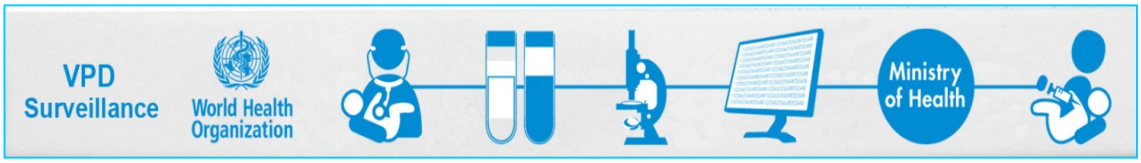

Strategic review of the global WHO-coordinated invasive bacterial vaccine preventable diseases and rotavirus sentinel hospital surveillance networks, 2013

Note:

SAGE members have received two documents in the Yellow Book that summarize the strategic review process, including the main findings and conclusions.

This draft document is provided should SAGE members require additional information on the strategic review.

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PREFACE

Since 2008, the World Health Organization (WHO) has coordinated two global surveillance networks for invasive bacterial-vaccine preventable diseases (IB-VPD) and rotavirus disease (RV). The past five years have been dedicated to generating high-quality data to provide countries and regions with quality data to help answer disease burden and vaccine impact questions and assist with the planning of public health programmes. Given the finalization of the 2011-2020 Global Vaccine Action Plan and the continued acceleration of new vaccine introductions, including pneumococcal conjugate and rotavirus vaccines, WHO and global partners undertook a strategic review of the global IB-VPD and RV surveillance networks to identify strengths and weaknesses and decide on strategies and actions to ensure that the networks are responsive to the information needs of all immunization stakeholders.

The first section of this report of the strategic review provides background on the IB-VPD and RV surveillance networks and the objectives and processes of the strategic surveillance networks review. Subsequent sections describe the methods and main findings from the following eight components of the review:

1. IB-VPD surveillance network data analyses
2. RV surveillance network data analyses
3. IB-VPD and RV laboratory networks review
4. Data landscape analysis
5. Use of surveillance data
6. Ministry of Health perspectives
7. WHO roles and responsibilities
8. Surveillance networks funding

The final section will summarize the conclusions and recommendations discussed by the Informal Technical Advisory Group (iTAG) members and WHO Headquarters and Regional Offices.

ACKNOWLEDGEMENTS

The IB-VPD and RV networks depend on the dedication and efforts of staff at sentinel hospital surveillance sites and laboratories, National Laboratories, Regional Reference Laboratories, Global Reference Laboratories, and all levels of WHO. The strategic review was successfully conducted due to these personnel who, in addition to normal duties, also provided information and feedback as requested for the review. The members of the WHO informal Technical Advisory Group for New Vaccines Surveillance generously gave their expertise ad time to help guide the strategic review. WHO's global partners similarly devoted substantial time and efforts to assist with the review process.

ABBREVIATIONS

ADIP	Accelerated Development and Introduction Plans
AFR	African Region of the World Health Organization
AMR	Americas Region of the World Health Organization
AMS	antimicrobial susceptibility
CRF	case report form
ELISA	enzyme-linked immunosorbent assay
EMR	Eastern Mediterranean Region of the World Health Organization
EQA	external quality assessment
EUR	European Region of the World Health Organization
GRL	Global Reference Laboratory
Hib	*Haemophilus influenzae* type b
IB-VPD	invasive bacterial-vaccine preventable diseases
iTAG	informal Technical Advisory Group
MoH	Ministry of Health
NL	National Laboratory
NUVI	New and Underutilized Vaccines Implementation
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
QA	quality assurance
QC	quality control
RRL	Regional Reference Laboratory
RV	rotavirus
RO	Regional Office
SEAR	South-East Asian Region of the World Health Organization
SOP	standard operating procedures
TWG	Technical Working Group
VPD	vaccine preventable disease
WHO	World Health Organization
WHO HQ	World Health Organization Headquarters
WPR	Western Pacific Region of the World Health Organization

EXECUTIVE SUMMARY

Genesis of the strategic review

Since 2008, WHO has been coordinating global sentinel hospital surveillance networks for invasive bacterial vaccine preventable diseases (IB-VPD) and rotavirus (RV) to provide quality data to assist with planning of public health programs around vaccine introduction and use. The objectives set for the network in 2008 were:

- During the pre-vaccine introduction period:
  - Document presence of disease, describe the disease epidemiology and provide data for estimating disease burden;
  - Establish a system to measure impact after vaccine introduction;
  - Identify circulating serotypes and measure serotype distribution; and
  - Monitor antibiotic sensitivity.
- During the post-vaccine introduction period also:
  - Assess disease trends over time;
  - Monitor vaccination program impact;
  - Monitor changes in circulating strains/serotypes; and
  - Develop a platform for effectiveness and safety evaluation.

The longer term vision has been to establish sentinel surveillance for selected vaccine preventable disease (VPD) in low- and middle-income countries to complement existing active surveillance for polio, measles/rubella and passive surveillance and reporting for other VPDs.

In February 2013, following 5 years of network coordination, WHO launched a full strategic review of both networks with its informal Technical Advisory Group for new vaccines surveillance (iTAG) to identify the networks' strengths and weaknesses and to prioritize future actions. The iTAG assessed the networks capacities to document vaccine impact via the accelerating introductions of pneumococcal conjugate and rotavirus vaccines in the light of the call for quality case-based surveillance in the 2011-2020 Global Vaccine Action Plan. Recognizing the resource constraints in the targeted countries and competing health priorities, it was deemed imperative to determine best strategies to target human and financial resources.

At the review's outset, the iTAG and WHO recognized that while great strides had been made in the development of both IB-VPD and RV global surveillance networks, improvements were still required to ensure strong and effective networks that meet the ultimate goal of providing reliable data. IB-VPD surveillance was particularly recognized to be more complex than RV surveillance due to lack of adequate methods for laboratory confirmation of pneumococcal pneumonia, the rarity of meningitis as compared with diarrhoea, the difficulties of specimen collection and transport, and the complex bacterial laboratory diagnostic testing required.

Prior to this review, in November 2012, WHO had established the following criteria for IB-VPD surveillance, in order to prioritize sites for support:

- Presence of a country surveillance management team, consisting of focal points at Ministry of Health (MoH), sentinel hospital, sentinel hospital laboratory, and for data management;
- Countries conducting only Tier 1 meningitis surveillance enrol at least 100 suspect meningitis cases[1] in children <5 years of age[2];
- Data is reported regularly to WHO according to the schedule agreed with the WHO Regional Office; and
- The hospital sentinel sites participate in the WHO IB-VPD laboratory external quality assessment programme.

[1] Any child aged 0-59 months admitted to a sentinel hospital conducting surveillance with sudden onset of fever (> 38.5 °C rectal or 38.0 °C axillary) and one of the following signs: neck stiffness, altered consciousness with no other alternative diagnosis, or other meningeal sign OR very patient aged under 5 years of age hospitalized with a clinical diagnosis of meningitis.

[2] Countries that do not enroll 100 suspect meningitis cases during 2013 but that significantly increased the number of enrolled cases over 2012 will be considered for funding on a case-by-case basis.

Objectives and methodology of the 2013 strategic review

The strategic review was conducted under the oversight of the iTAG that has been advising WHO on the conduct of sentinel surveillance since July 2011. The iTAG and WHO agreed on the following objectives for the strategic review:

1. Assess whether and to what extent the original 2008 objectives for the networks were met.
2. Critically assess the Ministry of Health (MoH) perspective, laboratory networks, and WHO activities for capacity building, funding, and data management and the use of data; and
3. Provide conclusions and recommendations for strengthening the networks including defining any needed complementary approaches for IB-VPD surveillance, and critically assess the networks' future utility as a platform for other vaccine preventable disease (VPD) surveillance.

The strategic review consisted of several methods including analysis of surveillance data; questionnaires to obtain MoH perspectives; external review of laboratory function; external review of data management; review of the literature and GAVI applications to evaluate whether WHO surveillance data has been used in decision making; internal review of WHO activities and funding disbursement.

Analysis of surveillance data was conducted on all data available to WHO, including IB-VPD case-based data collected by 4 Regional Offices (ROs) and data aggregated by sentinel site in 2 ROs. For RV, data for analysis was aggregated by sentinel site. Data from over 90 databases were consolidated and cleaned. IB-VPD variables were mapped across Regions, and the first uniform IB-VPD data analysis performed. Due to the volume of data and paucity of time, the iTAG and WHO agreed that sites would be categorized and analysis focused on sites that met defined performance characteristics to determine whether they achieved the original 2008 objectives.

For IB-VPD, sites that reported data during 2010 to 2012 were categorized as:

- New sites: site began reporting in 2011 or 2012
- A Sites: met both of the following criteria
    - Reported data in ≥11 months per year for at least two years during 2010-2012.
    - Enrolled ≥100 suspected meningitis cases per year for at least two years during 2010-2012 (tier 1) or enrolled ≥500 suspected meningitis/pneumonia/sepsis cases per year for at least two years during 2010-2012 (tier 2).
- B Sites: met both of the following criteria
    - Reported data in ≥10 months per year for at least two years during 2010-2012.
    - Enrolled a total of ≥100 suspected meningitis during 2010-2012 (tier 1) or enrolled ≥500 suspected meningitis/pneumonia/sepsis cases during 2010-2012 (tier 2).
- C Sites: Sites that improved in consistency of reporting and case enrolment between 2011 and 2012 but did not meet the criteria of A or B sites.
- D Sites: All other sites.

For RV, analysis focused on sites that reported $\geq$ 10 months of data during 2011 and 2012 as well as enrolled $\geq$ 100 cases during those years.

The iTAG and WHO collaborated closely during the strategic review via monthly conference calls to agree on the scope of the review and data analysis plan, as well as to assess progress made, and review data that had been collated. Additional ad hoc technical discussions focused on IB-VPD or RV specific issues and data. The results of all methods were reviewed at a 5 day meeting beginning the week of the 16th of September 2013, which brought together the iTAG, WHO and its partners to formulate agreed conclusions and recommendations.

Key findings of the 2013 strategic review of the IB-VPD and RV surveillance networks

1. IB-VPD surveillance findings

In 2008, the IB-VPD network comprised 36 reporting countries (69% GAVI-eligible) with 91 sites (60% in GAVI countries) that enrolled 16,124 children with meningitis and 20,098 children pneumonia /sepsis. In 2012 the network comprised 58 reporting countries (79% GAVI-eligible) with 150 sites (70% in GAVI countries) that enrolled 20,098 children with meningitis and 35,480 children with pneumonia and sepsis. Sites[1] that received financial support (e.g. sites in GAVI-eligible countries), in general, performed better. Excluding the 37 new sites, 48 (52%) of the 93 GAVI sites conducting meningitis surveillance were categorized as A, B, or C sites while only 10 (20%) of the 51 non-GAVI sites were (Table). Among the 34 category A sites conducting meningitis surveillance, 32 (94%) were located in GAVI-eligible countries.

Table: Invasive bacterial vaccine preventable disease surveillance sites conducting meningitis surveillance by category based on data reported to WHO, 2010 to 2012.

Sites Conducting Meningitis Surveillance	Category of Site				
	A	B	C	D	Total
	# (%)	# (%)	# (%)	# (%)	# (%)
GAVI sites	32 (94)	14 (64)	2 (100)	45 (52)	93 (65)
Non-GAVI sites	2 (6)	8 (36)	0	41 (48)	51 (35)
Total	34 (100)	22 (100)	2 (100)	86 (100)	144 (100)

*The 37 new meningitis sites are excluded; 28 of these sites are in GAVI-eligible countries.

The strategic review team agreed that the current IB-VPD network had met the original 2008 objectives for documenting presence of disease (e.g. 61 of 65 countries that reported data during 2008 to 2012 documented presence of pneumococcus), using surveillance as a platform to conduct special studies (e.g. Brazil and Mongolia), and using data to inform vaccine introduction decisions. Capacity for conducting surveillance had been built, not only for meningitis but for other VPDs (such as typhoid detection). Some countries had 2 years baseline data of pneumococcal isolates and 1 year post-PCV introduction data. However, the laboratory network assessment (see Annex) suggested that countries, regions and HQ were not working together as a network. The data generated was not being used in the most efficient and effective manner (see Annex). Because of the need for high-quality data and resource constraints, it was concluded that the investment of financial and technical support should be focused upon a smaller number of sites.

2. RV surveillance findings

During 2008-2012, 265 sites in 67 countries reported any data to WHO. Among sites that reported data during 2011-2012, 79 sites (80% GAVI-eligible) in 37 countries (86% GAVI-eligible) met the inclusion criteria. Thirteen of the 37 countries had introduced RV vaccine nationally, and 1 country introduced sub-nationally. Most sites included in the analysis met the targets for the 6 established surveillance performance indicators. Among these sites, the mean RV detection of the 75,353 tested children was 36%, with the largest percentage positive (42%) in the 6-11 month age group. Sixty-five deaths among RV positive cases were reported, with the case fatality ratio ranging from 0% to 5.9% of cases by site. RV seasonality differed by region and by AFR sub-region, with seasonal peaks seen more obviously in AMR, EUR, WPR and the AFR south sub-

[1] Year-to-year variability in the number of reporting countries and sites exists due to reasons including in-country conflict, and political change.

