MEETING REPORT

Global Rotavirus and Pediatric Diarrheal Surveillance Network Meeting

16th-17th November 2017

Hotel Royal
Geneva, Switzerland
Meeting Report: Global Rotavirus and Pediatric Diarrheal Surveillance Network Meeting
Thursday and Friday, 16th-17th November 2017
Hotel Royal, Geneva, Switzerland

Meeting Objectives
• Review the current status and priorities of the global rotavirus surveillance network
• Review the current status and priorities of the global pediatric diarrhea surveillance network
• Discuss global rotavirus surveillance data analysis
• Discuss current and future priorities and funding for surveillance

Day 1, Session I: Global overview of rotavirus surveillance and laboratory network
Presenters: Adam L. Cohen and Fatima Serhan, WHO HQ

In 2016, the WHO Global Rotavirus Surveillance Network (GRSN) had data reported from 59 Member States and 134 sentinel surveillance hospitals. Although rotavirus occurs in every country across the globe, mortality is highest for children in sub-Saharan Africa and much of Asia. Rotavirus vaccines are an important tool for reducing this burden. Rotavirus burden data from surveillance has been important for driving rotavirus vaccine introductions, but global coverage of rotavirus vaccine lagged behind PCV coverage in 2016 at about 25% of the global birth cohort. A few countries with large birth cohorts have not introduced rotavirus vaccine or are currently introducing rotavirus vaccine in a phased manner, such as Pakistan and India. Nigeria and Democratic Republic of the Congo have all applied for rotavirus vaccine introduction funding from Gavi and Bangladesh has been approved to introduce rotavirus vaccine in 2018. The lowest use of rotavirus vaccines globally is in Asia, in countries in WHO SEAR and WPR. As new rotavirus vaccines become available and more widely used it will be important to monitor their effectiveness and safety profiles in comparisons to other rotavirus vaccines. Understanding non-rotavirus pediatric diarrheal etiology is increasingly becoming important as the burden from rotavirus is decreasing and new vaccines for other pediatric diarrhea pathogens (Shigella, ETEC, norovirus) are in the pipeline. Surveillance data from GRSN have been valuable for country decision making, reports and publications including the WHO bi-annual bulletin and two 2017 supplements in Vaccine, and for global models of rotavirus mortality and age distribution. Surveillance data have also been used continuously to show vaccine impact, particularly in Asia. Rotavirus surveillance should be simplified and sustainable with as much country ownership as possible.

Overall, the sentinel sites that are part of GRSN have been performing well in terms of cases enrolled, stool samples collected, and samples tested by enzyme-linked immunosorbent assay (EIA). There is some concern that some countries are genotyping either a very low or a very high number of cases which makes genotype analyses difficult. WHO recommends GRSN sites genotype 50 samples per year. It is also a goal to decrease the number of non-genotypable cases. Excellent levels of performance are being reported globally through the U.S. Centers for Disease Control and Prevention (CDC) Global Reference Lab (GRL) external quality assurance (EQA) program, and high levels of concordance were reported between reference laboratories for external quality control. The WHO rotavirus laboratory manual is being updated and reviews are being finalized before the annex to the existing manual or a new manual is released. PCR and laboratory capacities have been increased in the past year, and enhanced molecular capacities have been established for seven RRLs participating in GPDS. Sustainability and increasing country-level surveillance and laboratory capacities are current priorities of the network.
Discussion

- A lesser appreciation of rotavirus burden compared to pneumococcal burden and concerns about vaccine safety and supply are all factors that contribute to rotavirus vaccine introduction lagging behind PCV introduction. A strategy to increase rotavirus vaccine uptake may be to leverage PCV introduction strategies.
- Vaccine coverage is an important consideration when assessing vaccine impact.
- WHO quality assurance programs (including EQA and QC) have been important tools to enhance laboratory capacities.
- Uniform laboratory protocols that are being updated will be important for long-term standardization of surveillance.
- Establishing a new EMR RRL is a priority despite the challenges that the region is facing. Reinforcing national lab capacities in Sudan and Pakistan will contribute to better genotype data from the region especially since shipping of samples has been very challenging in the last few years.

