are stored in a unique system. The system is robust but comes with limitations, including the limited number of variables accepted in MS Access or the lack of

customization options at the country level; customization is possible but it is recommended to avoid modifying the system. The WHO Global IB-VPD Surveillance Network has established variables which aim to be monitored by every WHO region. WHO/AFR modified its database to be aligned with the HQ requirements. The modification enhanced data quality as it allowed linkage of the surveillance and laboratory components of the IB-VPD surveillance network. Some of the main actions that were taken to improve linkage include three databases being integrated into one, certain variables changed from the old module, and restricted access to editing the database so countries cannot change the parameters that exist in the current module. Duplicated data were also identified, such as date of admission, date of birth, and names of parents. These errors found in the data are currently being revised to improve the data quality.

The discussion that followed the presentation highlighted some difficulties affecting data management in AFRO but also in other Regions, which were also discussed during dedicated data management sessions.

Discussion

- In the absence of dedicated data managers, some sites rely on laboratory technicians for data entry and other data management activities. Regular data management support should be provided to the sentinel sites in order to maintain/improve the quality of their data.
- Although the AFRO system allows users to run data consistency checks, these are rarely used at the site/country level. This problem is consistent across all regions. Sites/countries should be encouraged/reminded to perform data consistency checks and correct their data before submitted them to the Regional Offices/HQ.
- Identifying duplicates can be an issue because of problems with the assignment of unique case IDs. A decision needs to be made on which variables to look at when searching for duplicates. There also needs to be a more precise definition of cases when considering multiple admissions of the same child (e.g., minimum number of days after a first admission for a child to be counted as a new case). In AFRO, duplicates are identified using the date of admission, date of birth and patient names. Special care should also be given to the assignment and management of unique case IDs in each sentinel site.
- Collecting so many variables has a negative impact on routine data management work as well as on the quality of the data collected. The data dictionaries need to be reviewed and variables that are not used dropped when possible.
- For the records that do not get corrected at the country level, there needs to be a standardized way to deal with major errors (e.g., mandatory variables missing, errors with dates such as date of birth after date of admission, or age not matching date of birth/admission).
- Regional offices have access to aggregated data (either historical or from other sites) that could be shared with HQ and used for various analyses.
- The discussion also raised the possibility of creating one or more data quality/consistency indicator(s) to evaluate the data reported by the sites (e.g., % of cases with all core variables provided or without any errors).

Summary of Global IB-VPD Surveillance Network meeting

Presenters: Adam L. Cohen and Fatima Serhan

Please refer to summary at end of Global Rotavirus Surveillance Network meeting.

Global Rotavirus Surveillance Meeting, Day 1

Thursday, 17th November 2016

Session I: Global overview of rotavirus surveillance network and 2016

progress

Presenters: Adam Cohen and Fatima Serhan

WHO recommends the introduction of rotavirus vaccine in all countries. As discussed in the Global IB-VPD Surveillance Meeting, WHO's role in VPD surveillance is to generate and monitor VPD trends globally; to lead, coordinate, and advocate for surveillance activities with countries and partners, including EQA/QC ; to set global norms and standards for surveillance; to support countries with technical assistance and evidence-based policy decisions; and to support research that builds on surveillance platforms and informs immunization program monitoring and policy. WHO has coordinated two sentinel VPD surveillance networks since 2008: The Global Invasive Bacterial Vaccine-Preventable Disease (IB-VPD) Surveillance Network and the Global Rotavirus Surveillance Network. The objectives of the surveillance networks are evolving. We now focus on burden and vaccine impact in regions with data gaps, but also look at long-term impact after vaccine introduction and leveraging the surveillance platform to monitor other VPDs such as norovirus, ETEC, and Shigella. For rotavirus vaccine, it is also important to monitor the safety of the vaccine. Of the 55 countries that are part of the Global Surveillance Network, most meet the performance criteria, though they may not reflect the strength of the surveillance and whether the data is being used. Over 40,000 cases of diarrhea were enrolled globally in 2015 The rotavirus positivity overall is 30% (ranging from 10% to 50%) depending on whether or not the vaccine has been introduced. The surveillance data is being used for country decision making, publications, and global burden models.