Region. Guatemala had sites that met the inclusion criteria and had at least 2 years pre- and two years-post RV vaccine introduction data. In Guatemala, the proportion (mean) of children hospitalized with diarrhoea with RV dropped from 42% in the 2 years pre-vaccine introduction was 42% to 28% in the second year post introduction.

The strategic review team agreed that the RV network met the original 2008 objectives for documenting presence of disease, describing disease epidemiology, using surveillance as a platform for special studies in some countries, and using the data for policy decisions. At least 37 (55%) of 67 participating countries had collected at least 2 years of pre-vaccine introduction data that met the inclusion criteria for quality as defined via the strategic review.

3. Assessment of IB-VPD and RV laboratory networks

The independent assessment of the laboratory networks found both laboratory networks had made '*…huge advances in strengthening national and regional laboratory capacities, standardization of laboratory testing, improving laboratory quality and performance, and establishing functional international networks. Both, however, remain in a state of development. Of the 2 laboratory networks, the RV network is significantly closer to achieving effective support of the programme. The RV laboratory network has inherent advantages over the IB-VPD laboratory network in that not only is laboratory testing significantly less complex, but laboratory requirements are more compatible with those of existing global networks, including polio and measles/rubella. … While WHO has been very effective in providing and contributing to technical guidance of the laboratory networks, provision of overall management and oversight has been less impressive. …The fidelity with which laboratory data is entered into the reporting system and the completeness of reporting is clearly inadequate. This problem can be addressed to some extent by ensuring strict linkage between laboratory data and clinical and epidemiology data through the more effective use of unique case ID numbers. This is not a technical problem; it is one of network management and oversight.*' (full report in Annex).

4. MoH perspectives

Standardized questionnaires were received from 27 MoH respondents in AFR, 13 in EMR, and 8 from WPR. Respondents noted the main reasons for establishing surveillance were to assess disease burden, prepare for vaccine introduction, monitor vaccine impact, and to strengthen bacterial laboratory capacity. Overall, 89% of respondents felt surveillance provided information to advocate to, or within, the government on the importance of rotavirus diarrhoea or paediatric bacterial meningitis. National surveillance was reported as the most important factor in the decision to introduce a vaccine or to continue national funding for a vaccine, followed by availability of other national data (e.g. special studies, passive national health systems) and disease burden estimates from WHO or the literature. MoH respondents noted a desire to increase the number of existing sentinel sites in order to obtain more representative data for their country.

5. WHO support to the network

To achieve the aim of good quality data, WHO recognized the necessity of a solid infrastructure for surveillance; thus, WHO's activities during the past 5 years have been to develop the building blocks such as instituting laboratory external quality assurance, standardized sentinel site assessments, and training. In addition, WHO provided sites with specimen collection and laboratory supplies including rapid diagnostic kits. Access to advanced laboratory testing was provided via molecular testing at reference laboratories. Regional and global meetings brought together network members to share experiences and foster the feeling of belonging to a network, supported by the dissemination of twice yearly global surveillance bulletins. To improve quality, IB-VPD communication tools (posters and pamphlets) to support specimen collection, identifying bacterial causes of meningitis, and data management were also developed and distributed to sites. A field-based method for estimating the denominator of at-risk children at a sentinel

hospital was developed for meningitis surveillance to better understand catchment populations and enable estimation of incidence of meningitis hospitalizations.

From 2008 to 2012, GAVI provided $45.5 million in support of both surveillance networks of which $8.8 million (19%) supported WHO staff and $36.7 million (81%) supported surveillance activities. In general, two-thirds of activity funds supported the surveillance infrastructure of the reference laboratory network, regional/global meetings, trainings, technical support, and one-third supported sentinel sites including purchase of supplies. Additional funding provided by the U.S. Centers for Disease Control and Prevention included $530,000 for standardized site assessments, middle income countries and the data landscape analysis, as well as provision of 3 full-time staff and additional technical support.

The current year-to-year funding with uncertainty around funding sustainability has caused hesitation by countries and WHO to implement improvements. This uncertainty has been a particular problem for reference laboratories as the year-to-year funding prohibits hiring of staff and long-term planning. This has led to one reference laboratory withdrawing from the network.

6. Data landscape analysis findings

The assessment found the '*data management process is variable by WHO RO, and the data transfer and reconciliation process is cumbersome and time-consuming. Thus, it is warranted to explore new and different options to streamline the current system, while taking into account the unique setting and needs of each WHO RO. The general data flow in each RO is consistent … Data capture occurs at a sentinel site, sent to the country office, and then sent to the regional office and then finally submitted to HQ. Two of the ROs have opted to only collect aggregate data while the other 4 collect case-based data…Every RO has implemented a standard paper case report form, however … Each country and even site…may have made modifications to the standard forms to allow for capture of other variables... Every RO has implemented some type of standard data collection tool, however there is not any standardization across the tools. Some of the major factors affecting the quality of data …include relationship with Regional Reference Labs* [RRL] *with inability to link RRL data* [to the individual case data] *due to lack of use of unique identifiers and the general availability of resources and funding. A future data management system …needs to be flexible and dynamic to account for the different data infrastructures and approaches of each RO. The goal of the new system would to provide a centralized system which would allow for decentralized management and control of data in a case-based format'* (full report in Annex)

Key conclusions and recommendations from the 2013 strategic review

1. IB-VPD surveillance: Conclusions and recommendations

The IB-VPD programme is at a critical juncture in its development, and decisive changes will be necessary to produce high-quality data. It was recognized that building a strong and effective IB-VPD surveillance network is both complex and challenging. The overall opinion amongst all partners involved was a strong desire to continue strengthening the network; however, it was agreed that the quality of the network must be urgently improved, and that both technical and financial support should be targeted to a smaller number of sites. In the short-term, these sites would be those that met the defined funding criteria and minimum standards (in general, the A, B, and C category as well as new sites joining the network since 2011). The strategic review team recognized that the category D sites, in general, required investment of considerable human and financial resources before capacity is generated to produce quality data; thus, exclusion of Category D sites would enable focus on the other sites to further improve quality. Furthermore, it was discussed and agreed by ROs, HQ, and partners that collection and sharing of case-based data across all levels is essential to conduct the necessary data analysis to monitor and evaluate the programme, as well as to link clinical and laboratory data particularly of serotype/group data. Data analysis should be conducted more frequently and actively used to monitor surveillance

performance and outcome. Strengthening serotype/serogroup data availability and usefulness is also of importance.

Recommendations for the IB-VPD Network Size and Scope

- Network participation requires meeting minimum data quality standards regarding consistent reporting, enrolment of cases, laboratory, and surveillance performance indicators. In principle, all (GAVI and non-GAVI eligible) countries should be encouraged to participate in the network; however, network size may need to be limited as WHO support to countries to ensure generation of high-quality data is subject to financial and human resource constraints;
- In the coming year, the current number of sites in each country should not be expanded unless there is a compelling reason to do so. Since MoH expressed a desire to expand the number of sites, WHO should engage MoH officials in further discussion around this issue;
- Only sites that meet the established funding criteria should receive funding in 2014. Sites categorized as D, in general, do not meet these funding criteria, and should not be provided with GAVI funds, if located in GAVI-eligible countries. This decision should be based on data provided during the first 6 to 9 months of 2013, and countries should be notified of the decision by February 2014 (which is prior to receipt of 2014 funding);
- During early 2014, additional work is required to clearly define longer-term network objectives, as well as performance and funding criteria. Detection of a minimum number of pneumococcal cases per site per year in countries which have not introduced PCV should be included as a metric. Additionally, sites should be further categorized as:
  - 'Fully recognized site': site has been assessed within the past 2 years using the WHO standardized assessment tool, and is providing quality data for measuring vaccine impact (in pre-PCV introduction countries) or for monitoring serotype epidemiology (post-PCV introduction countries);
  - 'Supported site" site receives funding from WHO, agrees to share case-based data on a quarterly basis, and is either a fully recognized site or working towards that;
- Networking should be strengthened to share resources and to enhance laboratory collaboration with measles/polio surveillance efforts.

Recommendations for Data Management and Dissemination

- Institute a common case-based data system that shares standardized data across sites/regions/reference labs/HQ, with real-time verification and analysis capacity, and with improved data quality;
- Strengthen data management capacity for data analysis, interpretation and dissemination at all levels; and
- Modify the WHO Global Bulletin to show all reporting countries but limit analysis to a subset of sites reporting quality data, including reporting for at least 12 months and enrolling a minimal number of cases.

Recommendations for the IB-VPD laboratory network:

- Conduct in-depth Regional reviews of laboratory networks function and output to identify region-specific issues and provide region-appropriate priority activities;
- Reduce the number of participating network laboratories to more closely match programme capacity to fully support and supervise these laboratories to an extent that guarantees confidence in reported laboratory results;
- Review and revise the roles and responsibilities of WHO Regional and Global laboratory coordinators to place more emphasis on active management of network performance;
- Every effort should be made to assess every laboratory at least once each year;
- Continue the external quality assurance, and ensure quality control (all positive specimens and 10% sample of negative specimens should be submitted in a 'blinded' fashion for RRL testing) with data analysis to validate test and laboratory performance;
- Report serotype/serogroup data at least twice yearly to WHO HQ and more frequently to ROs

to enable more prompt detection of problems with subsequently actions to improve quality;
- Standardize sample selection for serotyping/grouping; and
- Link case-based clinical and epidemiological data from sentinel sites to local laboratory results and polymerase chain reaction results as well as serotype/group data from RRLs, which may require modification of existing data management systems.

Recommendations for sentinel sites
- Ensure sites meet a definition of a sentinel site so surveillance objectives can be met;
- Initiate zero reporting to enable differentiation between no cases enrolled or no report submitted to WHO;
- Develop strategies to improve performances at all sites (GAVI and non-GAVI) based on findings from monitoring and evaluation of the surveillance system; and
- Prioritize site assessments using external reviewers, MoH, local institutions, etc.

2. RV Surveillance: Conclusions and recommendations

The review team concluded that the RV surveillance network was overall generating quality data useful for decision makers. However, further targeted enhancements to the network would enhance its capacity to provide more standardized information to national, regional, and global policy makers. In particular, all sentinel sites must meet the standard definition for a site so that calculations of rotavirus positivity are based on hospitalized children, rather than children seen at peripheral clinics. Additionally, genotyping data generation should be further strengthened by development of standardized protocols for specimen selection and linking of case-based data that includes clinical and vaccination data.

Recommendations for the overall RV surveillance system
- Network participation requires meeting minimum data quality standards regarding consistent reporting, enrolment of cases, laboratory, and surveillance performance indicators. In principle, all (GAVI and non-GAVI eligible) countries should be encouraged to participate in the network; however, network size may need to be limited as WHO support to countries to ensure generation of high-quality data is subject to financial and human resource constraints;
- The current surveillance performance indicators should be examined for usefulness; and
- Encourage further networking including laboratory collaboration with measles, polio, IB-VPD surveillance and sharing of resources.

Recommendations for Data Management and Dissemination
- Countries should report case-based data to all regional offices and HQ, and gathered data should be further standardized;
- RRLs should report genotype data to ROs twice yearly to ROs, as feasible within current resource constraints; and
- Global Bulletins should be modified to show all reporting countries on a map, but limit analysis to subset of reporting sites that report every month and enrol $\geq$ 100 cases annually.

Recommendations for the RV laboratory network
- Standardize sample selection for genotyping;
- Begin to establish the linkage of case-based data to genotype data;
- Examine country-level genotype distribution in addition to distribution at regional and global levels;
- Build additional technical capacity at the national laboratory (NL) level, if possible; and
- Funding permitting, include all sites in the EQA programme.

Recommendations for sentinel sites
- Ensure sites meet a definition of a sentinel site so surveillance objectives can be met;
- Update eligibility criteria for inclusion in data analyses to include 12 months reporting and $\geq$100 specimens at a single site (no satellite sites)

- Initiate zero reporting to enable differentiation between no cases enrolled or no report submitted to WHO; and
- Develop strategies to improve performances at all sites (GAVI and non-GAVI). Strategies may be based on findings from monitoring and evaluation of the surveillance system.

3. IB-VPD and RV future vision and complementary approaches for IB-VPD surveillance: Conclusions and recommendations

Recommendations for complementary approaches to IB-VPD surveillance
For IB-VPD, there is an urgent need to improve the quality of the data, and to monitor ongoing serotype epidemiology. However, it is anticipated that data quality will be unable to quickly reach the desired level in all countries, particularly those with the weakest health and hospital systems. Thus, a complementary strategy to IB-VPD surveillance for measuring vaccine impact is required.