Day 1, Session II: Rotavirus age distribution project
Presenter: Mateusz Agopsowicz, WHO and LSHTM

A systematic review at The London School of Hygiene and Tropical Medicine (LSHTM) in partnership with WHO and Emory University aims to update the global evidence on the age distribution of rotavirus disease in children under five years of age and if vaccines provide protection for the peak age of rotavirus gastroenteritis (RVGE). Other aims include informing vaccine schedules, assessing vaccine impact, and assessing the burden of rotavirus in neonatal and early infancy. A literature search resulted in 131 epidemiology study datasets and the GRSN provided 169 datasets to inform study questions. Country datasets were defined as any pre- or post-vaccine dataset derived from a single study within a single country, reporting on a single outcome. Overall, 115 countries (69 from GRSN) were represented. Across all datasets, the median age of RVGE hospitalization was 46.7 weeks. A correlation was found between under-five mortality rate and median age of RVGE hospitalization with median age being lower in high mortality strata. The burden of RVGE before 10-13 weeks of age in the pre-vaccine era varied regionally for both hospitalized and community cases. Overall, 4.7% of hospitalized cases and 10.7% of community cases occurred before 14 weeks of age. Following vaccine introduction in EURO, the median age of hospitalization increased. However, this trend was inconsistent or not observed in other WHO Regions. This analysis will be developed into a peer-reviewed publication.

Discussion and recommendation

- When looking at vaccine impact on the age distribution, it may be important to consider the coverage in countries included in analyses and how to define vaccine introduction transition years. For these analyses there was no coverage cut-off (post-introduction was considered in any country with coverage over 0% from the year of introduction).
- When looking at vaccine impact on the age distribution, the age distribution of the children enrolled needs to be taken into account.
- No major differences were observed between hospital and community cases.

Day 1, Session III: Global Pediatric Diarrheal Surveillance (GPDS) updates

Global status update
The objective of GPDS is to leverage the GRSN for broader testing of enteropathogens using quantitative PCR via TaqMan Array Cards to better understand the etiology of pediatric diarrheal disease in the post rotavirus vaccine era and aid norovirus, ETEC, and Shigella vaccine development. GRSN sites selected for participation were required to meet the following criteria: continuous surveillance over a minimum of two years, high performance, minimum of 100 samples per year, use of the WHO case-based rotavirus surveillance protocol and ability to share surveillance data, ability to modify the data collection protocol to remove the exclusion criteria of persistent or bloody diarrhea, and ability to store all stool samples for a minimum of three months. From participating sites, 25 samples per quarter are randomly selected for TAC testing at RRLs. TAC results are uploaded by RRLs to a server at the University of Virginia for cleaning; the results are then merged with surveillance data at WHO. RRLs or the GRL will also genotype positive isolates for norovirus tested by TAC. Although some sites are testing bloody and persistent cases for rotavirus by EIA, this is not required and may lead to a higher rate of false positives.

Regional reference laboratories training and data handling

RRL trainings in Australia, South Africa (the National Institute for Communicable Diseases), Brazil, and Ghana occurred for TAC Phase I. For TAC Phase II, RRL trainings occurred in South Africa (University of Medunsa), Belarus, and China and a refresher training was held in Ghana. Trainings were 2.5-5 days long and included laboratory assessment, nucleic acid extraction, array card setup and run, qPCR data analysis, and utilization of the MuSIC database. During the laboratory assessment, swipe tests for laboratory contamination are done and training only proceeds after a clean laboratory environment is achieved. Raw data analysis for qPCR includes training on amplification curves, baseline adjustments, and recognizing and adjusting for noise. Data are then uploaded onto MuSIC, a secure database run by UVA. After data are uploaded onto MuSIC, it is cleaned at UVA. These data are available through MuSIC to RRLs, ROs, and HQ. The clean TAC data are merged with routine surveillance data at WHO and shared without patient unique identifier finally analyzed in collaboration with UVA to calculate pathogen prevalences and attributable fractions. It is important that unique case identifiers are used for the merging of TAC data with the surveillance data. It will also be important to ensure consistency among different hardware platforms and finalize database access.