Comparing and contrasting the two surveillance networks:

Rotavirus network	IB-VPD network
Need for broad surveillance	Could focus on fewer sites
Performing well	Sites need more support
Simpler diagnostics	Laboratory more complex but new techniques
Leverage platform for other VPDs	Leverage platform for other VPDs
Vaccine introduction stalled	Fewer gaps in vaccine introduction
Vaccine effectiveness variable	Vaccine very effective
Important to monitor genotype, but less than for PCV	Critical to monitor serotypes for replacement
Vaccine safety concerns	Less vaccine safety concern
Less concern about schedules	Could play a role in outbreak response

In 2015, 180 laboratories were part of the WHO coordinated surveillance network. Initial rotavirus testing at the sentinel site laboratory includes enzyme immunoassay (EIA) and genotyping of rotavirus positives is mainly done at the national or regional reference laboratories. In 2015, 92% of stool samples that were collected globally through the rotavirus surveillance network had an ELISA test performed of which 28% were RV positive. Genotypes were assigned to 26% of the positive cases and showed the higher prevalence of G1 P[8], G2P[4] and G9P[8] globally.

Global external quality assessment program (EQA), coordinated by WHO and the CDC global reference laboratory (GRL), consists in distributing proficiency testing panels to all participating laboratories. EQA results in 2015 showed a high level of performance with 94% of laboratories passing the EQA. In 2016, WHO started the process of reviewing the rotavirus laboratory manual with a small of experts and the plan is to conduct validation process of the most recommended protocols in the network in at least 3 regional reference laboratories before the finalisation of the manual annexes in 2017.

Discussion

- Why is PCV is more introduced in countries than rota vaccine? Many factors contribute to this such as the fact that PCV is more effective than rotavirus vaccine, pneumonia is a pressing issue in countries, and there is a concern on the safety of rotavirus vaccine. However, we should consider transforming the network from a rotavirus to a diarrheal network, and specimens will have the capacity to test for other pathogens using the TAC platform.
- Is Nigeria going to introduce rotavirus next year?_Nigeria has almost been approved for the introduction but there are still pending issue related to the co-financing.
- SEARO raised the fact that there are few countries involved in the network. The question is now how to include other countries in the network and discussing the benefit of being part of the network. Specific countries that are considering joining are Bangladesh and India.
- There was a question about whether the focus should be on rotavirus or other enteropathogens. For the time being the focus will be on rotavirus.
- We discussed that we should consider a global forum for monitoring the rotavirus program, like there is with measles.

Session II: Leveraging rotavirus surveillance network for other VPDs

Chair: Gagandeep Kang

Surveillance of other pathogens: Current WHO recommendations and EPI priorities

Presenter: Ben Satterfield

Please see summary from Global IB-VPD Surveillance Network meeting.

Norovirus survey update and current status of norovirus, ETEC and Shigella vaccines

Presenter: Birgitte Giersing

It was recommended in 2015 to look for norovirus, ETEC and Shigella for an enteric vaccine development. Currently the most advanced norovirus vaccine is in phase IIb trials. Norovirus has 7 serogroups, and the GII-4 is responsible of 60-90% of outbreaks. There is a need to assess whether the vaccine will provide protection. A norovirus laboratory capacity survey was conducted in summer 2016, which found that there is a lot of infrastructure in countries and there is good capability to genotyping. Shigella is more prevalent and has much higher mortality than ETEC. The ETEC vaccine is more advanced, and there is a discussion about whether to have a combination vaccine which is complicated and risky. We will use Phase 2 of the Global Pediatric Diarrhea

Surveillance to identify cases of norovirus, ETEC and Shigella, with additional serogrouping for norovirus.