- Develop tools and processes (models) that allow PCV impact assessment by input of quality data from IB-VPD as well as complementary existing data sources including pneumonia morbidity and mortality.

Recommendations for assessing future utility for surveillance of other VPDs
Both the IB-VPD and RV sentinel hospital surveillance networks have developed a surveillance platform of improved epidemiological and laboratory capacity. Careful consideration is warranted to determine whether other VPD surveillance activities can be added to this platform, without jeopardizing the quality of IB-VPD and RV data.

- Define how to best build upon these networks to conduct surveillance for other VPDs, including those prevented by current vaccines and future vaccines such as typhoid, as well to increase capacity for outbreak detection.
- Appropriate surveillance approach(es) for other VPD's should be developed based on the specific disease characteristics (incidence, hospitalization, diagnostic testing characteristics, etc.) and the key objectives for surveillance of that disease.

Recommendations for monitoring implementation of the strategic review's recommendations

- The iTAG should continue to engage in the on-going progress made from implementation of these recommendations via quarterly teleconferences or meetings, and advice WHO on any corrective actions that may be required.

Recommendations for funding

- Improvement of the data management system with a move to case-based data (including linking of data from reference laboratories) and more on-going data analysis, interpretation and dissemination will require additional financial support. Longer term funding would enhance commitment to make changes in the system.

The Informal Technical Advisory Group for New Vaccines Surveillance Assessment of the 2013 Strategic Review of the Invasive Bacterial Vaccine Preventable Diseases and Rotavirus Sentinel Surveillance Networks

Introduction and background:

The informal Technical Advisory Group (iTAG) would like to acknowledge the foresight of WHO in requesting a strategic review of the Rotavirus (RV) and Invasive Bacterial-Vaccine Preventable Diseases (IB-VPD) Surveillance Networks. As WHO and partners consider how the next phase of surveillance for RV and IB-VPD should be designed, reviewing the accomplishments and challenges during the first five years of network development has provided valuable insights into approaches that have been successful and identified areas of needed improvement. The accompanying Executive Summary and report provide the detailed scope, process, and results of the strategic review. This document highlights the iTAG's identification of several overarching issues and policy considerations.

The RV and IB-VPD networks have accomplished the 2008 objective of documenting the presence of disease; the resultant data have contributed to decisions of many countries to introduce RV vaccine and Pneumococcal Conjugate Vaccine (PCV). As a result, strategic surveillance objectives for many countries have changed from making the decision to introduce vaccine(s) to monitoring the impact(s) of vaccine introduction and obtaining data to support eventual country vaccine financing. In addition, the RV network has successfully initiated monitoring of rotavirus genotype distribution in all regions, and has promising results for the potential ability of the network to monitor impact of vaccine introduction. The laboratory capacity built for IB-VPD in some sites has detected disease due to other etiologic agents, as well as outbreaks of meningitis. Pneumococcal serotype information has been collected from previously under-represented countries and regions. The ability of most IB-VPD sites or network to serve as a platform to monitor impact of PCV introduction remains to be demonstrated.

The review process has confirmed that the capacity needed for a site to successfully implement RV surveillance is quite different from that needed for IB-VPD surveillance. Gastroenteritis is a common, easily recognized clinical condition, and sample collection to test for RV is non-invasive. IB-VPD Tier 1 sites are conducting surveillance for meningitis, and bacterial meningitis at a population level is an infrequent albeit severe condition, requiring a substantial population per site in order to detect more than a small number of cases. For the IBD-VPD Tier 2 sites which are also conducting surveillance for bacteremia, sepsis and pneumonia, case confirmation is challenging. Blood cultures are not routinely performed in many countries and widespread use of antibiotics prior to seeking medical care—coupled with poor blood culturing techniques—hinder isolation of bacteria. Also, bacteremia occurs in a small percentage of pneumonia cases, and diagnostic testing for non-bacteremic pneumococcal pneumonia is neither sufficiently sensitive nor specific with present assays. For both IB-VPD tiers, establishing laboratory capacity to isolate bacteria from normally sterile body fluids consistently and reliably remains a challenge in many sites; as Ray Sanders, the consultant who reviewed the network laboratory activities notes, the laboratory testing required for the RV network is "significantly less complex".

Since 2008, when the IBD-VP network development began, the field of PCV impact evaluation has gained substantially more experience in monitoring the changes in hospitalized pediatric pneumonia (i.e., impact on a syndromic outcome that is not specific for pneumococcal

pneumonia). It may now be possible to monitor PCV impact on hospitalized pediatric pneumonia in selected sites, to complement the original focus on Invasive Pneumococcal Disease as an outcome. However impact monitoring by using a pneumonia syndrome endpoint is also complex and feasible in only selected settings. RV surveillance for monitoring vaccine impact may also require special studies on vaccine effectiveness and intussusception, which may not be feasible in all sites.

In order to support country decision making for vaccine introduction and for sustaining vaccine programs, countries need to be able to estimate vaccine impact. New tools for such assessments are becoming available, including increased experience with models in which countries can use either their own data, data from special studies, or global burden of disease data to estimate the impact of introducing pneumococcal or rotavirus vaccine on their country's morbidity and mortality, as well as the cost-effectiveness of vaccination. Surveillance networks may need to consider how data generated through the network and other data sources could be used as inputs into such models, in place of monitoring actual disease impact data at the country level.

The iTAG review identified certain areas where modifications would substantially enhance the utility of the data and the allocation of resources.

Issues identified during the review:

1) As noted in both the laboratory review and the data landscape review, the system has developed and tends to function as six separate regional networks, rather than as a single network. Implementation of the IBD-VPD and RV networks has largely been designed and managed at the regional level. Some degree of regional flexibility is appropriate and necessary to permit accommodation of the surveillance to regional and national level needs and realities. However the network also needs overall project management and accountability, and the ability to undertake global assessment and analyses.

2) While the analyses of the system in the accompanying report provide useful information about the networks, additional analyses of the IB-VPD data at a global level that were proposed as part of the review were not feasible in the available time frame. Issues limiting analyses included the lack of case level data in an agreed upon standard format, as well as difficulty linking specimen laboratory results from some laboratories with the clinical and epidemiologic data on the same patient. This was also an issue with data collection with the RV network, although not as critical. The ability within the network to do real time performance monitoring was therefore limited.

3) The resources to support a network of this size at the country, regional and global level are insufficient and could benefit from more strategic allocation. Two specific examples were noted by the iTAG during the review. At the global level, there were inadequate resources for management, and data processing and analysis (exacerbated by the data system issues noted elsewhere in this document). The review also noted substantial differences in the regional staffing and management of the network(s). For example, the number of sites/countries supported by each Regional Office and Regional Reference Laboratory varied widely. In a region with a large number of sites, the regional staffing is unlikely to be sufficient to support the recommended on-site assessments of either the surveillance program or the site laboratories.

   In addition the decreased funding available in 2014 increases the urgency of decisions about appropriate resource utilization and sizing the network relative to the resources.

Representatives from the Regional Offices also note that the current approach of year-to-year funding has made it difficult to undertake longer-term planning and investment at all levels of the networks.

4) For the IB-VPD network, preliminary data suggest a wide range in the number of laboratory confirmed cases per site, with some sites identifying small numbers of cases, and showing substantial year-to-year variability.

5) The value of the networks for countries and regions includes the technical standards for surveillance that are established (which can serve as models for other countries to follow); the access to technical assistance, reference laboratories, and reagents; and the communication and collaboration that occur among participant countries and sites, including countries which are not GAVI eligible, but may be encouraged to undertake surveillance and introduction of vaccines.

Recommendations:

1) The RV and IB-VPD networks should build on the experience and results of the past five years to refine appropriate objectives and strategies to meet future surveillance needs.

   A) For RV, the network appears capable of meeting the primary objectives, monitoring the impact of vaccine introduction and monitoring changes in genotype distribution. It is important to define the minimum data required to meet surveillance objectives at the national and regional levels. Specific modifications for the RV network proposed in the review report will strengthen the network's ability to meet these objectives.

   B) For IB-VPD, the network should refine the objective and performance criteria for surveillance for Invasive Bacterial Disease, incorporating what has been learned from the initial experience. An updated objective should include the requirement that participating sites demonstrate the ability to document a substantial number of IPD cases, in order to establish a credible baseline of IPD for at least two years before vaccine introduction. A performance criteria of an average of 20 to 30 cases of invasive pneumococcal disease each year before vaccine introduction is proposed, based on the analysis of sentinel site comparability to population level trends in the US active surveillance systems. This target also reflects the concern that sites with smaller numbers are likely to exhibit greater year to year variability, increasing the potential for misleading interpretations of secular trend data, especially regarding non-vaccine serotypes. Relatively few sites may be able to identify this number of IPD cases annually in the target age range. However, focusing the surveillance resources on a smaller number of sites with more interpretable data may provide a better model of what can be accomplished by surveillance, and encourage countries considering vaccine introduction to invest country or donor resources in surveillance (see below).

   C) For countries and sites that are not currently able to meet the above performance criteria for IBD/IPD, other approaches to the core objectives should be explored.

      1. To address the objective of monitoring vaccine impact, WHO could explore the use of a hospitalized pediatric pneumonia endpoint in a limited number of sites where population size and available data sources suggest that such an

approach might be feasible, building on the conclusions from the PCV impact meeting.

2. To meet country needs for decision making on vaccine financing, WHO could explore encouraging the use of existing or future modeling approaches to estimate the impact of introducing pneumococcal vaccine on country specific morbidity and mortality, as well as the cost-effectiveness of vaccination.

3. Monitoring the impact of pneumococcal vaccine on NP colonization, especially for vaccine serotype strains, has also been proposed as an alternate method for countries to bridge to disease impact data from similar settings, using WHO – recommended methodologies for nasopharyngeal swabbing. WHO should consider the conclusions from the PCV impact meeting regarding the possible utility of this approach; concerns include the technical requirements for undertaking NP colonization surveys, the costs for such surveys, and the complexity of extrapolating from NP colonization data to disease impact especially for non-vaccine serotype disease.

D) An additional objective for IB-VPD surveillance is to support improved bacteriologic capacity to identify other important pathogens and outbreaks. Monitoring of anti-microbial susceptibility also remains an important question. However, the experience of the past five years suggests that either these objectives should be achieved by special studies in a limited number of well-resourced centers, or there needs to be a substantial improvement in sentinel site and laboratory performance, with increased technical assistance, site assessments, and close to real time performance monitoring.

The iTAG encourages efforts to further develop IB-VPD surveillance capacity to meet these objectives, and also to support sites that seek to eventually meet the performance criteria proposed in B above. WHO should encourage countries to explore strategies for supporting this capacity building, through alternative (or "supplemental") funding such as GAVI's Health Systems Strengthening, in-country support for VPD surveillance, and other sources. However the iTAG also notes that site funding is not the only needed input; the ability to support the network with access to technical assistance, reference laboratories, reagents, site assessments, data reporting systems, communication and collaboration also require substantial resources which are currently limited.

2) It is essential for the future that RV and IB-VPD surveillance each function as single global networks generating credible well-defined data. The network should also facilitate efficient use of the data collected for core network functions such as monitoring system performance in real time, contributing data for laboratory quality assurance, and evaluating the performance of new diagnostic methods. This will require modification of data systems and implementation of policies which facilitate relevant data collection and timely analysis.

Specific needs include:

A) Use of a standard approach for variable names and coding
B) Use of unique identification numbers for patients and/or specimens, policies which ensure that laboratory results (site and RRL) are linked with clinical and epidemiologic data on each specimen/patient, and policies that assure an appropriate sample of specimens are tested in Regional Reference Laboratories
C) With appropriate security safeguards, sharing of case level records among all levels of the system
D) System flexibility to incorporate new laboratory tests when officially added as standard procedure

E) Zero or negative reporting from sites, so that absence of cases or variables can be differentiated from lack of reporting
F) Software with editing and verification capability to improve data quality

Since it is unlikely that the time or funds will be available for development of entirely new data systems, the iTAG recommends a rapid evaluation of the feasibility of modifying existing web-based systems used within the networks to meet the above system requirements. The process of the strategic review itself has resulted in substantial work to map the variable names across sites and to understand what the values for variables mean from site to site, which should contribute to progress toward a single network. The need for stronger networking, communication, and policies at all levels cannot be over-emphasized.

3) There should be better targeting of resources linked to the refined objectives.

The iTAG commends the thoughtful effort by the IB-VPD network to define performance criteria for joining the network and for continuing to participate as a network site. These criteria have also been used to identify sites which have not met the criteria over the past two years. Given the decreased resources available for 2014, the iTAG concurs with focusing resources on those sites that are able to meet the performance criteria and eliminating funding for the sites that have not.