Discussion

- No analyses occur through MuSIC, it is a database to hold raw Ct values from TAC qPCR results for cleaning. MuSIC streamlines data entry and cleaning. During the cleaning process at UVA they look for positive, negative, and internal controls. It is expected that about 5% of specimens will fail a control and need to be removed from analyses.
- The epidemiological surveillance data needs to be linked with the TAC data because overall rates of disease are needed for attributable fraction analyses.
- Odds ratios from the Global Enteric Multicenter Study (GEMS; Kotloff et al., 2013) are used to adjust for seasonality and sampling.

Recommendations

- WHO will revise the GPDS protocol and share with regions and participating countries to clarify the data sharing, handling, storage, and use processes. Also, consider developing a letter for countries describing this process and clarifying the relationship between GPDS and GRSN.
Need an information sheet to accompany results to country with a clear description of the meaning of prevalence and AF and clarification as to why the results may differ.

Preliminary data: clinical presentation and data quality
Presenter: Julia Bennett, WHO and Johns Hopkins Bloomberg School of Public Health

Globally, surveillance data from 46 sites participating in GPDS has been reported to WHO HQ. Sites began using the expanded case definition between January and May 2017. The expanded case definition removes the exclusion criteria of persistent and bloody diarrhea. Diarrhea is defined as three or more loose or watery stools in a 24-hour period. Acute diarrhea is an episode of diarrhea that lasts less than 14 days; in contrast, persistent diarrhea lasts 14 days or more. Persistent diarrhea may be referred to as persistent or non-acute diarrhea. Prolonged diarrhea is a subset of acute diarrhea lasting more than 7 days but less than 14 days. Watery diarrhea is diarrhea without blood; dysentery, or bloody diarrhea, is diarrhea with blood in the stool, with or without mucus. A retrospective analysis of hospital records found the majority of pediatric diarrhea to be acute watery. However, there was significant variation between and within countries and a reduction in the proportion of acute watery diarrhea following vaccine introduction in Zambia. Preliminary global data analyses show about 91% acute watery, 8% acute bloody, 0.6% persistent watery, and 0.1% persistent bloody diarrhea. All persistent bloody diarrhea cases were reported from one country. Non-acute watery diarrhea cases had lower rotavirus positivity, less vomiting, and less dehydration. Data quality challenges include cases with inconclusive duration of diarrhea, cases without presence of blood reported, and sites reporting low numbers of cases. Communication through regional and country offices has been successful in resolving some of these issues.

Discussion and recommendations
• A priority is adding at least one site in EMRO, possibly Sudan or Pakistan. This will require a new EMRO RRL or shipping samples to a RRL outside of EMRO or the GRL.
• There may be an underestimation of persistent diarrhea because duration of diarrhea is measured on the day of admission to the hospital and diarrhea may continue during hospitalization. Similarly, watery diarrhea may become bloody during hospitalization. For the purposes of GPDS analyses, we decided to classify diarrhea as acute or persistent and watery or bloody upon the date of admission.
• Some regions and countries define acute as less than 7 days instead of less than 14 days. The countries include all of those in EURO and AFRO, as well as Nepal and India. For those countries, the analysis of duration of diarrhea will need to take into consideration that the variable asking acute Y/N uses a cut-off of 7 days. In addition. AFRO has separate variables for acute Y/N, duration in days if acute, persistent Y/N, and duration in days if persistent.

Etiology
Presenter: Adam L. Cohen, WHO

Determining the etiology of an illness episode by PCR is complicated by carriage and shedding pathogens; not every case where the pathogen is identified by PCR is caused by that pathogen. For the preliminary analyses, attributable fractions are extrapolated from the GEMS study (Kotloff et al., 2013). However, GEMS was not conducted in countries from EUR or AMR. The etiology data presented are preliminary and do not include a full year, therefore results may be biased because the peak of disease may be included or missing. In EUR, rotavirus has the highest attributable fraction followed by norovirus and Shigella. In India and Nepal, Rotavirus, Shigella, and adenovirus had the highest attributable
fractions. Next steps include analyzing the entire first year of data, reporting data by country, analyzing by clinical presentation, age, and vaccination status, and using estimates of diarrhea incidence to estimate attributable incidence.

