MEETING REPORT

Global Rotavirus and Paediatric Diarrhea Surveillance, Laboratory, and Disease Burden Meetings

28-30 November 2018

Southern Sun the Cullinan Hotel, Cape Town, South Africa
# Table of Contents

## Global Rotavirus and Pediatric Diarrhea Surveillance Meeting .................................................................3

Session I: Global overview ..........................................................................................................................3

GRSN and GPDS status, activities, and protocol .........................................................................................3

Analytic methodology for GPDS .............................................................................................................3

GRSN and GPDS preliminary results ........................................................................................................4

Session II: Regional Highlights .................................................................................................................5

AFRO .............................................................................................................................................................5

EURO .............................................................................................................................................................6

Session III: Deep-dive into GPDS implementation steps .............................................................................6

Group #1 (Sites) discussion points ............................................................................................................6

Group #2 (Lab) discussion points ..............................................................................................................7

Group #3 (Data) discussion points ............................................................................................................7

Group #4 (Countries/stakeholders) discussion points ................................................................................8

Session IV: New directions .......................................................................................................................9

Antimicrobial resistance pilot study in WPRO .........................................................................................9

Next generation TAC and etiology testing .................................................................................................9

GPDS contribution to global diarrheal data needs ..................................................................................10

Session V: Next steps for 2019 and beyond ............................................................................................10

## Global Rotavirus Laboratory Meeting ....................................................................................................12

Session 1: Rotavirus laboratory manual: Global summary and regional updates on rotavirus genotyping validation ...12

AFRO RRL (Ghana) ....................................................................................................................................12

AFRO RRL (SMU, South Africa) ................................................................................................................12

AFRO RRL (NICD, South Africa) ................................................................................................................12

PAHO RRL (Fiocruz, Brazil) ......................................................................................................................12

SEAR RRL (CMC Vellore) ........................................................................................................................12

RRL WPR (MCRI, Australia) .....................................................................................................................12

Session 2: External Quality Assessment (EQA) and Quality Control (QC) for Rotavirus ....................................13

Session 3: General overview and discussion of GPDS implementation at RRL ...........................................14
Global Rotavirus and Pediatric Diarrhea Surveillance Meeting

Wednesday, 28 November 2018

Meeting Objectives

- Review the current status, protocol, and preliminary results of Global Rotavirus Surveillance Network and Global Pediatric Diarrhea Surveillance
- Discuss priorities and future opportunities for global diarrheal disease surveillance

Session I: Global overview

GRSN and GPDS status, activities, and protocol
Presenter: Fatima Serhan, WHO HQ

WHO has updated VPD surveillance guidance, which includes guidance for rotavirus and pediatric diarrhea. The Global Rotavirus Surveillance Network (GRSN) has been ongoing. After pilot testing of TAC in 4 regional reference labs (representing 16 countries), rotavirus surveillance has been expanded to Global Pediatric Diarrhea Surveillance (GPDS) in 30 countries. 26 of these countries no longer have GAVI support and recently graduated. EMRO not yet participating but Pakistan is planning to participate so that EMRO will be included. With GPDS, the case definition was expanded to include ALL diarrhea cases, both acute and persistent, watery and bloody. The methodology at the site, RRL, and global level was described. Additional norovirus genotyping (GT) and sequencing will be done at RRLs to contribute to plans for norovirus vaccine development. Given limited GAVI funding, rotavirus surveillance to be focused on high performing countries and we will continue to collect GT data.

Discussion and Recommendations

- Much discussion was regarding the epidemiology and clinical presentation of norovirus and whether the current methodology will miss norovirus cases. The current focus of the network is diarrheal morbidity across all the pathogens, and some cases will be missed.
- Q: Why not include vomiting only cases? A: The network was designed for burden and etiology of diarrhea and not specifically focused on norovirus.
- Q: What is the incidence of vomiting only in children under 5 with norovirus? A: Information not available from this network. From a global systematic review – about 15% of medically attended norovirus is vomiting only; in young adults in US about 20-25% of norovirus cases are vomiting only.

Analytic methodology for GPDS
Presenter: James Platts-Mills, University of Virginia

The standard workup for diarrhea is expensive, complicated, and variably sensitive. TaqMan array was used in GEMS study with high sensitivity but variability across pathogens. It is hard to determine which pathogens are etiologic for disease since carriage and exposures are high in settings of GPDS. We need an analytic method to set a threshold for
subclinical infection. The GEMS case control study included moderate to severe diarrhea cases under 5 years in 7 sites in Asia and African. They did a reanalysis using qPCR. The attributable incidence was similar for rotavirus comparing the original analysis to qPCR; however, other pathogens did not line up as well. Overall qPCR showed 89% of diarrheal cases were attributable to a pathogen vs 49% in the original analysis.

Phase 2 of GPDS is prospective. Sample selection is randomized by 3-month intervals with inverse probability weighting (IPW) to adjust for seasonal variation in diarrhea incidence; this only works at sites with all 4 quarters of data. IPW was internally validated using rotavirus EIA. To calculate attributable fraction given the absence of controls, quantitative pathogen results from GPDS were combined with the modeled association between pathogen quantity and diarrhea in GEMS and Mal ED sites. To calculate attributable incidence in the absence of a defined catchment population at risk or health-care seeking behavior, IHME year- and age-specific estimates of severe diarrhea incidence were used to extrapolate a national estimate from site specific prevalence.

**Discussion**

- Q: Is ELISA done on all cases or only acute watery diarrhea? A: All sites are testing acute watery definition, the original rotavirus surveillance case definition; some sites are testing all diarrhea cases (bloody, chronic, acute, watery).
- Q: What is possible impact of not including mixed genotypes in the analysis? A: This assumption was made but can be changed.
- There appears to be some mismatch between genotyping on TAC and standard genotyping PCR assays, which could be due to the genotyping of all TAC detections and not etiologic attributed rotavirus infections.

**Recommendations**

- We will need to decide how to analyze and present mixed rotavirus genotypes.
- We will need to follow up on TAC genotyping and will not use for now.

**GRSN and GPDS preliminary results**

*Presenter: Adam L. Cohen, WHO HQ*

The preliminary results from the most recent year of GRSN and first year of TAC testing were presented. Despite the dramatic decline (~40%) in rotavirus disease due to use of vaccine, rotavirus remains the leading cause of severe diarrhea in children <5. Shigella, cryptosporidium, norovirus and adenovirus are the next most common etiologies of pediatric diarrhea, but there is wide variability by region and country. Ongoing surveillance is critical to generate data for use at country, regional and global levels. The surveillance needs to be responsive to national vaccine policy needs (e.g., rotavirus vaccine impact) and global policy implications (e.g., vaccines in development such as Shigella, ETEC, & norovirus). The plan is to continue GPDS for 2 full calendar years and strengthen and refine network, while maintaining sustainable rotavirus and pediatric diarrhea surveillance through capacity building and country and external funding.