Looking beyond 2014, funding and human resources should be more closely aligned with the refined objectives and strategies above. While the iTAG agrees the funding cycle should permit more than year-to-year funding, especially when staff must be hired, it is also critical that continuation of funding be contingent on sites meeting meaningful performance criteria. There should be performance agreements for all participants in the network, including the surveillance sites, regional offices, regional reference laboratories, global reference laboratories, and WHO HQ, specifying in detail responsibilities as well as resources to be received. Estimates for the approximate number of site visits to be made and specimens to be processed would contribute to a more realistic estimate of the number of sites that could be supported given limited human and financial resources. Available resources should be allocated to assure data capable of meeting system objectives; the number of sites that can be supported is finite.

The iTAG recommends that WHO implement structured performance-based agreements with all participants. Sites/countries could consider the refined list of objectives and identify, based on their experience to date, which approach for vaccine impact monitoring (e.g. IPD, hospitalized pneumonia, modeling, etc.) they would be best suited to undertake. Funding for reference laboratories could be linked to best estimates of the number of site visits to be done and the number of specimens to be processed.

While capacity building is a goal of the RV and IBVPD surveillance programs, regular monitoring and accountability are needed to ensure a level of performance that provides data to meet country and region specific needs. The network provides technical specifications and support; it also provides funding to country sites to establish successful models. Other countries can then build on these models, using country funds or other sources such as GAVI HSS funds. As countries introduce vaccines they are committing themselves to large investments in the future for vaccine procurement; surveillance costs are small compared with vaccine purchase costs but are essential to vaccine sustainability. The vision for the networks is that countries have models for disease surveillance that enable countries and regions to build credible, high quality surveillance systems which will provide reliable data on vaccine preventable diseases.

1. BACKGROUND

The Global Invasive Bacterial-Vaccine Preventable Diseases and Rotavirus Surveillance Networks

Prior to 2008, surveillance for invasive bacterial diseases and rotavirus disease primarily was conducted by special projects and regional surveillance networks that had been established through funding from the GAVI Alliance via the Accelerated Development and Introduction Plans (ADIPs) and the Hib Initiative. Given time limited funding through the ADIPs and the Hib Initiative, global immunization partners and Ministries of Health supported the transition of these special projects and regional surveillance networks to the formation of global invasive bacterial-vaccine preventable diseases (IB-VPD) and rotavirus (RV) surveillance networks that would operate under the auspices of the World Health Organization (WHO).

Since 2008, with support from the GAVI Alliance and coordination by WHO, the global IB-VPD and RV surveillance networks have operated under similar management structures, which include networks of sentinel surveillance sites and laboratories that enroll cases and conduct initial testing. Sentinel surveillance sites report data either to the local Ministry of Health, WHO Country Office or the WHO RO. The laboratory networks are structured under a tiered model in which sentinel site laboratories are support by National Laboratories (NLs) and/or Regional Reference Laboratories (RRLs); NLs are support by RRLs, and RRLs are supported by the Global Reference Laboratories (GRLs). Both clinical and laboratory data are reported to WHO HQ on semi-annual or annual basis.

From 2008-2012 under this new management structure, WHO implemented strategies to improve data quality, including provision of technical support, standardized site assessments, and purchase of supplies and equipment for sentinel sites. An overall timeline of key events includes:

- 2009-2009: transition of the networks to WHO coordination with GAVI financial support, data standardization meeting held with agreement on collection and sharing of data, culminating in the dissemination of the first global IB-VPD and RV surveillance bulletins in December 2009;
- 2010: RV standardized sentinel site assessment tool developed, first global surveillance meeting convened with agreement on standard meningitis case definitions, and revision of IB-VPD surveillance performance criteria;
- 2011: visual aid standard operating procedures begun for IB-VPD (posters for collection of cerebrospinal fluid and laboratory identification of bacterial from CSF as well as a data management pamphlet), IB-VPD laboratory external quality assurance programme piloted, second global surveillance meeting held with agreement to strengthen identification of bacterial pathogens by addition of rapid diagnostic tests and PCR at RRLs, and agreement for sharing data on all suspect meningitis cases identified rather than limited to cases classified as probable bacterial meningitis;
- 2012: IB-VPD standardize assessment tools finalized; IB-VPD EQA launched for all participating laboratories; IB-VPD visual aids finalized; manual for laboratory detection of CSF bacterial pathogens finalized; first RV and IB-VPD laboratory technical working group meetings held; RV EQA undertaken for RRLs; 3rd global surveillance meeting held;
- 2013: strategic review of IB-VPD and RV surveillance networks launched with review of experiences from 2008 to 2012.

During 2008 to 2012, both IB-VPD and RV surveillance networks expanded (Figures). In 2008, the IB-VPD network comprised 36 countries reporting sentinel site data (with one additional country reporting laboratory based data), of which 69% were GAVI-eligible countries. In total, 91 sentinel sites reported data with 16,124 meningitis cases and 20,098 pneumonia/sepsis cases reported. In 2012, 58 countries reported data, 79% GAVI-eligible, via 150 sentinel sites. In total,

20,098 meningitis cases and 35,480 pneumonia/sepsis cases were reported. For RV, the number of reporting countries increased from 36 (56% GAVI eligible) in 2008 to 60 (72% GAVI-eligible) in 2012. The number of sites increased from 131 (40% in GAVI-eligible countries) to 178 (55% in GAVI-eligible countries), and the number of children <5 years of age with acute gastroenteritis enrolled into surveillance increased from 28,148 in 2008 to 72,197 in 2012.