Discussion

- It was noted that norovirus is easy to integrate into rotavirus surveillance, but Shigella and ETEC would be more difficult since virology laboratories may not be able to conduct bacterial culture.
- There have not yet been discussions on the cost of norovirus vaccine. A potential market in high income countries is currently driving vaccine development.
- Issues of vaccine genotype cross protection are being looked into.
- All global norovirus surveillance platforms will be coordinated and integrated.

Introduction to RAVIN

Presenter: Umesh Parashar

Two initiatives for the acceleration of the introduction of rotavirus vaccine and how to use data to drive policy decision were presented. The first one is RAVIN (Rotavirus Accelerated Vaccine Introduction Network) by John Hopkins University, U.S. Centers for Disease Control and Prevention and John Snow International. There is a big gap in the rotavirus vaccine roll out. The focus of the initiative is on 6 countries mainly in Asia that will have a large impact when vaccine is introduced. The strategies for RAVIN are evidence, advocacy, and implementation. Data on impact are important to drive decisions on sustainability. The second initiative is the Rota Council. The objective is to accelerate the introduction of vaccine by providing the evidence for rotavirus vaccine introduction. This is an independent group which works with WHO. The group has published white papers which synthesize scientific evidence.

Discussion

- The main objective of these two initiatives is the coordination of efforts to meet the objective of rolling out vaccine. RAVIN began 4-5 month ago and the goal is to work with other partner like Gavi. It is not meant to replace existing efforts but will include other partners.
- What are the criteria for selecting a country to be part of RAVIN? The criteria are 1) to have a large birth cohort, 2) to have high rotavirus mortality, and 3) to help with regional efforts. It is still possible to suggest other countries to the project and partners.
- India stopped rotavirus surveillance after having decided to introduce the vaccine. It is not good to stop surveillance after introduction because there is need to document impact

Action items

- There should be collaboration and coordination between the various initiatives: RAVIN, Rota Council, PDVAC.

Session III: Using surveillance data for decision-making in countries

Chair: Kamal Fahmy

Rotavirus impact in Armenia

Presenter: Gayane Sahakyan

Data collected through the rotavirus sentinel surveillance system established by the Ministry of Health helped the Government of Armenia to make evidence based decisions that are comparable with those of other countries. Using surveillance data, Armenia decided to introduce RV vaccine into National Immunization schedule in 2012. To justify ongoing vaccination following GAVI graduation, Armenia studied the impact of rotavirus vaccine on the burden of diarrheal disease in children and carried out case-control studies of the effectiveness of vaccination. The studies found that monovalent rotavirus vaccine is effective in protecting Armenian children aged <2 years against hospitalization from rotavirus disease, demonstrating that the rotavirus disease burden can be markedly (and in infants, very quickly) reduced after successful implementation of rotavirus vaccination in CIS countries like Armenia.

The country collected data in 2 sites (hospitals) and the National Center for Disease Control for Reporting between 2009 and October 2012. A cost effectiveness study was conducted and the vaccine was introduced in 2012 as monovalent in 2 doses schedules with age restriction. The coverage achieved was higher than 90%. The impact and effectiveness studies were also conducted using a case control study in the 2 hospitals involving children born after September 2012. The rota positivity decreased from 38% in pre-vaccine period to 10% in the post- vaccine period. The greatest decline was in the target age group. Vaccine efficacy varied from 60-68% and was much higher for severe cases (79-83%). The country is also monitoring circulating genotypes. The main challenges are that surveillance does not cover all regions of the country, focuses on severe hospitalized cases, and that Gavi graduation will impact available resources.