**General discussion of first three talks**

- It is possible to stratify by vaccine introduction status, but we have not done that yet.
• Some country differences do not seem plausible. It was noted that these are preliminary analysis and some sites don’t yet have a full year of data tested.

• Q. Is there a potential for looking at mortality trends and case specific mortality? A. We have not looked at this yet, but there are few in-hospital deaths. Only 1-2% of enrolled children died.

• Q. Is cryptosporidium burden being overestimated by GEMS data? A. Children with diarrhea from other pathogens are secreting crypto. These findings are inconsistent with birth cohort studies. The current analysis with cryptosporidium are being driven by disease Africa.

Recommendations

• Future analyses include mortality (though few in-hospital deaths, 1-2%), mixed infections, rotavirus vaccine impact, including age at first dose (though not much post-vaccine introduction data).

• Will need to review rotavirus genotyping on TAC card.

Session II: Regional Highlights

AFRO

Presenter: Jason Mwenda, WHO AFRO

A presentation on highlights and next steps for rotavirus and paediatric diarrhea surveillance in the African Region was given. This included the structure, highlights, and achievements for the Regional AFR Rotavirus Surveillance Network, the status of rotavirus vaccine introduction in the region and vaccine coverage monitoring, evidence and documentation of early impact, vaccine effectiveness, and safety of rotavirus vaccine in routine EPI, and future perspectives for VPD sentinel surveillance in the region, including challenges and a way forward.

Discussion

• One of most challenging things in AFRO is distribution of reagents. To improve distribution, the WHO catalog is used for centralized procurement of supplies through WHO country offices, which can more easily be cleared through customs. EQA panels were initially shipped directly to countries but may now go through WHO country offices.

• Q: Is reduction in all cause diarrhea hospitalizations resulting in more empty hospitals or are beds being filled with other cases? A: No, the wards are emptier, particularly the diarrhea wards (e.g., Mozambique). However, there are some countries that have had some outbreaks (e.g. Botswana, eSwatini).

Recommendations

• Need to determine how to explain that the percentage of rotavirus positivity (prevalence) is still high despite introduction of vaccine.
EURO

Presenter: Danni Daniels

A presentation was given on an update on rotavirus and paediatric diarrhoea surveillance networks in the European Region. Of note, among 32 high income countries in EUR, 37% (12) have introduced rotavirus vaccine. Among 7 Gavi-eligible middle income countries, 71% (5) have introduced rotavirus vaccine. Among 14 remaining middle income countries, none (0%) have introduced rotavirus vaccine. Rotavirus surveillance has been used in country decision making, publications and reports, vaccine impact studies, global burden models, and as a platform for pediatric diarrhea surveillance. TAC testing results of a full year of 2017 EURO specimens indicate that rotavirus remains the leading cause of severe pediatric diarrhea with norovirus, *Shigella*, astrovirus and sapovirus being the next most common etiologies. Etiologies varied by country.

Discussion

- There are vaccine cost-effectiveness studies that have been done and PATH is willing to help. Need to look at both regionally and by countries. There are newly available vaccines that also need to be factored in.
- All EURO countries participating in GRSN have been using Rotarix. Kyrgyzstan will introduce but will not be able to introduce Rotarix because of the global shortage and will have to choose another vaccine.
- In Moldova, there is a region of instability in country without vaccine so there is low national coverage, but where the impact study was done, coverage is much higher.

Session III: Deep-dive into GPDS implementation steps

The participants divided into 4 small groups with 3 main objectives for each small group discussion.

**Small group topics and facilitators**

1. Sites: Enrollment of cases; Tomoka Nakamura & Kirkby Tickell
2. Lab: Shipment of samples, testing at RRLs, data upload, cleaning and linking to surveillance data; Fatima Serhan & Darwin Operario
3. Data: Analysis and dissemination; Sébastien Antoni & James Platts-Mills
4. Countries/stakeholders: How GPDS data can be used and sustainability; Jason Mwenda & Adam Cohen

**Small group discussion topics**

- What is the current status at your country/region?
- What are some of the major hurdles and challenges encountered?
- What are some of the possible solutions for these challenges?
- Any questions you might have to clarify the process of this level?

**Group #1 (Sites) discussion points**

- Broadening the case definition for GPDS from that used for GRSN had been successfully implemented, but this had presented substantial challenges and had required substantial input to get the new definition up and running.
• The case definition for inclusion was considered to include anyone admitted to hospital requiring treatment of diarrhoea, irrespective of whether this was the primary diagnosis (e.g. a patient with sepsis and diarrhoea would be included).
• The group considered that the recording of all cases coming to a site was probably complete, including cases presenting at night, even though specific staff in the hospital were not remunerated for the work involved in recording cases (sites currently receive $5000 a year to cover incidental expenses – e.g. freezers).
• Need dedicated people for enrolling and recoding cases.
• There was concern that at some sites some patients may be directed to other facilities if they had specific features and this may introduce some biases (e.g. malnourished patients may be directed to a malnutrition ward or, at one site, patients with bloody diarrhoea were directed to another hospital. Surveillance might be missing these cases.
• Recording of previous antibiotic treatment is not recorded or considered in the analysis. Antibiotic use could affect bacterial loads and would have implications for methods used to assign aetiology based on quantitative PCR.
• Systematic sampling will be used in some regions and sites. At sites with high loads of patients with diarrhoea, a systematic sampling system was used to included patients, such as enrolling every 5th or every 10th patient. If not conducted systematically, this sampling could be a potential source of bias, if included patients were not representative of all eligible patients.
• The stool samples selected for TaqMan analysis seemed to be centrally organized, by WHO, with sites being informed which stools to send for analysis. This system should ensure representativeness with respect to the specimens analysed, compared to those collected.
• There was concern that excluding samples with no, or a too small, stool sample might introduce bias. It was suggested that innovative methods for stool collection might be used – e.g. asking a mother to supply a used nappy from the child.
• It is unclear whether the centrally recorded data on each case is sufficient to assess severity (e.g. no data on fever or malnutrition?).
• Site assessments can mitigate the challenge of heterogeneity of enrolled cases in GPDS.