Discussion and recommendations

- James Platts-Mills can work with regional and country offices to explain the attributable fraction model being used.
- There is a lot of regional variability of carriage. Carriage is much higher in India and Nepal than Europe. GEMS data from Africa and Asia may not apply to Europe for attributable fraction calculations given the low levels of carriage.
- Although this data will provide important information on the etiology of diarrhea, it should not reduce expectations about the potential impact of rotavirus vaccines. For example, the burden of rotavirus in India is very high and vaccine introduction will result in a large decrease in diarrhea, despite the burden of diarrhea from other pathogens.
- The Malnutrition and Enteric Diseases Network (MAL-ED) data should be used to calculate attributable fractions for AMR to see if they differ from Asia and Africa.
- Consider a literature review of attributable fractions in EURO or enrolling controls to determine if the attributable fractions differ.

Day 1, Session IV: GPDS Regional Updates

AFRO
Presenter: Jason Mwenda, WHO AFRO

The objectives and feasibility of expanded pediatric diarrhea surveillance were reviewed by the regional office. Discussions of requirements resulted in procuring freezers for specimen storage. Training on the expanded surveillance occurred at three regional workshops. The case reporting form and database were modified to capture information on persistent and bloody diarrhea. Random sample selection has been put on hold pending further clarification. Funding has been a challenge as the expansion has required an increase in human resource, technical, and logistical capacity.

Discussion and recommendations

- AFRO added a variable into the surveillance database on prior antibiotics use with no specification on type of antibiotics. This may be useful, but with increases in antimicrobial resistance, it will be important to also know what antibiotic was used.
- Countries with less than 100 cases per year should not be included in GPDS. Ideally, each country will identify one surveillance site that meets the inclusion criteria and who will enroll cases as part of GPDS for TAC testing. If there are insufficient numbers of cases at one hospital, a country may choose two high performing and consistently reporting sites in the same geographic area of a country to reach the minimum of 100 cases per year. Select AFR specimens to be tested by TAC will be shipped for testing at the RRL as soon as possible.

AMRO/PAHO
Presenter: Gloria Rey, PAHO/WHO AMRO

Five sites in five countries were selected out of 23 sites in 10 countries for participation in GPDS based upon site requirements. Random selection of specimens is occurring at the regional office. The list of
specimens is shared with the country office and samples are sent to the RRL for testing. Following data analysis, the regional office will share results with the country offices and Ministries of Health. Shipment of specimens from Ecuador to the RRL will occur in the before the end of November 2017. Progress and implementation of GPDS will be presented during the next regional meeting in December 2017 in Lima. Other countries in the region are interested and may request to join GPDS.

EURO
Presenter: Danni Daniels, WHO EURO

All GRSN-participating countries were interested in GPDS. Five sites in five countries were selected out of eleven sites in seven countries for participation based on site requirements and country input. Regional meetings and non-GPDS site visits were fortuitous and provided additional GPDS training opportunities. These face-to-face meetings and preparatory calls at the end of 2016 contributed to a smooth transition of expanding the case definition, randomly selecting samples (with help from HQ), and sending samples to the RRL. All sites began using the expanded case definition in January of 2017. The RRL was equipped and staff were trained in mid-September to process specimens for GPDS. The RRL successfully processed specimens from all participating sites. Samples from one country were received at the RRL with inadequate volume which may have been due to melted ice packs. Shipping specimens once a year in the winter to avoid excessive heat may be a solution to this problem. Funding remains an additional challenge, particularly for Gavi graduated and graduating countries.

SEARO
Presenter: Sidhartha Giri, CMC Vellore

One site in Nepal, Myanmar, and Indonesia and three sites in India were selected for GPDS. Rotavirus genotyping and TAC qPCR laboratory trainings occurred in June 2017 in Nepal and additional trainings are planned for early 2018 in Indonesia and Myanmar. Initially, expansion of the case definition only included acute watery and acute bloody diarrhea. Beginning in October 2017, persistent diarrhea cases are being enrolled. Samples from India and Nepal were selected and sent to the RRL for TAC testing.