Rotavirus impact in Botswana

Presenter: Margaret Mokomane

A study conducted in Botswana showed a mortality from rotavirus of 2.8%. Based on these data the country decided to introduced the monovalent vaccine with a 2-dose schedule. The vaccines were fully funded by the country. The Ministry of Health set up a hospital-based surveillance network with the objective of studying the impact and effectiveness of the rotavirus vaccine. Four sites were selected. The study showed a decline in mortality and hospitalization in infants. Protection increased with the severity of illness. Overall vaccine efficacy was 54%. For the future, the country is working to strengthen the surveillance network. They will sensitize the personnel and train them as well as disseminate the result of the study to different stakeholders.

Rotavirus impact in Sudan

Presenter: Hanan Muktar

Gastroenteritis is the leading cause of hospitalization and the fifth leading cause of death in Sudan. In 2007, the country started surveillance with 8 sentinel sites; currently, 3 sites are functioning. The main objective was to assess the burden of disease in selected children and the strains as well as the

impact of the vaccine. The country achieved the target for surveillance indicators and introduced rotavirus vaccine (Rotarix) in August 2009 with age restriction until 2015. In 2016, the age restriction was lifted. The country noted a change in genotypes after vaccine introduction. In the future, the country will continue to assess the impact and strains and intensify other interventions.

Discussion

- For Armenia, though the 2 sentinel sites do not cover the whole country but still these two sites have enough data to show the evidence. With Gavi graduation, the country will cover the cost of vaccine up to 2019. For surveillance, there is need to ensure that the country will keep the surveillance functional after the graduation.
- There was a question about why countries were using age restriction even though recommendations from 2011. For Armenia, age restrictions were used to improve timely vaccinations and not for safety and that the country has no plans to remove age restrictions. For Sudan, when recommendations were made to remove age restriction the country discussed with advisory group. The NITAG first assessed the risk of intussusception through surveillance and only then did the NITAG approve the removal age restriction. It was discussed that many NITAGS (in about 60% countries) still apply age restrictions and do not follow WHO position paper recommendation to remove it. In Ghana, age restrictions have not been lifted so as not to confuse mothers and not to affect coverage rates for other co-administered vaccines. There is concern that people would wait to vaccinate their kids.
- Why is less of an impact seen in Sudan /Armenia/Botswana than other countries? Perhaps further analysis can help explain.

Session IV: Global Pediatric Diarrhea TAC Array Study

Chair: Umesh Parashar

Summary of Phase 1 results

Presenter: James Platts-Mills

In Phase 1 of the application of TAC technology for molecular detection of enteric pathogens in select WHO GRSN sites, we analyzed 840 samples with valid testing results selected from a total of 15,675 diarrhoeal episodes to determine pathogen-specific burdens of severe acute watery diarrhoea. Rotavirus was the leading aetiology across all regions (overall weighted attributable fraction [AF] 40%), though the burden was substantially lower in the Americas, based on samples from a single country with universal rotavirus vaccination. Norovirus GII, Cryptosporidium (5.8; 4.0 – 7.6), Shigella, heat-stable enterotoxin-producing E. coli (ST-ETEC), and adenovirus 40/41 also demonstrated high burdens. The early impact of rotavirus vaccine introduction was evident in AFR, with a reduction in the AF from 55% in RV age-ineligible children to 20% in age-eligible children. Prospective surveillance using this network can help identify priorities for further reducing the burden of diarrhoea.

Phase 2 updates and planning

Discussion

- EMRO was not included but discussions are ongoing to include EMRO given that there are countries that are performing surveillance very well.