Group #2 (Lab) discussion points
• Shipment of samples is always a challenge (e.g., logistically depending on the type of courier used).
  o Price of shipment is expensive particularly in African countries.
  o Dry ice
• Better communication is needed to collect the right amount of sample volume.
• Data cleaning at the lab level needs to be improved, both for handling of raw data and QC.
• Need to start thinking about testing isolates, which would involve bacteriology laboratories.

Group #3 (Data) discussion points
• Successes: Able to expand case definition.
• Data analysis demonstrates heterogeneity at local level.
• Within and beyond country level: urban hospitals with high number of specimens and cases enrolled. What about rural hospitals?
• Analysis at the regional level is robust, but when it comes to sub-regional level, data shown is less robust.
• Rules applied for case based using GEMS cutoffs.
• Can sampling randomization be done once a year?
• Incidence and extrapolation can be augmented by surveys to make more “accurate” incidence estimates.
• Is a single site representative of a country? Do we need to expand? This is a balance of breadth vs. depth, we need to find the right balance between the two

**Group #4 (Countries/stakeholders) discussion points**

- Ministries of Health and Finance, National Immunization Technical Advisory Groups (NITAGs), and academic groups are involved in product evaluation, selection, and introduction.
- What kind of data are being communicated?
  - Attributable fractions related to disease burden, impact and cost savings, cost beyond the disease itself
  - Individual and population benefit
  - Socioeconomic benefits
- General public and civil societies: these are the users of the vaccines and can be advocates of vaccines ultimately.
- Global level: burden numbers driving investment decisions including product development decisions and financing.
- Funders: Bill & Melinda Gates Foundation; Gavi, the Vaccine Alliance, U.S. CDC
- Successes: rotavirus network is a strong global network, GPDS can help vaccine investment decisions and set priorities.
- Hurdles/challenges: Sustainability and developing sense of ownership within countries.
- Surveillance data is the basis for decisions across product development

**Discussion**

- BMGF is more an active investor rather than a funder, focusing on interventions that have the greatest impact in a shortest amount of time. They de-prioritised 2 programmes at the foundation based on mortality estimates and vaccine development (namely ETEC and Cryptococcus).
- EMRO concentrates surveillance activities in four Gavi-eligible countries, since RO does not have funds to support other countries. EMRO does not have information for high income countries; middle income countries they don’t have funds to support vaccine introduction let alone surveillance. The lack of regional reference laboratories also plays a role. Pakistan and Afghanistan cannot ship outside of the country due to polio containment, Yemen cannot ship due to war, and Sudan has no courier.

**Recommendations**

- Caregivers to keep nappies for more sample to be collected.
- Need to include rural sites to increase representativeness.
- In addition to Region, consider stratifying data based on different levels like mortality rates or human development index.
- WHO Region is not a meaningful break down of regions so maybe divide countries into different ways, so you can include more countries in one region (e.g., including Pakistan in SEAR instead of EMR).
- Consider regional data dissemination workshops.
- Consider using data other than GEMS for estimating attributable fraction. This may involve enrolling controls in some sites where GEMS odds ratios are not ideal (e.g., Europe).
• Data analysis capacity building in countries to interpret their own data and advocate for more surveillance or for disease interventions.
• Integration of surveillance for sustainability: how to leverage technologies and expertise built up in labs for other diseases and programs and funding.
• Sending samples once a year rather than quarterly to avoid seasonal bias.

Session IV: New directions

Antimicrobial resistance pilot study in WPRO
Presenter: Sarah Thomas, Melbourne Child Research Institute

Early results from a pilot project on antimicrobial resistance of bacterial pathogens in paediatric diarrhoea from the Western Pacific Region was presented. Anti-microbial resistance is a worldwide problem. Due to the major threat they cause to global health, it is imperative that we understand the molecular epidemiology of anti-microbial resistance (AMR). Antibiotics with resistance genes of global concern include carbapenem (CRE), extended spectrum β-lactams (ESBL), colistin (mcr), methicillins (mecA), and vancomycin (VRE). MCRI had access to faecal samples from Phase 2 of GPDS, which will be used to look into AMR genes. This small pilot was made up of 3 Fiji samples and 28 Vietnam samples from children <5 years of age with any diarrhea. This study will better understand AMR in pediatrics and possible community acquired AMR. 89% of specimens tested were positive for an AMR gene: 79% for methicillin (mecA), 71% for β-lactams (ESBL), 29% for carbapenem (CRE), 18% for colistin (mcr), and 7% for vancomycin (VRE). It is possible to identify resistance genes in GPDS samples. Early results suggest a significant rate of isolates with resistant genes; however; not all are a high threat. The process was challenging; faecal samples were not very viable for culture. The plan is to continue this for 100 samples each from Vietnam, Fiji, and Lao.

Discussion
• The resistant genes are plasma mediated.
• Q. Are these frozen samples that you are culturing bacteria? A. Yes, and they are frozen and thawed multiple times, so we don’t know success rate of pathogen detection and range of bacteria able to culture.
• Acquisition of antibiotic resistance during hospitalization seems to happen very fast (in 24-48 hours).

Next generation TAC and etiology testing
Presenter: Eric Houpt, University of Virginia

The current and future TAC cards were discussed. TAC is simply qPCR in a convenient, reproducible and miniaturized platform. All standard operating procedures and primers and probes are available and open source. Possible TAC options for the future for GPDS include continuing TAC for now, leveraging the laboratory and data infrastructure that has been built, or using a new disc. Can we drive the cost down? The TAC 8x48 format is fixed right now, though we could explore simpler platform for top ~10 diarrhea pathogens, e.g. disc. Or we could keep the TAC card and incorporate additional testing, for instance, AMR genes for AMR surveillance.

Discussion
• It might be possible to test CSF without extracting it first. Manual extraction is a weakness and not aware of some sort of robot which could do this.
• Q. Reducing the number of pathogens tested will reduce cost. How much will cost be reduced if focus on top ten pathogens? A. The 8x48 TAC structure if fixed so in current format reducing number of pathogens does not save money.
• Q. What are your thoughts about the disc instead of the TAC card? A. The disc will need to be evaluated. This would reduce targets and the cost about half, but it can only run samples one at a time.
• Q. How would we look at AMR? Can we reduce number of pathogens and look for AMR genes? A. Yes, there are certain ones that could be targeted, and it would be useful from a baseline standpoint.
• Q. Are we going to need actual pathogens so do we need culture beside molecular testing? A. The reason the TAC card has worked so well for diarrhea is because of the large number of pathogens (not like blood where you would need large quantities) and the easy to obtain specimen.

Recommendations
• We need to start asking what diagnostics countries have and to start a formal process if we are going to reduce number of pathogens. Don’t necessarily just choose top 10 most prevalent pathogens.