WPRO
Presenters: Nyambat Batmunkh, WHO WPRO, and Sarah Thomas, MCRI

Lao People’s Democratic Republic, Fiji, Vietnam, and China are participating in GPDS. At this time the site in the Philippines could not be included due to data sharing issues, but the institute is interested. Mongolia could not be included at this time because different diarrhea syndromes are treated at different hospitals. In Vietnam a separate surveillance system for GPDS has been established parallel to the GRSN surveillance. This may introduce a selection bias and plans are set to combine the two systems in 2018. Samples shipped from Vietnam were compromised due to arrival at ambient temperature. A second shipment is planned. The three sites in China were already including all diarrhea cases in their surveillance, so an adjustment in the case definition was not required. Sample shipments in WPRO were delayed and samples have not yet been received from Lao, in part because of the need for a new computer with an updated database. Other challenges include confusion about which samples to send and unreliable shipping companies. The RRL in Australia successfully used swipe tests to document decontamination of the laboratory and were able to test 17 samples using TAC cards.

Day 2, Session I: Practical discussion of regional updates and summary of GPDS and way forward
Presenter: Adam L. Cohen, WHO HQ
GPDS has been successfully implemented in many sites yielding preliminary data. The current GPDS project grant funded by BMGF ends in Q1 of 2019 and the objective is to have two full years of data from each site by this time. Steps to strengthen GPDS over the next 3-6 months include determining which sites meet inclusion criteria, adding 1-2 sites in EMR, and determining which sites are urban, rural, and peri-urban. Over the next 1-2 years, GPDS goals include adding more sites, obtaining more laboratory equipment, and increasing coordination and oversight of data cleaning and analysis by WHO. Regional meetings, site visits, phone calls, RRL trainings, and QC between RRLs for GPDS have led to the successful implementation. Protocol clarifications include that cases will be excluded if they have had any hospitalization during the illness, including hospitalizations prior to admission and enrollment.

Discussion
• Should controls be gathered in EURO (and possibly AMRO) to develop more accurate attributable fractions?
  o Data from MAL-ED may be able to be used for calculating attributable fractions in AMRO. It is likely unfeasible to gather the number of controls needed to calculate pathogen-specific odds ratios. There is a potential for drawing upon other pathogen-specific data sets through a literature review.
• Should different pathogens be included on the swipe test?
  o Every laboratory has contamination at some point, so swipe tests are part of good standard laboratory practices. Contamination is usually found at laboratories at the start, and as practices improve it becomes less common. Using TAC cards for swipe tests may be unnecessary and costly. The swipe test currently tests for four pathogens: giardia, adenovirus, E. coli and rotavirus.

Recommendations
• Determine which GPDS sites are meeting the minimum criteria (100 specimens per year tested at RRL).
• Add 1 or 2 sites in EMRO (Pakistan or Sudan) and consider other sites on an ad hoc basis. New sites need to have a minimum of 12 months of data by Q1/Q2 of 2019.
• Determine which GPDS sites are urban, rural, and peri-urban. Consider site location in site selection for countries (mostly in AFRO) that have not shipped samples to a RRL yet.
• Provide more regional training on attributable fraction calculations and potentially develop information sheets. Include data cleaning and including looking critically at Ct values in RRL refresher trainings.
• Determine the budget necessary to add norovirus to the swipe test and decide if norovirus should be added to the swipe test.
• Plan a meeting for the second half of next year to discuss a full year of GPDS data.
• Darwin will estimate the cost of adding other target genes in the swipe test; there was a discussion about adding norovirus or replacing another target for environmental testing.
• Follow ups with all sites in WPRO are planned for and will mainly address the surveillance methodology in Vietnam, the reason of low number of cases in Fiji and data management issues in Lao People's Democratic Republic.