Figure 1. Map of Sentinel Sites in the WHO IBD Surveillance Network in 2008

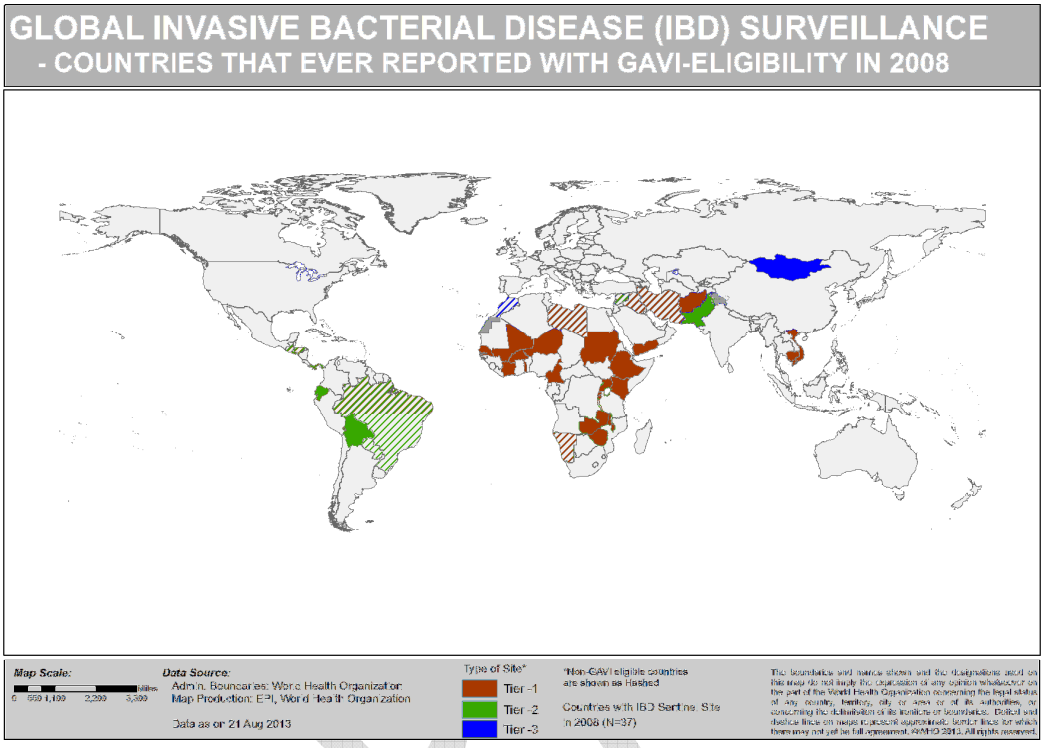


Figure 2. Map of Sentinel Sites in the WHO IBD Surveillance Network in 2012

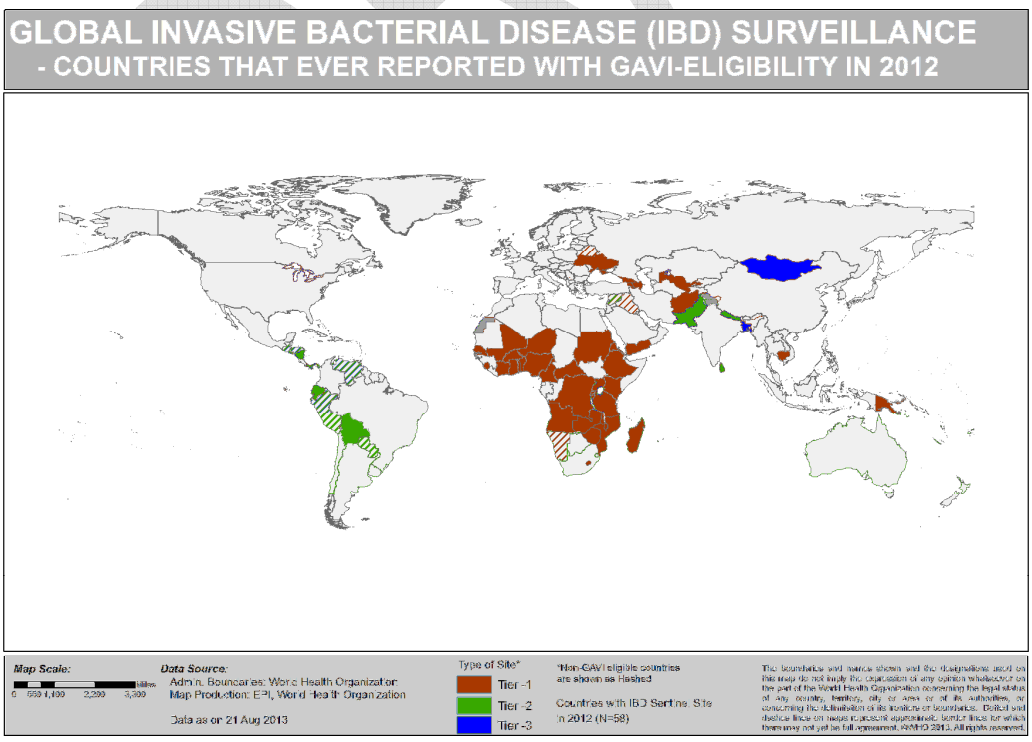


Figure 3. Map of Sentinel Sites in the WHO RV Surveillance Network in 2008

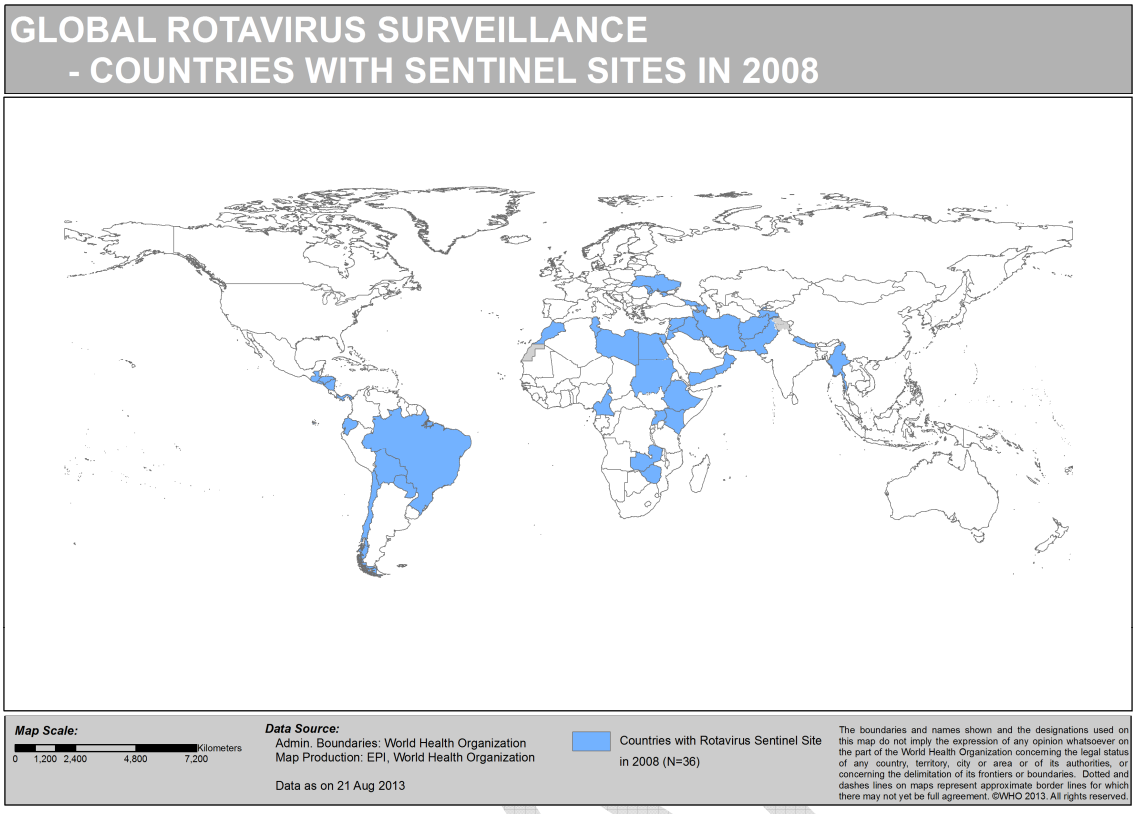
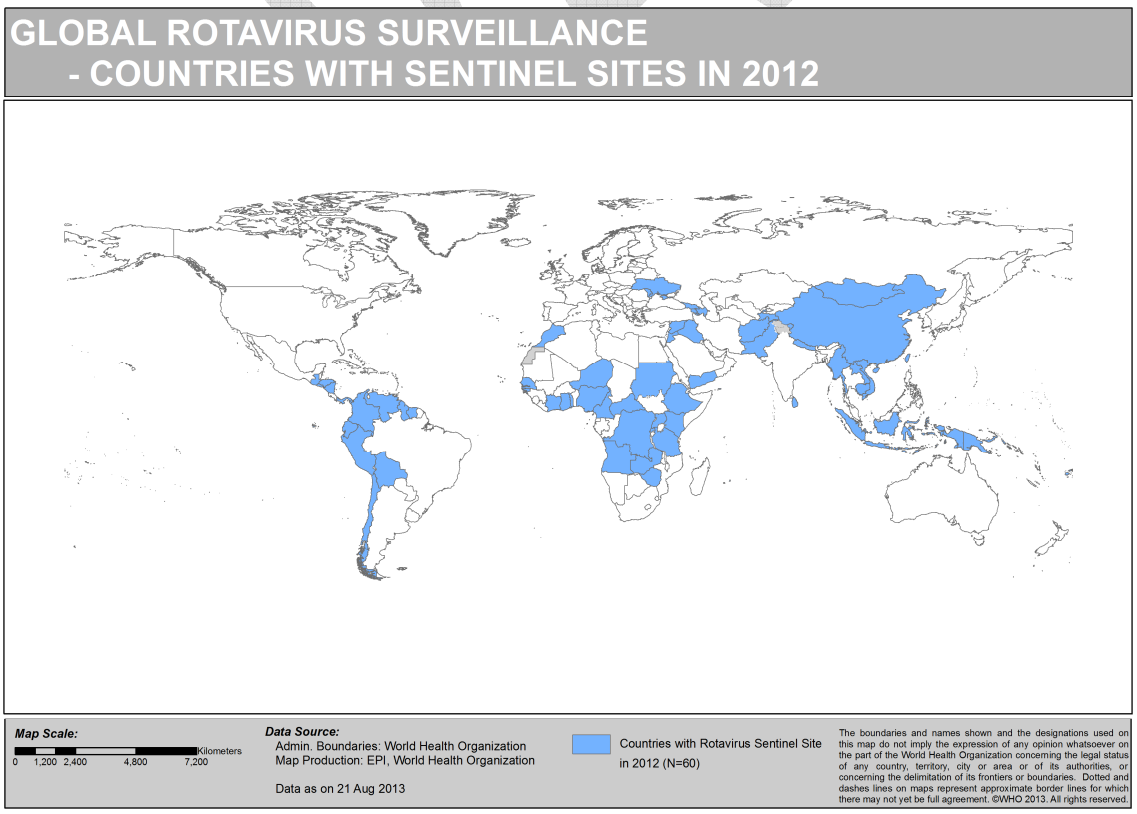


Figure 4. Map of Sentinel Sites in the WHO RV Surveillance Network in 2012



In 2008, the following overarching objectives were established for the global IB-VPD and RV surveillance networks:

1. To generate local data for decision making and informing policy regarding *Haemophilus influenzae* type b (Hib) vaccine, pneumococcal conjugate vaccine (PCV), and rotavirus vaccine introduction and sustained use
2. To assess and monitor disease trends and serotype/genotype distribution over time (nationally, regionally, globally)
3. To develop a platform for vaccine impact studies
4. To highlight the value of surveillance data and use for fundraising and advocacy

More specific objectives included the following, according to pre- and post-vaccine introduction periods:

Time period	Objectives
Pre-vaccine introduction period	• To document presence of disease, describe the disease epidemiology and provide data for estimating disease burden • To establish systems to measure impact after vaccine introduction • To identify circulating serotypes and measure serotype distribution • To monitor antibiotic sensitivity (IB-VPD only)
Post-vaccine introduction period	• To assess disease trends over time • To monitor vaccination programme impact • To monitor changes in circulating strains/serotypes • To use the surveillance networks as platforms for vaccine effectiveness and safety evaluations

To meet these objectives, the WHO-coordinated IB-VPD and RV surveillance networks have worked to build infrastructure in countries and regions to provide quality data to assist with the planning of public health programmes. These global surveillance networks also include sentinel sites within countries not eligible for GAVI support that have chosen to provide data voluntarily; many of these sites are located within WHO's Region of the Americas of the World Health Organization (AMR) and the Eastern Mediterranean Region.

Strategic review of the IB-VPD and RV surveillance networks

Many elements are needed to build a strong surveillance infrastructure, such as training, laboratory support, data management, and communication, and although much progress has been made in strengthening these developing surveillance networks, more can be done. WHO and global partners determined that it would be timely to conduct an in-depth, five-year strategic review of the IB-VPD and RV surveillance networks to identify strengths and weaknesses and

decide on strategies and actions to ensure that the networks are responsive to the information needs of all immunization stakeholders.

For this strategic review, WHO's informal technical advisory group of experts (iTAG) for new vaccines surveillance provided guidance and technical direction (Appendix A). WHO and the iTAG agreed that the strategic review would have the following objectives:

1. To assess whether and to what extent the original 2008 objectives for the IB-VPD and RV surveillance networks have been met
2. To critically assess the current IB-VPD and RV surveillance networks, to specifically include:
    - Ministry of Health (MoH) perspective;
    - IB-RV laboratory networks;
    - Capacity building conducted in support of developing and maintaining the IB-VPD and RV networks; and
    - Data management, production, dissemination, and use by the IB-VPD and RV networks
3. To provide conclusions and recommendations for the future vision for the networks, including those around enhancing country ownership, laboratory networks, capacity building and data management, particularly:
    - Clarify what should be the current objectives for both networks including contributing to vaccine impact assessments (short- and long-term);
    - Determine optimal strategies to meet these objectives and overcome identified common challenges;
    - Define key indicators/milestones to monitor progress; and
    - Define potential complementary approaches for IB-VPD surveillance

To accomplish this, beginning in March 2013, the iTAG met via monthly teleconferences to discuss the scope of the review, data analysis plans and, later on, results from the various components of the review. A 5-day global meeting on the strategic review was convened 16th September 2013, during which findings were presented and discussed, and country specific examples of IB-VPD and RV surveillance systems and surveillance data use were presented by representatives from each of the WHO ROs. Final recommendations from the strategic review process are provided in this report.

2. IB-VPD SURVEILLANCE NETWORK DATA ANALYSES

Analysis of Data Reported to WHO

METHODS

Source of surveillance data

In the second quarter of 2013, WHO Headquarters (HQ) requested that the Regional Offices (ROs) submit case-based sentinel site-level meningitis (tier 1), pneumonia (tier 2) and population-based (tier 3) data. Analysis of IB-VPD surveillance data was conducted on all data available to WHO, including case-based data collected by 4 ROs and data aggregated by sentinel site in 2 ROs. Data from over 70 databases were consolidated and cleaned. Due to variability in the data

reported to WHO HQ, the data from each region was analyzed separately and one region required separate analyses by country. IB-VPD variables were mapped across Regions, and the first uniform data analysis performed. Due to the volume of data and paucity of time, the iTAG and WHO agreed that sites would be categorized and analysis focused on sites that met defined performance criteria to determine if they achieved the original 2008 objectives (refer to data analysis plan in Annex)

Components of the surveillance data analysis

The below Table lists the components of the data analysis performed as part of the strategic review. All sites were assessed for whether the presence of disease was documented. The additional components of the analysis were limited to A category sites.

Table 1. Summary of data analysis components for the 2013 IBD surveillance network strategic review.

Category	Data analysis components
Document presence of disease	• Number and percent of countries / sites that documented the presence of the VPD bacterial pathogens
Surveillance performance indicators and data completeness	• Percent of sites that report according to the agreed timeline • Percent of suspected meningitis cases that have a lumbar puncture (LP) performed • Percent of meningitis cases with age data available • Percent of lumbar punctures performed that have a culture result recorded
Describe disease epidemiology and provide data for estimating disease burden	• Percent age distribution of suspected meningitis cases • Percent probable bacterial meningitis • Percent age distribution of probable bacterial meningitis • Percent age distribution of lab-confirmed cases (Hi, Spn, Nm) • Percent probable bacterial meningitis due to Hi, Spn, Nm organisms • Percent lab-confirmed cases from suspected meningitis cases with an LP • Percent culture-positive suspected meningitis cases with VPD organisms detected by culture • Percent Binax positive for Spn from suspected meningitis cases with an LP • Percent Latex positive for Hi, Spn, Nm organisms from suspected meningitis cases with an LP • Percent PCR positive for Hi, Spn, Nm organisms from suspected meningitis cases with an LP • Percent of suspected meningitis cases of known outcome that died (CFR)
Assess disease trends over time	• Monthly distribution of suspect and probable meningitis cases, by year • Monthly distribution of lab-confirmed cases, by year

Document presence of disease

During 2008 to 2012, all but 4 participating network countries identified Spn cases via IB-VPD surveillance. The figures below also display the number of cases identified by each country as well as the year of PCV introduction. Despite most countries having introduced Hib vaccine during 2008 to 2012, over half the countries were able to identify Hi cases. The final figure shows identification of Nm.

Figure 5 Numbers of countries and sites participating in the WHO-coordinated IB-VPD surveillance network that identified *Streptococcus pneumoniae*, 2008-2012

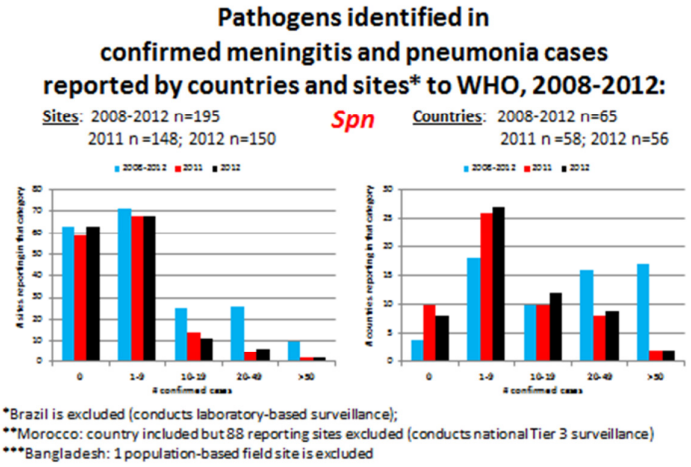


Figure 6 Map of countries and sites participating in the WHO-coordinated IB-VPD surveillance network that identified *Streptococcus pneumoniae*, 2008-2012

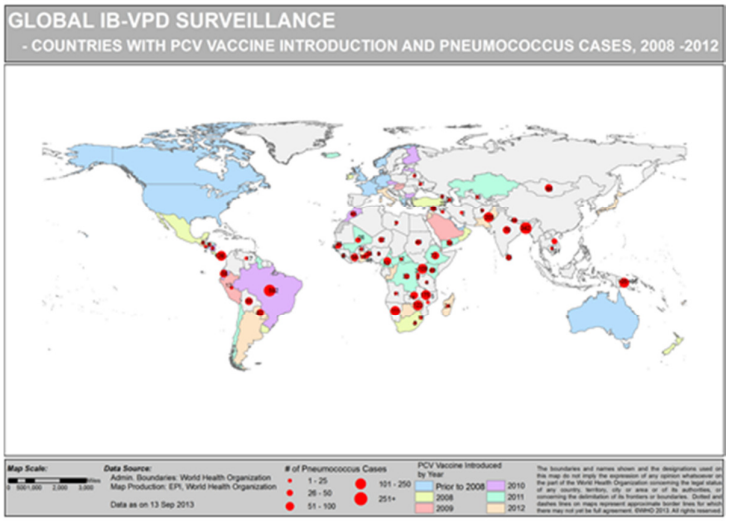
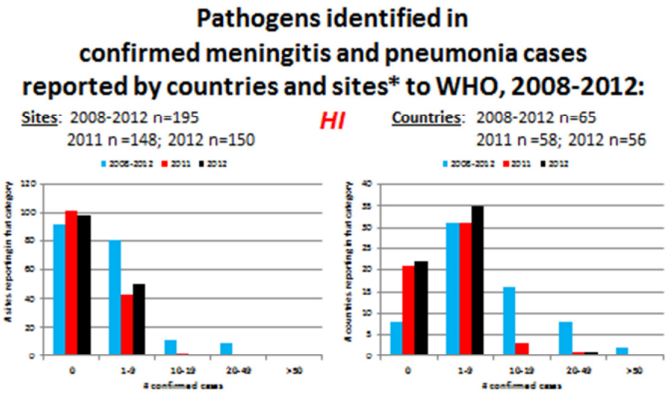