GPDS contribution to global diarrheal data needs

Presenter: Duncan Steele, Bill & Melinda Gates Foundation

Three possible usages of the data generated by GPDS was presented:

1. Additional data for global burden of disease estimates
   a. IHME ongoing Global Burden of Disease analyses and forecasting
   b. WHO MCEE evidence generation
   c. Understanding diarrheal-associated morbidity
2. Evidence generation of specific disease targets
   a. WHO and Regional Office awareness / policy
   b. Country awareness of regional / sub-regional data for decision makers
   c. Vaccine impact assessment
3. Identification of clinical trial sites for Phase 2 and 3 studies
   a. Multiple enteric pathogen vaccines in development
   b. Large efficacy studies which are likely to require multi-site and multi-country sites

Discussion
• Cryptosporidium has been deprioritized at BMGF based on earlier TAC data. However, in this network in AFRO, cryptosporidium may be an important pathogen. This will be continually re-evaluated, though there are no promising interventions—either vaccine or drug treatment—at this time.

Session V: Next steps for 2019 and beyond

Discussion
• There was a desire to get EMRO re-engaged.
• Lack of controls is a huge problem. It will be difficult to make changes, and if done, there would need to be an increase in the level of funding support.

• Q. What is Gavi’s position for continued funding of rotavirus surveillance? A. Gavi provides a lot of funding for surveillance, but it increasingly gives funds directly to countries, so it is difficult for WHO to ensure that it is directed toward a particular pathogen or surveillance platform. Hard for us to be accountable. It will also be a challenge when funding for impact and vaccine effectiveness evaluations end because these are also helping to prop up the network.

• There is concern of the ownership of the data and integrating surveillance data into Ministry data.
Global Rotavirus Laboratory Meeting

Thursday 29th November

Meeting objectives

- Finalization the global rotavirus laboratory manual
- Review 2017 rotavirus EQA and QC results and logistics for 2018 EQA
- Review and discuss laboratory testing for GPDS and way forward in 2019 and beyond

Session 1: Rotavirus laboratory manual: Global summary and regional updates on rotavirus genotyping validation

AFRO RRL (Ghana)
- When using Qiagen method, there was a good concordance with the WHO common approach.

AFRO RRL (SMU, South Africa)
- From sentinel surveillance, QC and strain distribution, G2P[4] was dominant followed by G1P[8].
- Best results were obtained with the one step (new CDC protocol).

AFRO RRL (NICD, South Africa)
- 3 genotype methods tested using new CDC protocol, common and alternative approach, but concordance was poor. One reason can be that “One Step Ahead” kit from Qiagen was used.
- Two-step protocol worked well with the CDC primers except for the G3 primer that can cross-react with G8.

PAHO RRL (Fiocruz, Brazil)
- 100% concordance between their protocol and WHO common approach, confirmation done by sequencing.
- Increase of G3 since 2016. Sequencing showed some of these samples were G8, and point mutations were identified but this needs more investigation.
- During years 2017/2018, G3P[8] was dominant, NoV GII most common in 2017, but mixed GI+GII presented in 2018. However, Kajiyama primers used which is a very uncommon method.

SEAR RRL (CMC Vellore)
- 50 samples tested positive by Rotaclone and out of these 50 samples, 6 samples were tested for confirmation. Out of the 50 samples, 45 samples were 100% concordant (detected single G and P type) and 5 were untyped (VP6 PCR positive) when comparing with new CDC multiplex protocol vs. current CMC protocol.
- Alternate EUR RRL protocol results: Majority of P and G types had good concordance except for G12.
- Common WPR RRL protocol results: 100% P and G typing concordance except for G12.

RRL WPR (MCRI, Australia)
- 4 different PCR methods compared: MCRI method, common, alternative, CDC one step.
- Primer concentration varied significantly between protocols in both 1st and 2nd rounds.
- 1 step protocol picks up equine line G3, but one G3 was mistyped as G1, and G8 (nonprime) mistyped as G1 or G9.
- Common protocols mistyped eqG3s as G9.
- P typing had 49 out of 50 concordance with RRL-MCRI and CDC one-step method, but extremely poor concordance when comparing either method with common (MCRI-adapted) and alternate approaches.
- Adapting primer concentration did not improve concordance.

**Recommendations**

- WHO HQ to continue working with the small working group on revising the laboratory manual by compiling all of the final validation results and capturing all data (including different reagents used, concentrations of reagents, and PCR condition) from the RRLs. Plan to reconvene over a teleconference to finalize the new appendix that will be attached to the WHO manual.
- Consider PCR machine validation and ramp rates. Consider the possibility of combining the rotavirus manual with norovirus laboratory methods for detection and characterization.

**Session 2: External Quality Assessment (EQA) and Quality Control (QC) for Rotavirus**

- QC among RRLs: Great reduction seen in the proportion of discrepant results between labs. In 2017, there was at least 97% concordance with all RRLs on their QC while it used to be around 80% concordance in the earlier years.
- The one-step protocol does not have a G8 primer, but this is now in development; CDC is re-evaluating the G3 primer.
- QC showed very few discrepancies mostly around mixed infections, and storage conditions may be responsible for those.
- It was proposed that a rotation of labs is considered for the QC. There may be some barriers to this through need for new import permits. Regional links should be maintained to avoid regional strain/method-specific issues.
- EQA identifies persistently failing labs very efficiently, and remedial action requires a visit to the lab to identify systemic problems.
- There is difficulty in regulating the usage of expired reagents. Although it is definitely not encouraged to use expired reagents, this can be a big challenge because many countries do not receive reagents and kits on time.

**Recommendations**

Consider the possibility of penalizing laboratories that use expired kits on EQA.

- Two new ELISA kits were used (China and Korea), so it would be useful to validate new kits for future proofing by having access to diverse kit throughout the WHO Global Rotavirus Laboratory Network.
- WHO HQ to develop a template that will capture all the information on specifications of each protocol and testing conditions when samples are submitted for the QC exercise.
WHO HQ to schedule a teleconference to meet with the small working group (including all RRLs, GRL and Regional Offices) at least twice a year to hear updates and any arising issues.

CDC to mix the order of samples for China samples for 2019 EQA.

RRLs at AFR, EUR, and WPR to do an inter-lab QC. This should be extended to improve cooperation and identification of potential issues in laboratories at an early stage.

NICD to send 2018 QC results to CDC GRL and WHO HQ.

QC for detection of other pathogens (non-rotavirus): Need to make sure we are doing QC for norovirus in the next couple of years. Consider including norovirus in the RV EQA panel.