Day 2, Session II: Burden of diarrheal diseases

Baseline burden of rotavirus in WPR
The WHO Western Pacific Region contains over 1.8 billion people in 37 countries and a wide range of socioeconomic development and health status. A high proportion of countries in WPR have yet to introduce rotavirus vaccine. There is a range of rotavirus positivity in the region. In Lao People's Democratic Republic and Fiji the rotavirus positivity for children under 5 years of age is 49% and 9% respectively. For all countries in the region, rotavirus positivity was 32% in 2016. Seasonal rotavirus patterns are seen and vary by country. A rotavirus supplement currently under review in Asia included many country-level disease burden estimates. Other activities include establishment of intussusception surveillance in Lao People's Democratic Republic with the U.S. CDC, a vaccine cost-effectiveness study in Mongolia with PATH, a vaccine effectiveness study in the Philippines with the U.S. CDC, and establishment of GPDS sites in four countries. Surveillance data from the network have been critical in generating evidence for vaccine introduction and for evaluating vaccine impact.

Global norovirus surveillance
Presenter: Jan Vinje, U.S. Centers for Disease Control and Prevention

The Global Norovirus Strain Surveillance project is currently called NoroPed. Globally, norovirus causes an annual estimated 685 million cases, 200 million in children under five and about 200,000 deaths, 54,000 in children under five, annually. The GII.4 genotype is causing significant disease, although there are regional and epidemiological differences that are still not fully understood. Several norovirus vaccine candidates are in the pipeline, and better understanding of the distribution of disease-causing norovirus genotypes will help to inform the vaccine development process. Subunit vaccines are being developed against the VP1 protein of common norovirus strains by several companies. For surveillance of norovirus in children, the NoroPed web portal has been developed by CDC and collaborators to upload basic data, such as age and gender from diarrhea cases in hospitalized children and community infections. In addition to patient data, sequence files can be uploaded and stored in the database where they can be compared to other sequences in the database by phylogenetic analysis methods. Samples identified as positive for norovirus from TAC cards in GPDS will be genotyped for norovirus at RRLs. Other non-GPDS sites may also be included in NoroPed. The primary goal of NoroPed is to genotype samples and evaluate trends over time.

Discussion and recommendation

- If norovirus sequencing will be done on the norovirus positives samples, the countries where the samples are originated need to be informed in advance.
- There is a need to consider data sharing issues and the security of the data entry portal.
- Concern over long-term shedding of norovirus should be addressed.
- It is important that standardized sequencing protocols are used.
- Follow-up on proposal for use of GPDS specimens in NoroPed.

Day 2, Session III: Rotavirus vaccine impact

Global vaccine impact
Presenter: Negar Aliabadi, U.S. Centers for Disease Control and Prevention
The impact of national rotavirus vaccine introduction on rotavirus positivity within GRSN was described globally and regionally. Sites reporting cases for all 12 months of a year and testing a minimum of 100 cases per year for rotavirus by EIA were included. The analyses were also conducted in a subgroup of sites with surveillance data from both pre- and post-vaccine introduction periods and a subgroup of sites with rotavirus vaccine coverage at a minimum of 60%. In all primary and sub-group analyses, significant reductions in rotavirus positivity were observed following vaccine introduction. Globally, a 35% decline in rotavirus positivity was observed among 302 sites in 76 countries from 2008-2015. The median age of rotavirus illness was found to be younger during the pre-vaccine era. The analyses will be updated with 2016 surveillance data and stratified by age and vaccine coverage and developed into a peer-reviewed publication.

Conclusion

- The strict inclusion criteria may result in losing data from smaller countries or countries that have been using the vaccine for many years and consequently have low rates of pediatric diarrhea. Despite this, large amounts of data were included (210 site years from 28 countries testing 63,847 cases for rotavirus by EIA).
- This analysis shows the value of historical aggregated data in showing vaccine impact.

Genotype Distribution

Presenters: Fatima Serhan, WHO HQ, Danni Daniels, WHO EURO, George Armah, Ghana, and Mapaseka Seheri, University of Medunsa

GRSN collects case-based genotype information for a subset of rotavirus positive cases. There is an overall interest among the group in evaluating genotype distributions following vaccine introduction; however, many questions remain on how to best present the data. Because some sites genotype a higher number of cases than other sites, genotype distributions can be biased towards one country when the distributions are pooled globally or regionally. Genotype distributions from 2008-2016 in EUR were presented. During this time, G1P[8], G2P[4], G3P[8], G4P[8], G9P[8] accounted for about 90% of the cases. Annual variation in genotypes was observed in individual countries both before and after vaccine introduction. Genotype data were also presented from AFR.