Figure 7 Numbers of countries and sites participating in the WHO-coordinated IB-VPD surveillance network that identified *Haemophilus influenzae*, 2008-2012



*Brazil is excluded (conducts laboratory-based surveillance);
**Morocco: country included but 88 reporting sites excluded (conducts national Tier 3 surveillance)
***Bangladesh: 1 population-based field site is excluded

Figure 8 Map of countries and sites participating in the WHO-coordinated IB-VPD surveillance network that identified *Haemophilus influenzae*, 2008-2012

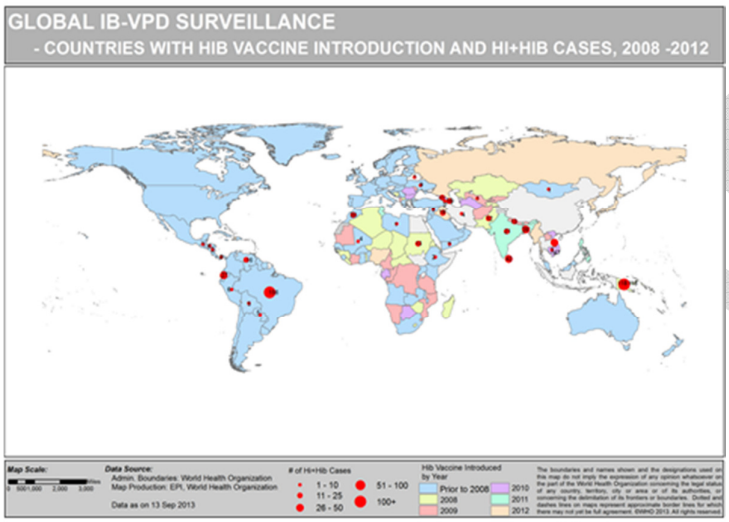
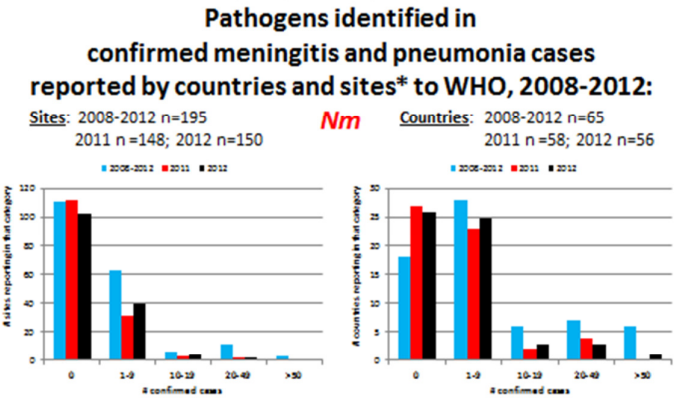


Figure 9 Numbers of countries and sites participating in the WHO-coordinated IB-VPD surveillance network that identified *Neisseria meningitidis*, 2008-2012



*Brazil is excluded (conducts laboratory-based surveillance);
**Morocco: country included but 88 reporting sites excluded (conducts national Tier 3 surveillance)
***Bangladesh: 1 population-based field site is excluded

Determination of inclusion sites

The strategic review focused on 'sites most likely to have accomplished the original 2008 surveillance tasks most completely,' sites were thus categorized into performance levels "A", "B", "C","D" or "new" based on the following criteria.

- New: Sites new to the surveillance network in 2011 or 2012.
- A Sites: met both criteria
  - Reported ≥11 months of data per year for at least two years during 2010-2012.
  - Enrolled ≥100 suspected meningitis cases per year for at least two years during 2010-2012 (tier 1) or enrolled ≥500 suspected meningitis/pneumonia/sepsis cases per year for at least two years during 2010-2012 (tier 2).
- B Sites: met both criteria
  - Reported ≥10 months of data per year for at least two years during 2010-2012.
  - Enrolled a total of ≥100 suspected meningitis during 2010-2012 (tier 1) or enrolled a total of ≥500 suspected meningitis/pneumonia/sepsis cases during 2010-2012 (tier 2).
- C Sites: Sites that improved in consistency of reporting and case enrolment between 2011 and 2012 but did not meet the criteria of A or B sites.
- D Sites: All other sites.
- Only data from sites that met the "A" criteria were analysed in detail.

Figure 10. Categorization of sites reporting meningitis data to WHO, 2010-2012

Region	A: Strict		B: Moderate		C: Improved		D: Other		New		Total
	#	%	#	%	#	%	#	%	#	%	
AFR	17	35%	6	12%	2	4%	8	16%	16	33%	49
AMR*	0	0%	9	19%	0	0%	28	58%	11	23%	48
EMR**	11	26%	5	12%	0	0%	25	58%	2	5%	43
EUR	0	0%	2	17%	0	0%	3	25%	7	58%	12
SEAR***	5	71%	0	0%	0	0%	2	29%	0	0%	7
WPR	1	5%	0	0%	0	0%	20	91%	1	5%	22
Total	34	19%	22	12%	2	1%	86	48%	37	20%	181

Figure 11. Map of Meningitis Sentinel Sites Categorized by Levels A, B, C, D, and New, 2010-2012

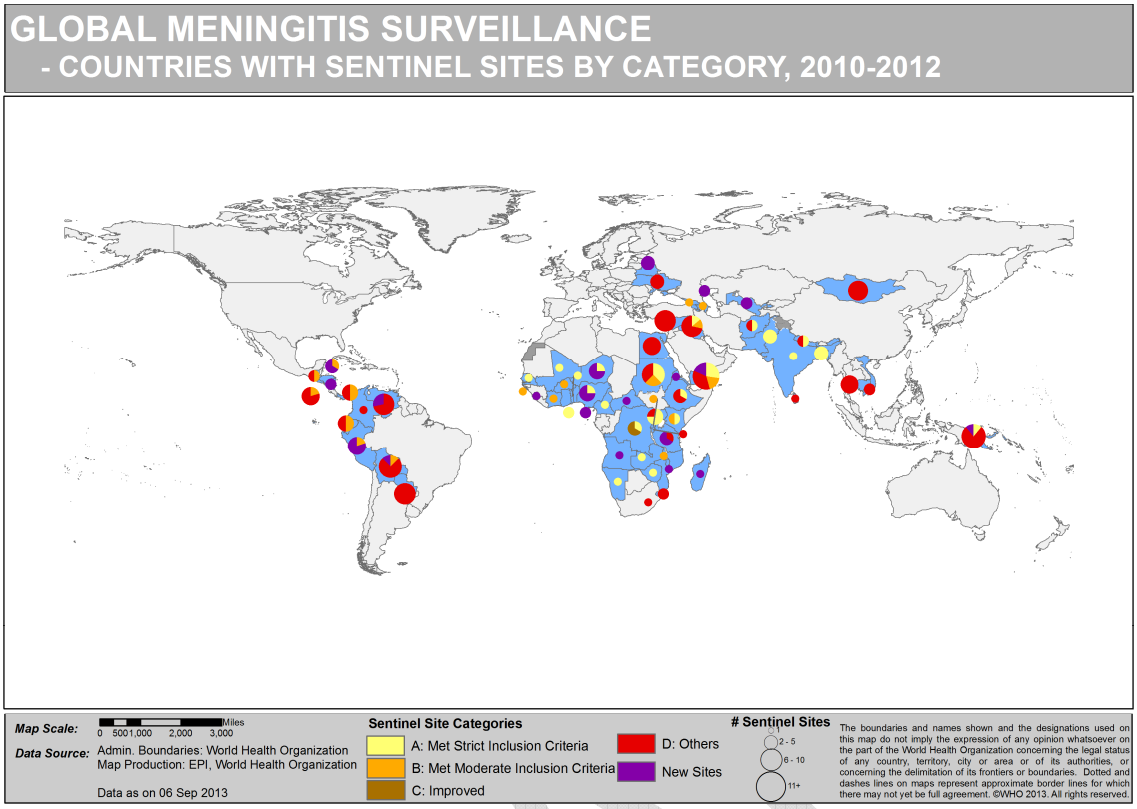
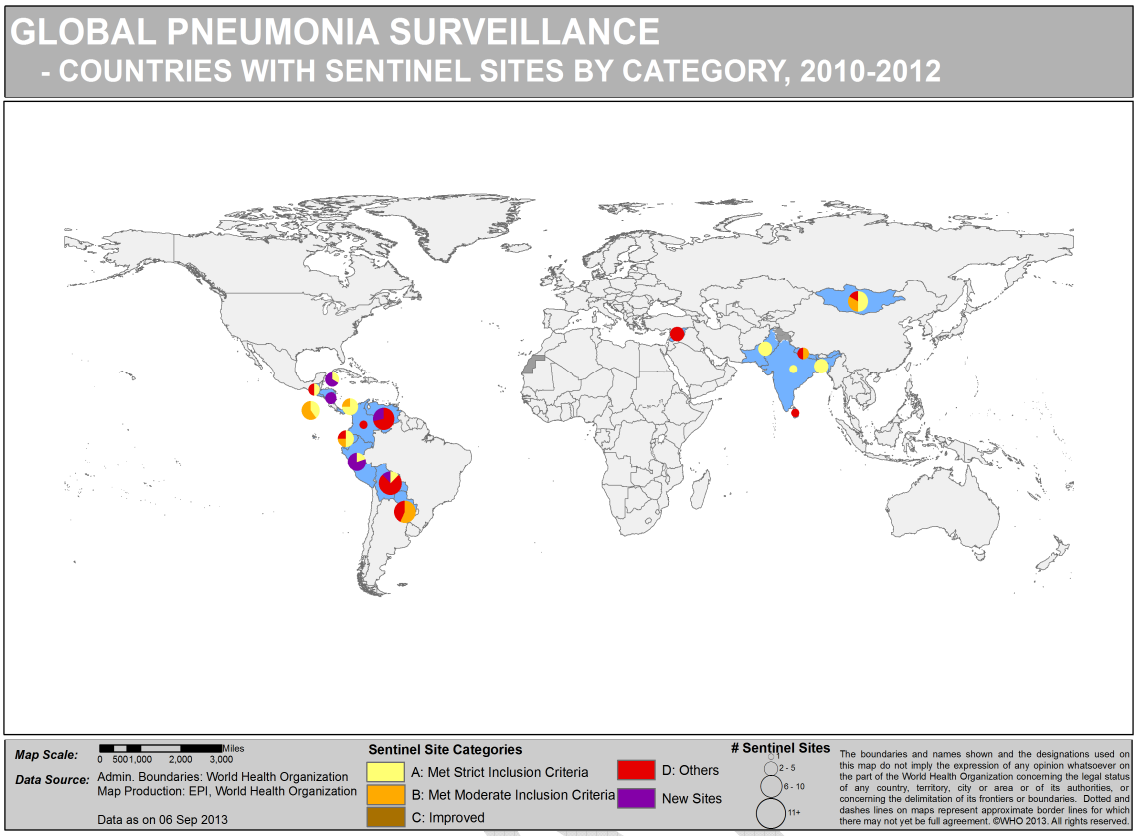


Figure 12. Categorization of Sites Reporting Pneumonia Data to WHO, 2010-2012

Region	A: Strict		B: Moderate		C: Improved		D: Other		New		Total
	#	%	#	%	#	%	#	%	#	%	
AFR											
AMR*	11	23%	9	19%	0	0%	17	35%	11	23%	48
EMR**	3	50%	0	0%	0	0%	3	50%	0	0%	6
EUR											
SEAR***	4	57%	1	14%	0	0%	2	29%	0	0%	7
WPR	3	50%	2	33%	0	0%	1	17%	0	0%	6
Total	21	31%	12	18%	0	0%	23	34%	11	16%	67

Figure 13. Map of Pneumonia Sentinel Sites Categorized by Levels A, B, C, D, and New



Data analyses

All analyses were stratified by region and GAVI funding eligibility. As per surveillance network protocol, any country eligible for GAVI support at the start of the WHO-coordinated IBD surveillance network has remained eligible for GAVI support; this includes countries that have graduated from GAVI eligibility. The data analyses were done for all sites that met the aforementioned level "A" inclusion criteria.