- It may be good to differentiate between countries that have introduced the vaccine many years ago, countries that have just introduced the vaccine, and countries that have not yet introduced the vaccine.
- In phase II, the most important thing is the quality of data, including the ability to enroll children prospectively.
- Discussions regarding what to do about reconciling that Shigella accounts for 20% in GEMS and around 10% in GRSN. Some suggested that in order to get best estimates for Shigella, we need to include all the eligible cases. Therefore we should look for all pediatric diarrheas from the hospital, including cases of bloody diarrhea.
- Phase II should begin in January 2017 and will have the following characteristics:
 - More countries. 5 per RRL, and for AFRO Medunsa will join.
 - Specimens will be selected randomly.
 - There will be 3000 specimens over 2 years, 25 specimens from each surveillance site quarterly. Since the current reporting system is every 3 months, the reporting of the data to WHO should not change.
 - Resources will be provided for harmonization workshops.
 - There will be a uniform protocol.
- The work requires a lot of sample management for the site. The sites will continue Elisa for rotavirus. The storage at the sites and the shipment should evaluate the quality of specimens.
- In phase II, only cases whose data are submitted to the network will be considered for inclusion. When data are submitted, then RO or HQ will decide on the 25 cases that will be collected. HQ and RO will make sure that the core variables are included. The random selection will be used on data submitted every 3 months.
- There will be a need to look at data for 2015 to predict storage capacity needs.
- The case definition to bloody and chronic must be expanded to capture the Shigella. There is a need to add one variable on duration of diarrhea which will add approximately 10% additional cases.
- For specimen shipments, money will be provided to the sites. There is need to coordinate the shipment of EQA, genotyping, and the TAC project.
- Some countries would like to submit the protocol to ethical review committees which could take some time. However, we are only expanding the existing surveillance system, so additional ethical review would not be necessary.
- Vaccination status was not required at the individual level and countries would just be classified based on vaccine introduced or not.
- Adding a one variable will have implication on data analysis tool.
- The case definition needs to change only for countries participating in TAC Phase 2. But others are welcome to change their case definition.
- For phase 2, we would like a mix of pre- and post-introduction countries.
- We will not enroll controls as part of this surveillance, but there is a need for more data from pediatric controls in broader settings.
- The list of countries proposed to be included was displayed and it was proposed that all countries start on January 1st. Phase II is limited to 5 RRL and 30 sites per region. We discussed the status country by country. We may be able to add additional sites since we may be able to get more cards at a reduced price. January deadline might not be feasible for all countries.
- For authorship in phase I and II, one representative for each site will be included.
- Only slight change in suspect case definition (include chronic diarrhea and bloody) will be made to include these extra specimens and database needs to be updated.
- Questions were raised regarding blood inhibiting the binding of some antigens, but Elisa seems to be able to detect rotavirus in specimens including dysentery and bloody diarrhea.

- In order to keep things simple it was suggested that all cases must be tested for bloody diarrhea and that the chronic or bloody diarrhea cases could be excluded during analysis phase for GRSN rotavirus surveillance.
- Budget/ funding should be allocated to sentinel sites and that regional offices should look at the country level because the process varies.
- Due to instability some EMRO sites may not be able to continue as a part of the surveillance networks. Possibilities of using new sites or new countries which were not a part of the initial network were discussed and the example of Bangladesh (are only a part of the IB-VPD network not rotavirus but have been approached for the Taq study and so may join GRSN) was used to show that something like this could be possible but feasibility and the ability to start quickly would be factors to consider.
- Concerns regarding the future of the expansion of case definition and whether the case definition will revert back were discussed. Preliminary results from the Taq study and usefulness of the data will need to be assessed after the data is generated and only then can it be decided if the case definition will remain the same or revert back.
- Concerns regarding the Taq study being a short term project. It was proposed to use the study as an expanded surveillance format and that it may attract donors in the future as a broader diarrheal surveillance network versus just rotavirus surveillance that exists now.
- There was a discussion about whether we should also test all pediatric deaths using the TAC study to monitor the cause of pediatric deaths globally.

Global Rotavirus Surveillance Meeting, Day 2

Friday, 18th November 2016

Laboratory Technical Working Group for Rotavirus

Session I: Quality Assurance/ Quality control systems

Presenters: Dr. Mike Bowen, Nicola Page and Sarah Thomas

Dr. Mike Bowen presented a review of 2015 External quality assessment (EQA) program data and update on the 2016 EQA survey . A panel of 10 lyophilized, non-infectious samples was sent out to 116 laboratories in 2015. There were 7 positive and 3 negative samples, one positive was the Rotateq vaccine. Following the testing from the referee laboratories (NICD, South Africa and University of Liverpool), it was decided that if two G types were reported from the Rotateq sample that would result in a full score. Overall, there was a >90% concordance for EIA and >80% concordance for genotyping across all the levels of surveillance.