TAC QC for GPDS: TAC data analysis QC will be implemented from 2019 because the methodologies for data analysis and cleaning are critical for TAC data interpretation. Equipment validation and maintenance needs to be agreed on a common system.

Expense of TAC system make it not possible to have a QC system similar to the rotavirus one.

**Session 3: General overview and discussion of GPDS implementation at RRL**

**Laboratory and data management**

- Each RRL needs to make sure that the samples tested can be linked back to the epi/surveillance data. Need to report all the results (including original lab specimen number and the unique case ID needed to link back to epi data).
- Unique case IDs must always be assigned by the sentinel site so the sample can be traced back to the clinical information!

**Shipment**

- Couriers are region specific.
- Temperature tracking would be advisable to ensure samples arrive in optimal condition; this is available from most of the couriers.
- Marken is a good shipment courier because it specializes only on biological specimens. Should be able to delivery globally.
- Improved communication between RRL, RO and sentinel sites to minimise shipping delays.

**Randomization**

- Two potential randomization processes can be done to ensure samples with appropriate volume are sent and analyzed by TAC:
  - Select 30 samples, send list to site, site sends these 30 samples to RRL, RRL tests first 25 adequate samples.
  - Assign a random number (unique) to all cases in surveillance, sort dataset by that number, ask site to go through that list in that order, send first 30 samples with enough specimen to RRL, RRL tests first 25 adequate samples. This second method is preferable to ensure 25 samples are tested per quarter.
**Testing**

- RRLs: TAC runs should be analysed immediately after run for blanks and internal control, and the contamination kit should be used. Full results analyses can be batched, but these controls need to be done before moving onto next card.
- There is a suitable automated extraction protocol using the QIAcube that has been validated, and can be shared, but no changes to current protocol are needed. No problem with cross-contamination happening with QIAcube. RRLs that have the extraction robot can use it using the validated protocol.
- Testing timeline: No cost extension already agreed.

**QA/QC**

- QA at the RRL level can be done through a wipe test, blank and IC.
- Data from RRLs are centralized and cleaned at UVA through a 2-stage process during data cleaning:
- Pathogen detection EQA: proposed similar to rotavirus EQA with a panel of 7 samples encompassing the most common pathogens, allowing for 1 blank for a full plate. **This idea will be for 2019 and onwards.**
- TAC analysis EQA: run files selected centrally; 3 raw files suggested to be shared and tested at each RRL once a year. Results will be assessed qualitative and quantitatively. **This can immediately start as it does not require funding.** Darwin needs a selection of 3-4 files from each RRL for year 1 to analyse (by December 31st so that the EQA can be established in 2019 (before end of Feb). Turnaround time should be approximately 1 month.
- QA at RRL level **in the future**: exchanging files between RRLs and score for concordance; this can be done for samples as well as for data files. Not a priority currently.
- Maintenance of TAC machine: 2-year warrantee

**Norovirus**

Global Pediatric Norovirus Surv Network, NoroSurv

- Countries can register with CDC-supported International Reagents Resource (IRR)) and get all the reagents needed for detection and sequencing of norovirus.
- Current web portal is owned by CDC, but with Amazon temporarily (not US government), for type and also sequence data collection that will have capacity to show country specific data interactively; data can be accessed aggregated as well as by country.

**Recommendations**

- Each RRL to check and register with IRR and check how easy is to get the reagents shipped.
- Check which countries can and want to share norovirus genotype data (identify country specific restriction for data sharing).
- Norovirus is detected as part of GPDS: If countries would like to take part in norovirus surveillance, they need to be informed about the objective of the surveillance and what additional steps are required to genogroup norovirus. Only DNA is required to type norovirus but will need to select samples that were sufficiently tested positive for norovirus when tested with TAC.
Diagnostic tool for surveillance and vaccine evaluation for ETEC and Shigella

- Current Diagnostics of ETEC and Shigella are all very time consuming and expensive and dependent on trained personnel specific equipment
  - Culture followed by colony PCR
  - ELISA
  - Quantitative PCR (Highly sensitive but expensive and instrument dependent)
- Option 1: Using qPCR
  - There is variability in the ETEC and Shigella attributed cases depending on where the cases were being collected within the same country.
- Option 2: Simple, rapid and sensitivity assay used, without a central lab facility.
  - Rapid process because you can isolate colonies from positive samples for downstream characterizations.
  - ETEC and Shigella can be detected directly from stool specimens.
  - No cold chain required.
  - Lowest detection limit: $10^5$ CFU/gram of stool. This limit of detection is the same for TAC array.
  - Heat block needed (heating 5 minutes required).
  - $7000$ for the machine as the reader is needed.
  - Inexpensive strips for the rapid test ($4/strip$).
  - Possibility to detect co-infections of both ETEC and Shigella.
  - Very high concordance when compared with qPCR results. Higher sensitivity compared to culture and may likely be compared to qPCR.

Polio containment in the rotavirus surveillance network

- Responsibility for compliance to polio containment is the country’s (which means it’s the facility and the national authorities’ responsibility).
- Nucleic acids may be extracted from polio virus (PV) potentially infectious materials (PIMs) or the materials may be inactivated using an appropriate method, but these need to be contained appropriately.
- Facilities with wild type PV or vaccine derived PV PIMs that do not plan to become a PEF lab must destroy, inactivate or transfer the materials to a PEF.
- Risk level of the stool specimens is low based on the risk mitigation strategies that need to be followed for polio containment.
- Based on a CDC experiment that was done, inactivation at $70^\circ C$ for 3 hours can kill PV1 and PV3 in stool samples but resulted in significant reduction in the sensitivity of rotvirus genotyping. The challenge now is how to standardize the number of hours required to inactivate PV1 and PV3 in stool.

Recommendations

- Alternate methods that are proposed
  - Suspension of stool samples in chaotropic agents (e.g., lysis buffers).
  - Presence of such lysis buffers in ratio higher than 1 in 100 will kill cell cultures automatically. (Although ratio of stool to lysis buffer needs to be established. Researched by Jan Vinje at U.S. CDC using poliovirus).
- Advantage of this is that we can avoid the need to extract nucleic acid from large sample collections, and it’s time saving and involves minimal manipulation.
- Need to make sure that we can appropriately demonstrate that these samples do not contain PV or Sabin strains.
- Establish a repository of PV free certified virus stocks that is accessible to the labs that require the use of live rotavirus OR labs can have the rotavirus stocks tested and certified by national or regional laboratories.
- Need to remember how to regulate the sentinel site laboratories because these are the laboratories that need guidance and supervision of RRL.
- CAG meeting to take place in December 2018, so a short proposal will be compiled and written together by Miren Iturriza-Gomara (rotavirus) and David Brown (measles) so the technical counterparts can review a potential guidance that’s targeted for handling rotavirus/norovirus/measles specimens.