Discussion and recommendations

- Comparing genotyping data pre- and post-vaccine introduction is challenging for rotavirus because we do not have a clear hypothesis as the vaccine provides cross-protection against multiple genotypes.
- To reduce the bias from certain countries, consider weighting the proportion by population. Consider also comparing annual genotype distributions between neighboring countries where only one has introduced the vaccine.
- There was an analysis in Australia in which 15 years of pre- and 10 years of post-vaccine genotyping data were analyzed. Several years of post-vaccine data may be necessary to determine if changes in the genotype distribution are sustained or rather caused by regular fluctuations. An overall decrease in G1P[8] was observed in Australia; however, a novel G1P[8] strain (single amino acid change) has emerged and does not appear to be protected against by the vaccines.
- Global, regional and country genotype distribution are valuable and capacities for genotyping should be sustained.
Day 2, Session IV: Future directions for rotavirus and global pediatric diarrheal surveillance

Vaccine development (Shigella, norovirus, ETEC)
Presenter: Birgitte Giersing, WHO HQ

There is a need to link surveillance data from systems such as GRSN and GPDS to the value proposition of vaccines. Early in the vaccine development process, the necessary components of a vaccine to meet the Gavi vaccine investment strategy criteria need to be considered. The leading enteric vaccines in the pipeline are Shigella, ETEC, and norovirus. The most recent Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease (GBD) estimates show ETEC mortality to be decreasing and this has resulted in less of an interest in ETEC vaccines. However, ETEC does have long term sequelae when children are infected early in life. These disease burden estimates are very important in driving vaccine development interest. Shigella has a high burden of disease and is also a WHO GLASS priority pathogen and may provide an opportunity to demonstrate the impact of vaccines on AMR. For GPDS surveillance, it would be beneficial to identify as many subtypes of Shigella (such as sonnei and flexneri) to determine which are the most important for vaccines. The current TAC card broadly detects Shigella species as well as Shigella sonnei. For norovirus, there is a lot of interest in how well vaccines will provide cross-protection to non-vaccine genotypes.

Discussion
- Shigella types are on the TAC card; however, there are not any AMR targets on the current TAC card. We will consider testing for AMR on future or additional TAC cards; however, there are many AMR targets which would make it difficult to create a comprehensive AMR TAC card.

The MuSIC database
Presenter: Darwin Operario, University of Virginia

The MuSIC database allows UVA to collect all of the data from TAC cards in one place with standard formatting to facilitate data cleaning. Each site can only see its own data within MuSIC. There are three flags in MuSIC: noise, bad ROX, and spike flags. When the data are received in MuSIC there is a manual (extraction blanks and Ct values) and an automated (R script) clean-up run. MuSIC is not a platform for analysis, but instead is only used to store data.

Discussion and recommendations
- It may be possible to share clean data with regions through MuSIC and the long term vision should include enhancing RRL capacities in conducting the data cleaning through trainings
- Moving forward, more analyses may be done at WHO HQ and ROs as capacities increase.
- Determine who from WHO RO, RRLs, and countries should have access to MuSIC.
- Provide cut-off values for different pathogens so countries and regional offices can estimate crude distribution of etiologies from TAC data, before attributable fractions are calculated.

Day 2, Session V: Sustainability, funding, and future activities
Presenters: Adam L. Cohen and Fatima Serhan, WHO HQ

Gavi and BMGF are the two main funders for GRSN and GPDS. There is a shift in the data priorities at Gavi and surveillance in its current cycle of funding and surveillance has become less of a focus. At the country level, funding for surveillance is still available through Gavi. Work is ongoing with Gavi to learn how to use current funding channels to support surveillance work. The BMGF has been funding the
GPDS expansion and there is interest in continuation beyond the current two-year grant cycle, assuming that GPDS is successfully implemented and useful data are generated. The U.S. CDC has also provided support to the networks. Many countries receive funding from other sources, including budgeting national resources for surveillance. However, expansions such as TAC testing require financial and technical support beyond what most countries can provide on their own. Proposal is to host the 2018 surveillance meeting in Cape Town, South Africa.