Performance indicators. The performance indicators calculated were the following:

Performance indicator	Target
Percent of sites that report according to the agreed timeline	80%
Percent of suspected meningitis cases that have a lumbar puncture (LP) performed	90%
Percent of meningitis cases with age data available	
Percent of lumbar punctures performed that have a culture result recorded	90%

Percent age distribution of suspected meningitis cases. The percent age distribution of all suspected meningitis cases was calculated using data from all cases enrolled at a site from 2008-2012. The age stratification for this and subsequent distributions are:

Region(s)	Age groups reported

AFR, EMR, EUR, WPR	0-5 months
	6-11 months
	12-23 months
	24-59 months
AMR	0-11 months
	12-23 months
	24-59 months
	All ≤59 months

Percent probable bacterial meningitis: The percent of all suspected meningitis cases that had probable bacterial meningitis was calculated using all available data from a site for 2008-2012. Only suspected meningitis cases that had data to calculate probable bacterial meningitis status were used as the denominator.

Percent age distribution of probable bacterial meningitis: The percent age distribution of cases classified as probable bacterial meningitis was calculated using data from all cases enrolled at a site from 2008-2012.

Percent age distribution of lab-confirmed Haemophilus influenzae (HI), *Streptococcus pneumonia* (Spn), and *Neisseria meningitides* (Nm)*:* The percent age distribution of all suspected meningitis cases with a lab-confirmed diagnosis (Hi, Spn, Nm) was calculated using data from all cases enrolled at a site from 2008-2012.

Percent probable bacterial meningitis due to Hi, Spn, Nm organisms: The percent of all probable bacterial meningitis cases due to each pathogen was calculated for each year, for 2008-2012.

Percent lab-confirmed cases from suspected meningitis cases with an LP: The percent of all suspect bacterial meningitis cases due to any lab-confirmed pathogen was calculated for each year, for 2008-2012. Lab-confirmation was by any method (culture, latex, Binax, PCR).

Percent culture-positive suspected meningitis cases with VPD organisms detected by culture: The percent of cases with a positive culture for Hi, Spn or Nm was calculated from the total number of cases tested with culture.

Percent Binax positive for Spn from suspected meningitis cases with an LP: The percent of all suspected meningitis cases that test positive for Spn by Binax was calculated from the total number of cases tested with Binax.

Percent Latex positive for Hi, Spn, Nm organisms from suspected meningitis cases with an LP: The percent of suspected meningitis cases that tested positive for Hi, Spn or Nm by latex agglutination was calculated from the total number of cases tested by Latex.

Percent PCR positive for Hi, Spn, Nm organisms from suspected meningitis cases with an LP: The percent of suspected meningitis cases that tested positive for Hi, Spn or Nm by PCR was calculated from the total number of cases that were tested by PCR.

Percent of suspected meningitis cases of known outcome that died (case fatality rate): The case fatality rate of suspected meningitis cases was calculated from the total number of suspected meningitis cases that had a known outcome recorded.

Monthly distribution of suspect and probable meningitis cases, by year: The monthly distribution of probable meningitis cases was analyzed overall and for the years 2008-2012.

Monthly distribution of lab-confirmed cases, by year: The monthly distribution of suspected meningitis cases with a lab-confirmed diagnosis was analyzed overall and for the years 2008-2012.

MAIN RESULTS

Sentinel site reporting and inclusion criteria

During 2008-2012, 181 sites reported data to WHO HQ as per the reporting requirements for the 2013 Strategic Review. After applying the inclusion criteria mentioned before, there were 72 sentinel sites that enrolled cases in at least 11 months per year for two years from 2010-2012 and of those, there were 34 sites that also enrolled more than 100 suspected meningitis cases per year in two years from 2010-2012, thereby meeting the "A" site criteria.

Table 2. Sentinel sites meeting reporting and testing criteria, 2010-2012

Region	Total # of Sites	# (%) sites that enrolled cases ≥ 11 months per year for at least 2 years during 2010-2012	# (%) sites that enrolled ≥100 suspected meningitis cases per year at least 2 years during 2010-2012	# (%) of sites that meet both criteria (A designation)
AFR	49	19 (39)	25 (51)	17 (35)
AMR*	48	23 (48)	---	---
EMR**	43	15 (35)	11 (26)	11 (26)
EUR	12	2 (17)	---	---
SEAR	7	5 (71)	6 (86)	5 (71)
WPR	22	8 (36)	1 (5)	1 (5)
Total	181	72 (40)	43 (24)	34 (19)

*Brazil is excluded (conducts laboratory-based surveillance);

**Morocco: country included but 88 reporting sites excluded (conducts national Tier 3 surveillance)

***Bangladesh: 1 population-based field site is excluded

Table 3. Percent of suspected meningitis cases that have a lumbar puncture (LP) performed amongst A-level sites

Region	# of sites that meet criteria	Total # of suspected meningitis cases	# of suspected meningitis cases that had an LP performed	mean % of suspected meningitis cases that had an LP performed	median % of suspected meningitis cases that had an LP performed	range % of suspected meningitis cases that had an LP performed
AFR	17	19,294	19,150	100	100	(100, 100)
AMR	---	---	---	---	---	---
EMR	11	9,414	7,323	78	88	(19, 100)
EUR	---	---	---	---	---	---
SEAR	5	10,783	6,455	60	66	(17, 93)
WPR	1	268	268	100	---	---
Total	34	39,759	33,196	84	100	(17, 100)

Surveillance performance indicators and data completeness

The 34 sentinel sites that met both criteria during the period of 2010-2012 were further evaluated by two of the key meningitis surveillance performance indicators – the percentage of suspected meningitis cases that had a lumbar puncture (LP) performed (target: at least 90%) (Table 2), as well as the percentage of LP performed that had a culture result recorded (target: at least 90%) (Table 3). In addition, the completeness of data reported by these sites was assessed by the availability of age data (Table 4). Age data was not available in some regions because of the absence of case-based data.

Table 4. Percent of meningitis cases with age data available

Region	# of sites that meet criteria	# of cases in database	# of cases with age data available	mean % cases with age data available	median % cases with age data available	range % cases with age data available
AFR	17	31,771	31,227	98	100	(81, 100)
AMR	---	---	---	---	---	---
EMR	11	16,216	16,216	100	100	(100, 100)
EUR	---	---	---	---	---	---
SEAR	5	---	---	---	---	---
WPR	1	300	300	100	100	(100, 100)
Total	34	48,287	47,743	99	100	(81, 100)

Table 5. Percent of lumbar punctures performed that have a culture result recorded

Region	# of sites that met criteria	# of suspected meningitis cases that had an LP performed	# of LPs performed that have a culture result recorded	mean % LPs performed that have a culture result recorded	median % LPs performed that have a culture result recorded	range % LPs performed that have a culture result recorded
AFR	17	19,150	12,934	68	64	(11, 99)
AMR	---	---	---	---	---	---
EMR	11	7,323	6,294	86	93	(29, 98)
EUR	---	---	---	---	---	---
SEAR	5	6,455	5,132	80	74	(55, 85)
WPR	1	268	265	99	---	---
Total	34	33,196	24,444	74	85	(11, 99)

Describe disease epidemiology and provide data for estimating disease burden

Percent age distribution of suspected meningitis cases, 2010-2012

The age distribution of suspected meningitis cases was analyzed across regions. Only information from sentinel sites where the age of suspected meningitis cases was provided during the period 2010-2012 was used. The distributions vary widely between and within regions. Disease typically occurs in children too young to be vaccinated which is represented in the WPR age distribution but only in some sites in AFR and EMR.

Figure 14. Percent age distribution in AFR for 2010-2012

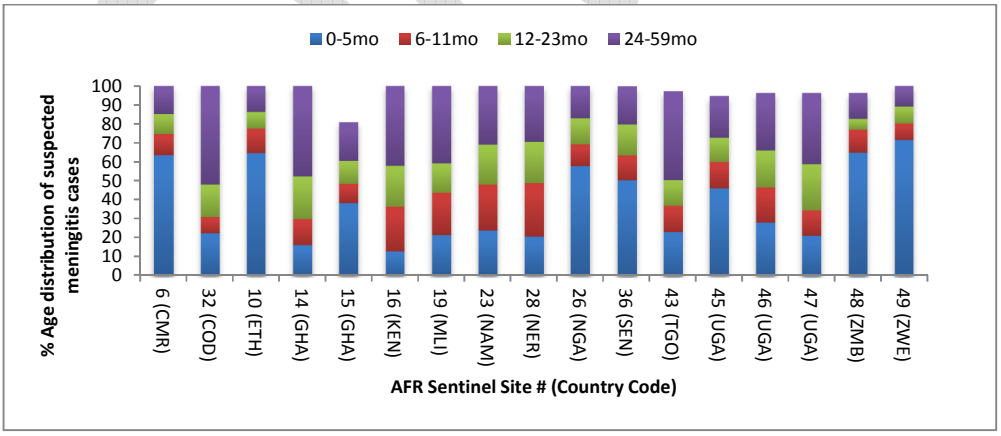


Figure 15. Percent age distribution in EMR for 2010-2012

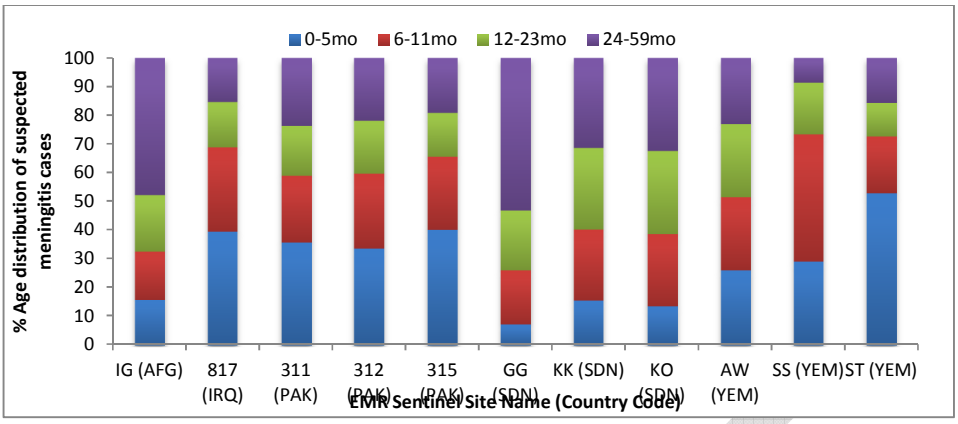
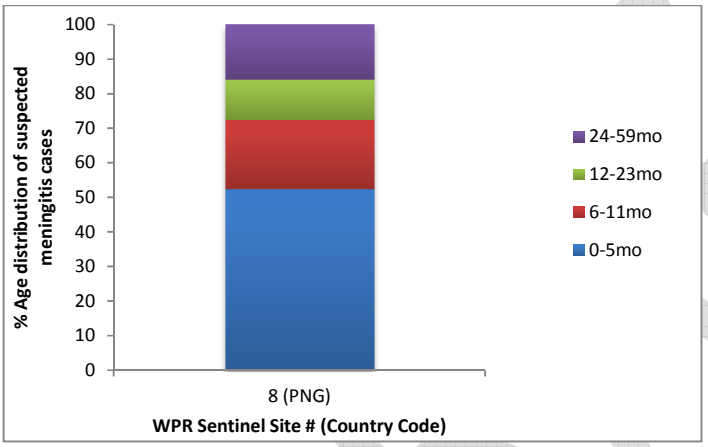


Figure 16. Percent age distribution in WPR for 2010-2012



Percent of suspected meningitis cases that meet the definition for probable bacterial meningitis, 2010-2012

Probable bacterial meningitis (PBM) is defined as a suspected meningitis case with CSF examination showing at least one of the following: 1) Turbid appearance; 2) Leukocytosis (> 100 cells/mm3); 3) Leukocytosis (10-100 cells/ mm3) AND either an elevated protein (>100 mg/dl) or decreased glucose (< 40 mg/dl). In the absence of protein and glucose results, the first two conditions were used for case categorization. Sentinel sites demonstrated a variable but fairly low percentage of PBM cases among suspected meningitis cases.