No notes for the Data Management meeting. In addition, the Global Pediatric Diarrhea Disease Burden meeting report will be published separately.
GLOBAL ROTAVIRUS AND PAEDIATRIC DIARRHEA SURVEILLANCE, INVASIVE BACTERIAL DISEASES, LABORATORY, AND DISEASE BURDEN MEETINGS
26-30 NOVEMBER 2018
SOUTHERN SUN THE CULLINAN HOTEL, CAPE TOWN, SOUTH AFRICA

Objectives of Global Rotavirus and Pediatric Diarrhea Surveillance Meeting
1. Review the current status, protocol, and preliminary results of Global Rotavirus Surveillance Network and Global Pediatric Diarrhea Surveillance
2. Discuss priorities and future opportunities for global diarrheal disease surveillance

Participants: WHO HQ and RO epidemiology, laboratory and data surveillance focal points, rotavirus Regional Reference Laboratories, external technical experts

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9h00-9h15</td>
<td>Introduction, welcome and objectives of the meeting</td>
<td>Umesh Parashar (chair)</td>
</tr>
<tr>
<td>9h15-9h45</td>
<td>Global overview: GRSN and GPDS status, activities, and protocol</td>
<td>Fatima Serhan</td>
</tr>
<tr>
<td>9h45-10h15</td>
<td>Analytic methodology for GPDS</td>
<td>James Platts-Mills</td>
</tr>
<tr>
<td>10h15-10h45</td>
<td>GRSN and GPDS preliminary results</td>
<td>Adam Cohen</td>
</tr>
<tr>
<td>10h45-11h00</td>
<td>Coffee/tea break</td>
<td>All participants</td>
</tr>
<tr>
<td>11h00-11h30</td>
<td>Discussion of morning presentations</td>
<td>Umesh Parashar &amp; speakers</td>
</tr>
<tr>
<td>11h30-12h30</td>
<td>Regional Highlights</td>
<td>Jason Mwenda</td>
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<td></td>
<td>o AFRO</td>
<td>Danni Daniels</td>
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<td>o EURO</td>
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<tr>
<td>12h30-13h30</td>
<td>Lunch break</td>
<td>All participants</td>
</tr>
<tr>
<td>13h30-15h30</td>
<td>Deep-dive into GPDS implementation steps</td>
<td>Adam Cohen</td>
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<tr>
<td></td>
<td>o Introduction to small group work (10 minutes)</td>
<td>All participants</td>
</tr>
<tr>
<td></td>
<td>o Small group work (40 minutes)</td>
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<tr>
<td></td>
<td>▪ Sites: Enrollment of cases</td>
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<tr>
<td></td>
<td>▪ Lab: Shipment of samples, testing at RRLs, data upload, cleaning and linking to surveillance data</td>
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<td></td>
<td>▪ Data: Analysis and dissemination</td>
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<td></td>
<td>▪ Countries/stakeholders: How GPDS data can be used and sustainability</td>
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<tr>
<td></td>
<td>o Feedback from each small group (10 minutes each group)</td>
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<td></td>
<td>o Full group discussion (40 minutes)</td>
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<tr>
<td>15h30-16h00</td>
<td>Coffee/Tea break (continuation of GPDS discussion)</td>
<td>All participants</td>
</tr>
<tr>
<td>16h00-17h00</td>
<td>New directions</td>
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<tr>
<td></td>
<td>o Antimicrobial resistance pilot study in WPRO</td>
<td>Sarah Thomas</td>
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<tr>
<td></td>
<td>o Next generation TAC and etiology testing</td>
<td>Eric Houpt</td>
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<tr>
<td></td>
<td>o GPDS contribution to global diarrheal data needs</td>
<td>Duncan Steele</td>
</tr>
<tr>
<td>Time</td>
<td>Event</td>
<td>Organizer</td>
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<tr>
<td>17h00-18h00</td>
<td>Discussion: Next steps for 2019 and beyond</td>
<td>Umesh Parashar</td>
</tr>
<tr>
<td>18h00-20h00</td>
<td>Reception</td>
<td>All participants</td>
</tr>
</tbody>
</table>
**Objectives of Global Rotavirus Laboratory Meeting**
- Finalization the global rotavirus laboratory manual
- Review 2017 rotavirus EQA and QC results and logistics for 2018 EQA
- Review and discuss laboratory testing for GPDS and way forward in 2019 and beyond

**Participants:** WHO laboratory surveillance focal points, Rotavirus RRLs and GRLs, external technical experts

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<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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</thead>
<tbody>
<tr>
<td>9h00-9h15</td>
<td><strong>Objectives of the day</strong></td>
</tr>
<tr>
<td>9h15-10h30</td>
<td>Rotavirus lab manual: Global summary and regional updates on rotavirus genotyping validation (5-10 min each)</td>
</tr>
<tr>
<td>9h15-10h30</td>
<td>Ghana RRL (AFR)</td>
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<tr>
<td>9h15-10h30</td>
<td>South Africa RRL (AFR)</td>
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<tr>
<td>9h15-10h30</td>
<td>South Africa (NICD)</td>
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<tr>
<td>9h15-10h30</td>
<td>Brazil RRL (AMR)</td>
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<tr>
<td>9h15-10h30</td>
<td>India RRL (SEAR)</td>
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<tr>
<td>9h15-10h30</td>
<td>Australia (WPR)</td>
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<tr>
<td>10h30-11h00</td>
<td>Coffee/tea break</td>
</tr>
<tr>
<td>11h00-12h30</td>
<td>Group Discussion on way forward for lab manual</td>
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<tr>
<td>11h00-12h30</td>
<td>Quality assurance</td>
</tr>
<tr>
<td>11h00-12h30</td>
<td>Overview of rotavirus EQA results from 2017 and the way forward</td>
</tr>
<tr>
<td>11h00-12h30</td>
<td>EQC (between the different RRLs)</td>
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<tr>
<td>12h30-13h30</td>
<td>Lunch break</td>
</tr>
<tr>
<td>13h30-15h00</td>
<td>General overview and discussion of GPDS implementation at RRLs</td>
</tr>
<tr>
<td>13h30-15h00</td>
<td>Laboratory data cleaning and uploading to MuSIC</td>
</tr>
<tr>
<td>13h30-15h00</td>
<td>Troubleshooting and discussion on any issues with TAC</td>
</tr>
<tr>
<td>13h30-15h00</td>
<td>Review of testing from 2017-18 and timeline for 2019 testing</td>
</tr>
<tr>
<td>13h30-15h00</td>
<td>Review of TAC array lab SOPs, reagents and expiration date</td>
</tr>
<tr>
<td>13h30-15h00</td>
<td>Discussion on norovirus genotyping procedure and logistics</td>
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<tr>
<td>Time</td>
<td>Session</td>
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<tr>
<td>15h00-15h30</td>
<td>Coffee/tea break</td>
</tr>
<tr>
<td>15h30-16h00</td>
<td>Polio containment in Rotavirus and Pediatric Diarrhea Surveillance Network</td>
</tr>
<tr>
<td>16h00-17h00</td>
<td>Wrap-up discussions, timelines and conclusions</td>
</tr>
</tbody>
</table>