Working group questions, meeting agenda and list of participants follow.
Global Rotavirus and Pediatric Diarrheal Surveillance Network Meetings

16-17 November 2017
Hotel Royal, Geneva, Switzerland

Objectives
1. Review the current status and priorities of the global rotavirus surveillance network
2. Review the current status and priorities of the global pediatric diarrhea surveillance network
3. Discuss global rotavirus surveillance data analysis
4. Discuss current and future priorities and funding for surveillance

Thursday, 16 November 2017
Day 1

Morning Session
Chair: George Armah
Rapporteurs: Julia Bennett, Negar Alibadi

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<td>Registration</td>
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<td>9h00-9h30</td>
<td>Welcome and introduction</td>
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<td>Global overview of rotavirus surveillance and laboratory network</td>
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<td>Rotavirus early age distribution project</td>
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<td>GPDS Global Updates</td>
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<td>o Preliminary data: clinical presentation and data quality (15 min + 30 min discussion)</td>
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Afternoon Session
Chair: Eric Houpt
Rapporteurs: Julia Bennett, Nicola Page

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<td>o SEAR (15 min)</td>
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<td>o WPR (15 min)</td>
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<td>Practical discussion of Regional Updates (1 hour)</td>
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<tr>
<td>17h30-18h30</td>
<td>Reception</td>
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</table>
### Friday, 17 November 2017
**Day 2**

#### Morning Session
**Chair:** Umesh Parashar  
**Rapporteurs:** Julia Bennett, Ben Lopman

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Presenters/Topics</th>
</tr>
</thead>
<tbody>
<tr>
<td>9h00-9h30</td>
<td>Summary of GPDS TAC and way forward</td>
<td>Group discussion</td>
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<tr>
<td>9h30-10h30</td>
<td>Burden of Diarrheal Diseases</td>
<td>Nyambat Batmunkh, Jan Vinje</td>
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<tr>
<td></td>
<td>o Baseline burden of rotavirus in WPR (15 min presentation + 15 min discussion)</td>
<td>Jan Vinje</td>
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<tr>
<td></td>
<td>o Global norovirus surveillance and topics (15 min presentation + 15 min discussion)</td>
<td>Nyambat Batmunkh</td>
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<tr>
<td>10h30-11h00</td>
<td>Coffee/tea break</td>
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<tr>
<td>11h00-12h30</td>
<td>Rotavirus vaccine impact</td>
<td>Adam Cohen, Negar Aliabadi, Tomoka Nakamura</td>
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<tr>
<td></td>
<td>o Introduction (10 min)</td>
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<td></td>
<td>o Global vaccine impact (15 min)</td>
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<td></td>
<td>o Genotype distribution (pre-post vaccine intro) (15 min)</td>
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<td>o Discussion on vaccine impact (30 min)</td>
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<tr>
<td>12h30-13h30</td>
<td>Lunch Break</td>
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</table>

#### Afternoon Session
**Chair:** Umesh Parashar  
**Rapporteurs:** Julia Bennett, Tomoka Nakamura, Jon Gentsch

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Presenters/Topics</th>
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<tbody>
<tr>
<td>13h30-15h00</td>
<td>Future directions for rotavirus and global pediatric diarrhea surveillance</td>
<td>Group discussion</td>
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<td>o Current objectives of diarrhea surveillance</td>
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<td>o Disease focus</td>
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<td>o Vaccine development (Shigella, norovirus, ETEC)</td>
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<tr>
<td>15h00-15h30</td>
<td>Coffee/tea break</td>
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<tr>
<td>15h30-16h00</td>
<td>Sustainability, funding, and future activities</td>
<td>Adam Cohen, Fatima Serhan</td>
</tr>
<tr>
<td>16h00-16h30</td>
<td>Meeting wrap-up and final discussions</td>
<td>Adam Cohen, Fatima Serhan</td>
</tr>
</tbody>
</table>
Global Rotavirus Surveillance Network & Global Pediatric Diarrhea Surveillance (TAC) Meetings, 16-17 November 2017
Hotel Royal, Geneva, Switzerland

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