The 2016 survey is ongoing with a panel of samples distributed to 105 laboratories. Results have come back from many laboratories, and the report is expected to be completed by February 2017. Preparation and development of the proficiency testing (PT) panels at the CDC GRL is underway for the 2017 panel.

Actions to be taken in case of persistent failure in EQA was discussed and it was decided that this would be a site visit by the RRL or GRL. It was also discussed whether accreditation or certification visits conducted for the Measles laboratory network can be used as opportunities to include some of the rotavirus issues, and a recommendation was made that WHO staff involved in coordinating these visit to look into the formats to add that component depending of countries/regional context and feasibility. All regions engaged in the ongoing QA activities find the time lines somewhat challenging, but coordination is improving.

On the quality control for confirmatory testing, presentations were made by NICD on analysis between the two South African laboratories, and for this year also with Ghana RRL and then national laboratory in Central African republic (CAR). The concordance was higher with the two South African laboratories than with Ghana and CAR labs, but the exercise was helpful in identifying where primer binding and result interpretation is an issue. The WPR RRL at MCRI Australia presented on their testing with Vietnam, China and Philippines where concordance was generally high, except for one site where G3s were identified as G8s, based on the use of a different primer, and some mis-priming with the G9 primer resulting in misinterpretation of reassortant G3 strains. Testing of samples from India and Korea will be performed.

Discussion

- There was a discussion on the value of quality control exercises, and how useful these exercises are for laboratories to review their processes and primers. It was highlighted that discrepancies in typing results between laboratories are useful because it allows more detailed consideration of typing approaches than happen during routine genotyping through the year.

Action Points

- WHO will continue engaging all regions and laboratories to enhance the QA/QC exercises and improve laboratory procedures use to produce high level of data to support surveillance networks.

Session II: Optimization of laboratory procedures in the rotavirus network

Presenters: Fatima Serhan and Jon Gentsch

Given the duration since the WHO Rotavirus Manual was published in 2009, it was discussed at the laboratory technical working group (TWG) meeting in 2015 that there was a need for updating the manual. The WHO HQ requested protocols and primers from all RRLs. A small meeting of experts was organized end-October in London to review the testing protocols and oligos to make a plan for development of a common protocol as well as modification of the manual. The meeting reviewed also the QC for confirmatory testing 2015 data and found that there was a high degree of overlap in the methods being used and therefore summary review showed the feasibility of a broadly similar approach to extraction and typing, using Qiagen or similar RNA extraction and a one-Step RT-PCR for the first round. The second round primers are generally similar, but alternate primers are available for both first and second round PCRs (using VP7F and R for 1st round and Beg 9 End 9 as alternative for VP7, with Con2 Con3 common for VP4 and and VP4FR as alternative). The new Esona, et al. single round procedures are available and should be evaluated by more laboratories.

Next steps are to develop consensus protocols, and follow that with a process for validation at the RRLs, with validation data to be shared with WHO for consolidation and review. These will become an appendix to the existing manual, which remains useful for general processes and for the ELISAs.

SEAR, Ghana AFR, Australia WPR and MEDUNSA AFR RRLs will perform the validation exercise selecting 100 samples each from QC samples to cover the broadest range of genotypes feasible. Dr. Gentsch will help WHO develop the validation protocol and a TWG teleconference will be scheduled early 2017 to discuss the process. The timeline for completion of the validation exercise will be approximately 3 months, with completion of the manual following the validation by mid-2017.