- RDT: ETEC Shigella: Subhra Chakraborty
Objectives of the meeting

- To discuss global pediatric diarrhea surveillance data management activities including issues, bottlenecks and ways to improve processes
- To develop high level outline for VPD Surveillance Data Management Pamphlet
- To present existing and future Information Systems for sentinel surveillance (e.g. VINUVA casos)

Participants: WHO HQ and RO data managers for rotavirus, pediatric diarrhea, and IB-VPD surveillance, RRL data managers

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>8h30 – 8h45</td>
<td>Welcome and introduction</td>
<td>Sébastien Antoni</td>
</tr>
<tr>
<td>8h45 – 10h00</td>
<td>GPDS data management activities including issues and way forward (Follow up from Wednesday’s session)</td>
<td>All participants</td>
</tr>
<tr>
<td>10h00 – 10h30</td>
<td>Coffee/tea Break</td>
<td></td>
</tr>
<tr>
<td>10h30 – 11h00</td>
<td>VINUVA casos</td>
<td>Claudia Ortiz</td>
</tr>
<tr>
<td>11h00 – 12h30</td>
<td>VPD Surveillance Data Management Pamphlet</td>
<td>All participants</td>
</tr>
<tr>
<td>12h30 – 13h30</td>
<td>Lunch</td>
<td></td>
</tr>
<tr>
<td>13h30 – 14h30</td>
<td>Data Managers to join the Lab meeting</td>
<td>All participants</td>
</tr>
</tbody>
</table>
Global Rotavirus and Pediatric Diarrhea Surveillance, Laboratory, Data and Disease Burden Meetings
26-30 November 2018
Southern Sun Cullinan Hotel, Cape Town, South Africa

LIST OF PARTICIPANTS

Irene T. Araujo Maciel
Oswaldo Cruz Foundation
Ministry of Health
Rio de Janeiro
Brazil
Email: iretrig@gmail.com

Joseph Armachie
Department of Electron Microscope & Histopathology
Noguchi Memorial Institute for Medical Research
University of Ghana
Accra
Ghana
Email: armachiejoseph@gmail.com

George Armah
Department of Electron Microscope & Histopathology
Noguchi Memorial Institute for Medical Research
University of Ghana
Accra
Ghana
Email: GArmah@noguchi.ug.edu.gh

Robert Black
Institute for International Programs
Johns Hopkins Bloomberg School of Public Health
Baltimore
United States of America
Email: rblack1@jhu.edu

Michael Bowen
Division of Viral Diseases
Centers for Disease Control and Prevention
Atlanta
United States of America
Email: mkb6@cdc.gov

Robert Breiman
Emory Global Health Institute
Emory University
Atlanta
United States of America
Email: rfbreiman@emory.edu

Subhra Chakraborty
Global Disease Epidemiology and Control
Johns Hopkins Bloomberg School of Public Health
Baltimore
United States of America
Email: schakr11@jhu.edu

Andrew Clark
Health Decision Modelling
London School of Hygiene and Tropical Medicine
London
United Kingdom
Email: Andrew.Clark@lshtm.ac.uk
Francis Dennis  
Department of Electron Microscopy & Histopathology  
Noguchi Memorial Institute for Medical Research  
University of Ghana  
Accra  
Ghana  
Email: FDennis@noguchi.ug.edu.gh

Mathew Esona  
Division of Viral Diseases  
Centers for Disease Control and Prevention  
Atlanta  
United States of America  
Email: mdi4@cdc.gov

Sidhartha Giri  
Department of Gastrointestinal Sciences  
Wellcome Trust Research Laboratory  
Christian Medical College  
Vellore  
India  
Email: sidharthgiri@cmcvellore.ac.in

Eric Houpt  
University of Virginia Health System  
Division of Infectious Diseases and International Health  
Charlottesville, VA  
United States of America  
Email: ERH6K@hscmail.mcc.virginia.edu

Miren Iturriza-Gomara  
Institute of Infection and Global Health  
Department of Clinical Infection, Microbiology and Immunology  
University of Liverpool  
Liverpool  
United Kingdom  
Email: miren@liverpool.ac.uk

Mark Jit  
Modelling and Economics Unit  
Public Health England  
Colindale  
United Kingdom  
Email: Mark.Jit@lshtm.ac.uk

Gagandeep Kang  
The Wellcome Trust Research Laboratory  
Division of Gastrointestinal Sciences  
Christian Medical College  
Vellore  
India  
Email: gk@gmcvellore.ac.in

Carl Kirkwood  
Enteric and Diarrhoeal Diseases, Global Health  
Bill & Melinda Gates Foundation  
Seattle WA  
United States of America  
Email: Carl.Kirkwood@gatesfoundation.org

Laura Lambert  
Enteric and Diarrhoeal Diseases, Global Health  
Bill & Melinda Gates Foundation  
Seattle WA  
United States of America  
Email: laura.lambert@gatesfoundation.org

Claudio Lanata  
Instituto de Instigación nutricional  
Lima  
Peru  
Email: clanata@iin.sld.pe

Deog-Yong Lee  
Division of Enteric Diseases  
Center for Infectious Disease  
National Institute of Health, CDC Korea  
Seoul  
Republic of Korea  
Email: leedy0610@korea.kr

Benjamin Lopman  
Emory University
Atlanta
United States of America
Email: benjamin.alan.lopman@emory.edu

Calman MacLennan
Enteric and Diarrhoeal Diseases, Global Health
Bill & Melinda Gates Foundation
Seattle WA
United States of America
Email: Calman.MacLennan@gatesfoundation.org

Magagula Nonkululeko
Sefako Makgatho Health Sciences
University of SMU
South Africa
Email: nonkululeko.magagula@smu.ac.za

Inacio Mandomando
Manhica Research Centre (CISM)
Maputo
Mozambique
Email: inacio.mandomando@gmail.com