TAC array study to detect other diarrheal pathogens

Presenters: Darwin Operario

The TAC Array Study laboratory training modules were described. The minimum training is 2.5 days but for achieving proficiency 4-5 days training is recommended. The training modules are as follows:

- i. Laboratory and equipment analysis (introduced a posteriori): 0.5 day which includes decontamination procedures for lab surfaces and equipment, and swab testing for PCR contaminant organisms in all the equipment used in the extraction process
- ii. Nucleic acid extraction: including bead beating 0-5 to 1 day, maximum of 9 samples used for the training

- iii. Array card setup and run: 1 day, 3 TAC runs which include standard material supplied to the labs, all 3 runs must be completed in one day
- iv. qPCR data analysis (emphasis on setting real time baselines for achieving accurate CT values): 0.5 to 1 day. From basic qPCR analysis to use of QC analysis and optimising data visualization.
- v. Use of Study secure database: MuSIC. TAC data upload to MuSIC hosted at UVA: collates data and uses a clean-up script.

SOPs are shared prior to training starts to give time for review. The prevention of contamination and the requirements for data analysis was discussed. The discussion on decontamination was that 10% bleach was effective, but as it is corrosive, that was followed by ethanol. It was highlighted that QiaCube protocol for extraction is validated and can be used if considered appropriate by the laboratory.

Discussion

- The TAC Array Study phase II start dates were discussed, and it was decided that January 1st would be a start date and this would be reviewed in case it was not possible to start on time. WHO HQ was asked to provide a letter summarizing the study to assist with country specific revisions and for permissions. Training for MEDUNSA and Minsk will be provided in the first half of 2017 and sub-contracts between CDC foundation and RRLs will start in the first quarter of 2017. For sentinel site funding the funds will go through WHO HQ to Regional office and to sites from beginning of January. Potential list of countries in Phase II is a target of 30, and a greater number should be chosen as some may drop out.

Action Points

- The phase I data manuscript draft will be shared for review and is aimed at the Bulletin of the World Health Organization.

Session III: Polio Containment

Presenters: Nicoletta Previsani

A presentation on polio containment discussed the plans for the polio end-game and the plans for containment. Wild poliovirus type 2 (PV2) was declared eradicated in 2015 and the world has switched from the use of tOPV to the use of bOPV in 2016. The retention of any PV2 is now subject to the requirements described in the Global Action Plan for polio containment (GAPIII). The global polio eradication programme is developing guidance to support countries and facilities in identifying samples likely to be contaminated with PV2 (including WPV2, VDPV2, OPV2, Sabin2 viruses), categorizing samples into high, moderate or negligible likelihood categories of being contaminated with PV2 and recommending appropriate actions for their destruction, or storage and handling.

The WHA resolution in May 2015 included agreement from member states to implement polio containment even though this is not a legal requirement. The switch to bOPV and the rationale for polio containment, including for Sabin polioviruses, was discussed. An update was provided on the process so far, along with the guidance on categorization of level of likelihood for containing polioviruses and for which facilities should consider becoming poliovirus essential facilities. Phase I of GAPIII has not yet been completed and the date has been tacitly extended. Guidance is expected for the completion of Phase I of GAPIII; the draft guidance document is being circulated for

comments. It will then be released for public review and pilot tested, revised, and submitted to the Containment Advisory Group (CAG) for approval before global implementation.

The CAG is being constituted and will meet to look at the guidelines in early 2017, following which the guidelines will become available. There are ongoing efforts to evaluate what and whether treatment procedures are appropriate for retention of sample derivatives. There was extensive discussion on what kinds of samples might be considered infectious now and in the future and what the real risks might be of accidental release and resulting infection or disease. A GAP III containment certification scheme (GCC) is applicable in Phase II which proposes three levels of certifications (participation, interim certification and certification). At the moment, the guidance for the rotavirus surveillance is to continue as they are doing until further guidance is available.

Session IV: Improving data quality and management in the network

Presenters: Sébastien Antoni, Adam L. Cohen, and Negar Aliabadi

Data from the network globally and from the different regions were presented, highlighting large differences in the numbers of samples processed and in the number of years available for analysis. There were large differences in the numbers of samples processed and for the duration of the reporting. The data were analysed by age, mortality, seasonality, trends post-vaccine introduction. Case ID, site code, admission date and age are frequently missing fields. Vaccine data is captured in less than half the cases. There are also issues with duplicate data, entry errors and coding errors. Issues largely relate to quality of data and the ability to use it appropriately in analysis, and these could partly be addressed by ensuring that factors that affect the ability of countries to generate quantity and quality are documented by regional offices so that data can be analysed appropriately at HQ, understanding the constraints. Countries have access to aggregated data that could be used to support the case-based data analyses. The use of data from countries not formally part of the network in the global analysis should also be encouraged. Data quality issues were also highlighted, including the high number of missing values for important variables (e.g. >50% missing for vaccination data). Factors affecting data quality should be documented at the regional level to ensure that data can be analysed and interpreted appropriately at the global level. Overall, standardization of the datasets submitted to HQ should be improved, for example through the use of consistency checks at all levels.

Discussion

- There was a discussion on the value of quality control exercises, and how useful these exercises are for laboratories to review their processes and primers. It was highlighted that discrepancies in typing results between laboratories are useful because it allows more detailed consideration of typing approaches than happen during routine genotyping through the year.

Action Points

- WHO will continue engaging all regions and laboratories to enhance the QA/QC exercises and improve laboratory procedures use to produce high level of data to support surveillance networks

- The discussions highlighted that future analyses could and will include aggregate data, and pre- and post-vaccine introduction.
- Use of data from countries not formally part of the network in the global analysis is to be encouraged. WHO HQ and regional offices will work together to ensure that data quality issues are addressed.
- The meeting ended with recognition of the amount of work that has been done and the amount of data that is continuing to emerge. The expansion of the network to other pathogens is a huge opportunity, but the original focus of the network should not be lost. Sustainability is a key issue, and working with stakeholders to ensure that high quality surveillance that generates data which is useful to countries is able to continue.

Summary of Global Rotavirus and IB-VPD Surveillance Network meetings

Presenters: Adam L. Cohen and Fatima Serhan

The Networks are performing well and generating useful data for country and global decision making. Funding for surveillance is uncertain, and IB-VPD surveillance in particular is not easy, but it is critical to advocate for surveillance and use data to guide policy and monitor disease and programs. We discussed the future of the Global IB-VPD Surveillance Network and 2017 plans. These activities include the following:

- Strengthen the network sustainably by building national and regional capacity with country ownership
 - Building and reinforcing national laboratory capacity
 - Considering enrolling fewer cases (specifically for pediatric diarrhea), testing fewer specimens, maintaining fewer sites, and reducing number of core variables
 - Developing more efficient laboratory techniques, especially for GISN
 - Supporting and coordinating with other surveillance networks
 - Communicating and using the data
- For laboratory activities
 - Continue quality assurance activities, including developing a certificate of participation and ensuring corrective actions to follow up on the results of EQA and confirmatory testing
 - Continue to work with partners on polio containment for GRSN
- For the Global Rotavirus Surveillance Network
 - Launch Phase 2 of the TAC study
 - Consider whether the network should actively monitor other causes of pediatric diarrhea in addition to rotavirus as the Global Rotavirus and Pediatric Diarrhea Surveillance Network
- Consider revising performance criteria, such as for sites that enrol fewer than 100 specimens, if the number of cases has declined after vaccine was introduced. We suggested that we would include sites that have enrolled more than 100 cases/year if they meet that criteria for most months before vaccine was introduced. We will also consider including sites that do not enrol cases for 1-2 months if we can extrapolate the burden of disease in those months from other years and surrounding months.
- Support publications from the global and country level, including the planned rotavirus journal supplement. We will consider an IB-VPD journal supplement in 2017.
- Conduct surveillance costing studies
- Support EPI VPD surveillance guidelines revision