Khutso Mothapo
Sefako Makgatho Health Sciences
University of SMU
South Africa
Email: kmothapo@gmail.com

Farzana Muhib
PATH
Washington DC
United States of America
Email: fmuhib@path.org

Liu Na (Unable to attend)
Department of Viral Diarrhea
Institute for Viral Disease Control and Prevention
Centers for Disease Control and Prevention
China
Email: unali@163.com

Wilfred Ndifon
AIMS Global Network
African Institute for Mathematical Sciences (AIMS)
Kigali
Rwanda
Email: wndifon@aims.ac.za

Darwin Operario
University of Virginia Health System
Division of Infectious Diseases and International Health
Charlottesville
United States of America
Email: do2s@virginia.edu

Nicola Anne Page Mounsear-Wilson
Centre for Viral Enteric Diseases Research
National Institute for Communicable Diseases
Johannesburg
South Africa
Email: nicolap@nicd.ac.za

Umesh Parashar
Division of Viral Diseases
Centers for Disease Control and Prevention
Atlanta
United States of America
Email: uap2@cdc.gov

Virginia Pitzer
Yale School of Public Health
New Haven
United States of America
Email: virginia.pitzer@yale.edu

James Platts-Mills
University of Virginia Health System
Division of Infectious Diseases and International Health
Charlottesville
United States of America
Email: JP5T@hscmail.mcc.virginia.edu
Chad Porter
Walter Reed Army Institute of Research
Silver Spring
United States of America
Email: chad.k.porter2.civ@mail.mil

Bobby Reiner
Institute for Health Metrics and Evaluation
Seattle
United States of America
Email: bcreiner@uw.edu

Mark Riddle
Walter Reed Army Institute of Research
Silver Spring
United States of America
Email: mark.riddle@usuhs.edu

Mapaseka Seheri
WHO Rotavirus Regional Reference Laboratory
Memorial Institute for Medical Research
Pretoria
South Africa
Email: mapaseka.seheri@smu.ac.za

Galina Semeiko
Laboratory of Vaccine-preventable diseases
Republican Research and Practical Center for Epidemiology and Microbiology
Minsk
Belarus
Email: g-semeiko@yandex.by

Peter Smith
London School of Hygiene and Tropical Medicine
London
United Kingdom
Email: Peter.Smith@lshtm.ac.uk

Duncan Steele
Enteric and Diarrhoeal Diseases, Global Health
Bill & Melinda Gates Foundation
Seattle WA

United States of America
Email: Duncan.Steele@gatesfoundation.org

Jacqueline Tate
Division of Viral Diseases
Centers for Disease Control and Prevention
Atlanta
United States of America
Email: jqt8@cdc.gov

Sarah Thomas
Murdoch Children’s Research Institute,
The Royal Children’s Hospital
Melbourne
Australia
Email: sarah.thomas@mcri.edu.au

Kirkby Tickell
Global Center for Integrated Health of Women, Adolescents, & Children
Department of Global Health, University of Washington
Seattle
United States of America
Email: kirkbt@uw.edu

Chris Troeger
Institute for Health Metrics and Evaluation
Seattle
United States of America
Email: ctroeger@uw.edu

Jan Vinje
Centers for Disease Control and Prevention
Atlanta
United States of America
Email: ahx8@cdc.gov

Jenny A. Walldorf
Global Immunization Division
Centers for Disease Control and Prevention
Atlanta
United States of America
Email: igf4@cdc.gov
IB-VPD Participants (26-27 November 2018)

Martin Antonio
Medical Research Council (MRC)
Banjul
The Gambia
Email: mantonio@mrc.gm

Linda de Gouveia
National Institute for Communicable Diseases (NICD)
University of the Witwatersrand
Johannesburg
South Africa
Email: lindad@nicd.ac.za

Mignon Du Plessis
National Institute for Communicable Diseases (NICD)
University of the Witwatersrand
Johannesburg
South Africa
Email: mignonnd@nicd.ac.za

Brenda Anna Kwambana
Medical Research Council (MRC)
Corby
United Kingdom
Email: rekgbak@ucl.ac.uk

Anne von Gottberg
National Institute for Communicable Diseases (NICD)
University of the Witwatersrand
Johannesburg
South Africa
E-mail: annev@nicd.ac.za

Joseph Biey
WHO Regional Office for Africa
Ouagadougou
Burkina Faso
Email: bieyj@who.int

Reggis Katsande
WHO Regional Office for Africa
Barazzaville
Republic of the Congo
Email: katsander@who.int

Jason Mwenda
WHO Regional Office for Africa
Brazzaville
Republic of the Congo
E-mail: mwendaj@who.int

Goitom G. Weldegebriel
WHO Regional Office for Africa
Harare
Zimbabwe
Email: weldegebrielg@who.int

Maria Teresa Da Costa
WHO Regional Office for the Americas
Washington DC
United States of America
Email: dacostmar@paho.org

Lucia Elena de Oliveira
WHO Regional Office for the Americas
Washington DC
United States of America
Email: oliveirl@who.int

Claudia Ortiz
WHO Regional Office for the Americas
Washington DC
United States of America
Email: ortizcla@paho.org

Gloria Rey
WHO Regional Office for the Americas
Washington DC
United States of America
Email: reyglori@paho.org

Danni Daniels
WHO Regional Office for Europe
Copenhagen
Denmark
Email: danielsd@who.int

Hossam Ashmony
WHO Regional Office for the Eastern Mediterranean
Cairo
Egypt
Email: ashmonyh@who.int

Kamal Fahmy
WHO Regional Office for the Eastern Mediterranean
Cairo
Egypt
Email: fahmyk@who.int

Nyambat Batmunkh
WHO Regional Office for the Western Pacific
Manila
Philippines
Email: batmunkhn@who.int

Varja Grabovac
WHO Regional Office for the Western Pacific
Manila
Philippines
Email: grabovacv@who.int

Josephine Logronio
WHO Regional Office for the Western Pacific
Manila,
Philippines
Email: logronioj@who.int

WHO Headquarters staff, Geneva, Switzerland
Sébastien Antoni
Email: antonis@who.int

Adam Cohen
Email: cohena@who.int

Birgitte Giersing
Email: giersingb@who.int

Mateusz Hasso-Agopsowicz
Email: hassoagopsowiczm@who.int

Raymond Hutubessy
Email: hutubessyr@who.int

Tomoka Nakamura
Email: nakamurat@who.int

Holly Prudden
Email: hollyprudden@hotmail.com

Fatima Serhan
Email: serhanfa@who.int

Ajantha Ranajeewa
Email: ranajeewaa@who.int