Figure 17. Percent of suspected meningitis cases classified as PBM in AFR

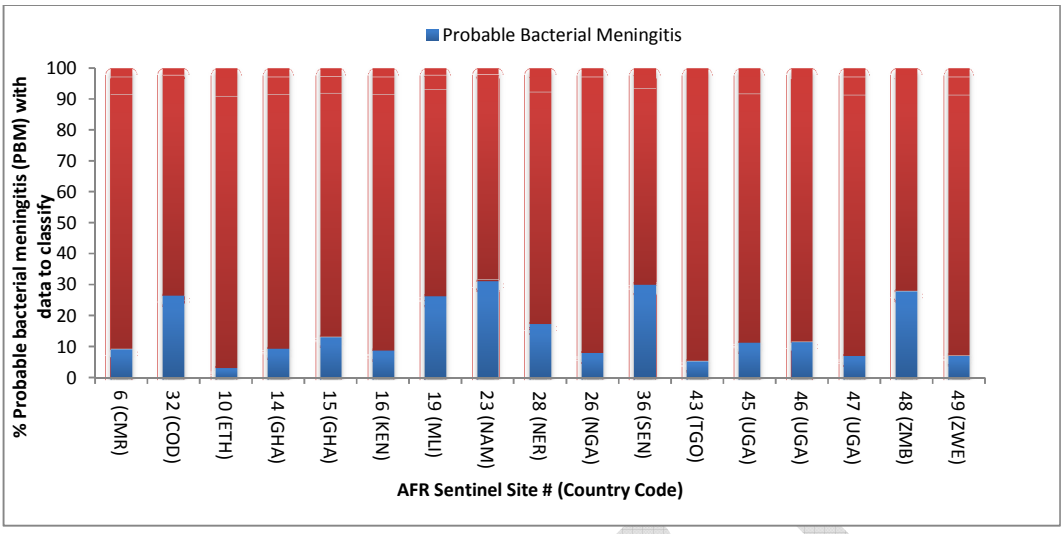


Figure 18. Percent of suspected meningitis cases classified as PBM in EMR

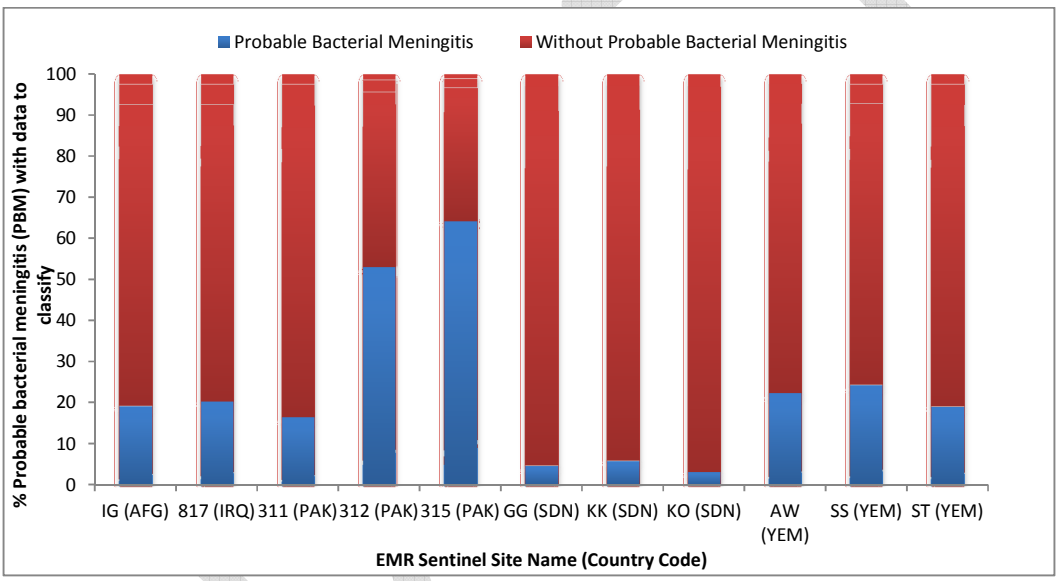


Figure 19. Percent of suspected meningitis cases classified as PBM in SEAR

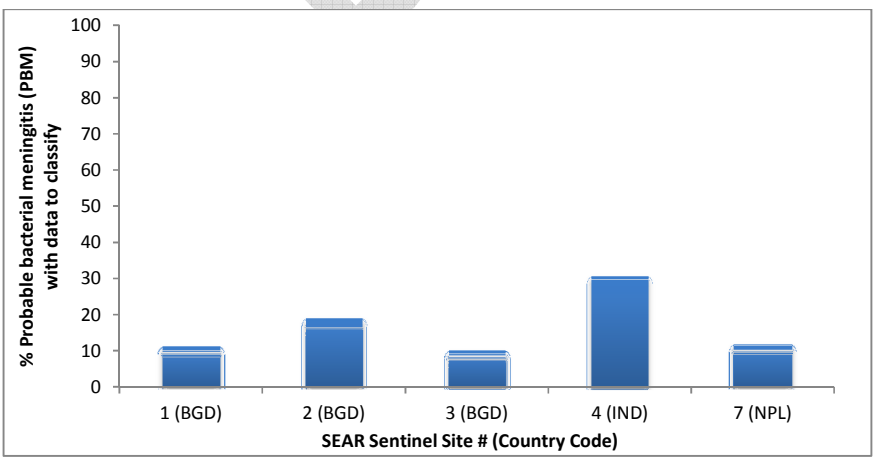
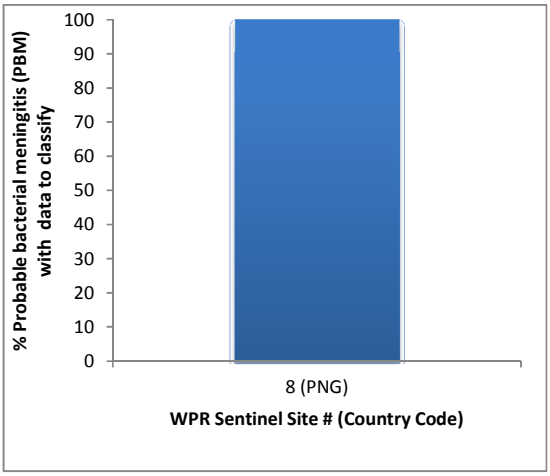


Figure 20. Percent of suspected meningitis cases classified as PBM in WPR



Percent age distribution of probable bacterial meningitis, 2010-2012

The age distribution of PBM cases was examined by region, based on sentinel sites that reported the age of cases during the period 2010-2012. Age distributions were observed to be relatively more consistent compared to the age distribution of suspected bacterial meningitis cases, with regions AFRO and WPRO showing a majority of cases in the '0-5 months' category (Figure 8, 10).

Figure 21. Percent age distribution of PBM cases in AFR

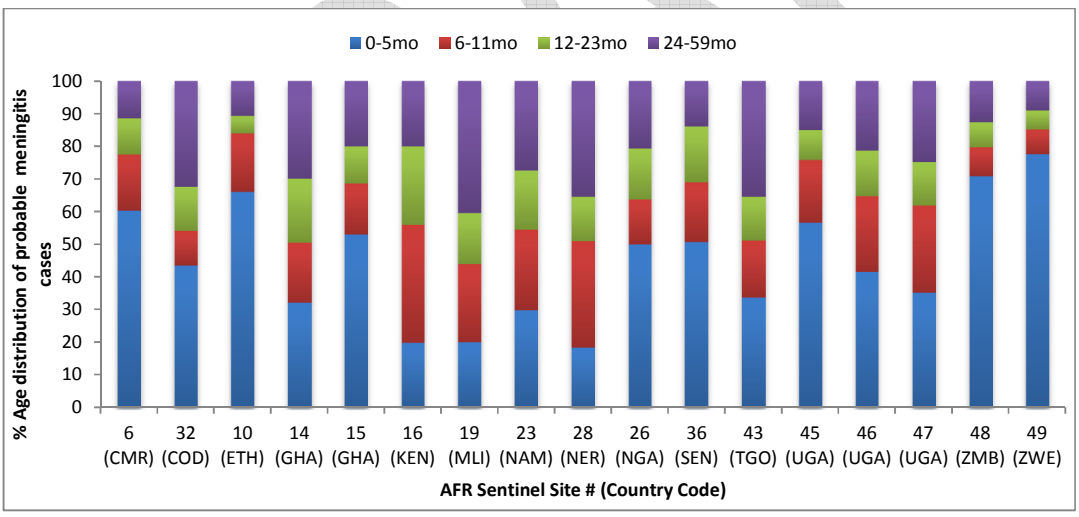


Figure 22. Percent age distribution of PBM cases in EMR

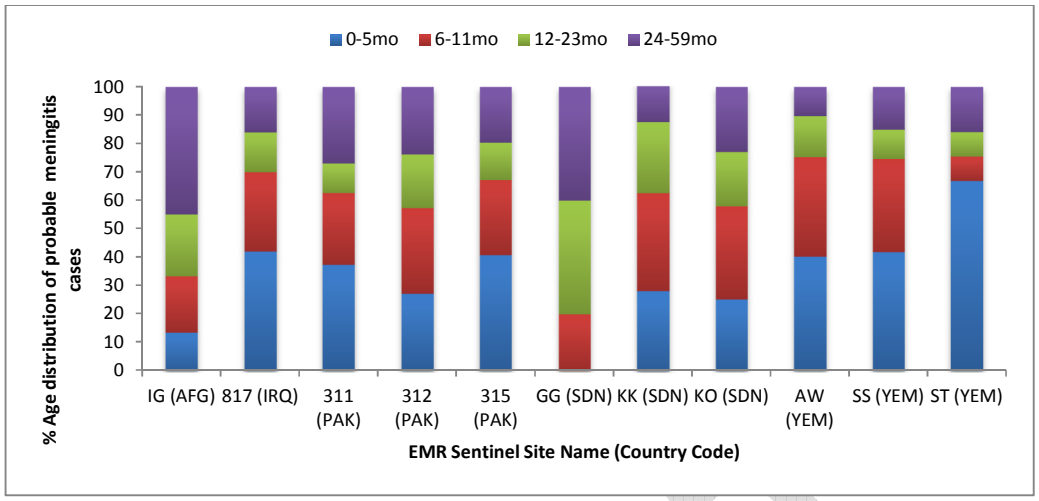
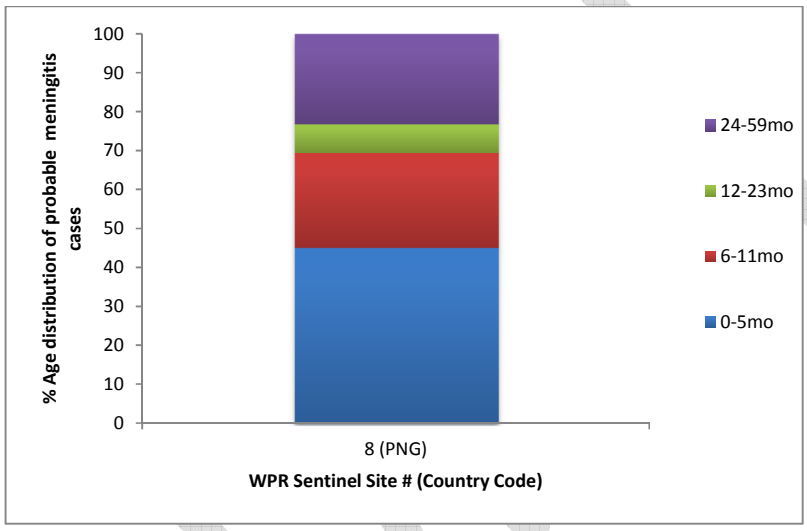


Figure 23. Percent age distribution of PBM cases in WPR



Age distribution of laboratory-confirmed cases (Hi, Spn, Nm)

Meningitis cases that were lab-confirmed (i.e. tested positive by culture, binax, latex agglutination, and/or PCR) were stratified by age and region for each type of vaccine-preventable disease (VPD) organism isolated (Hi, Spn, Nm).The age distribution for each pathogen varied within regions and between regions.

Figure 24. Age distribution of Hi in AFR

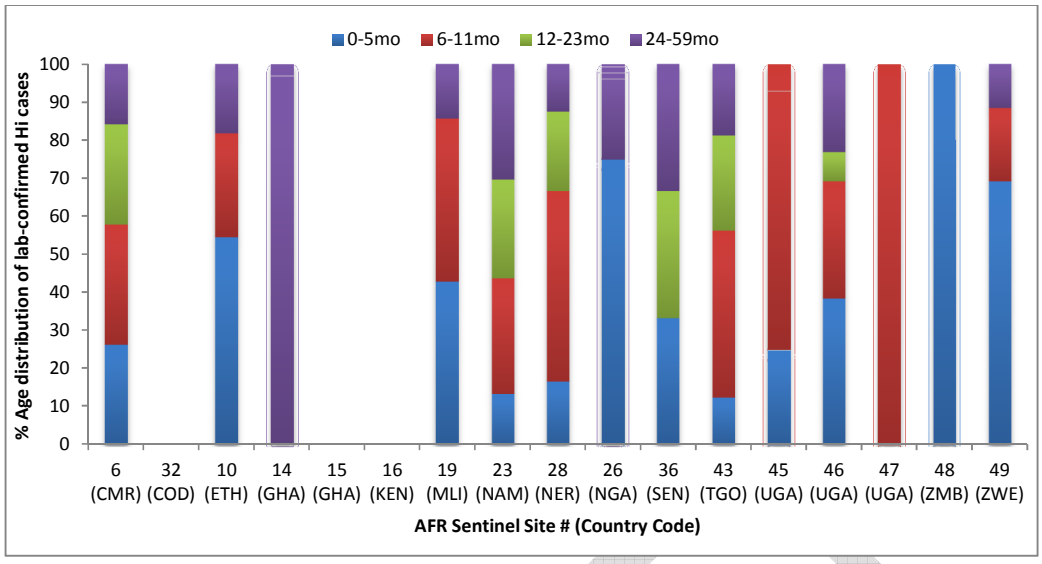


Figure 25. Age distribution of Spn in AFR

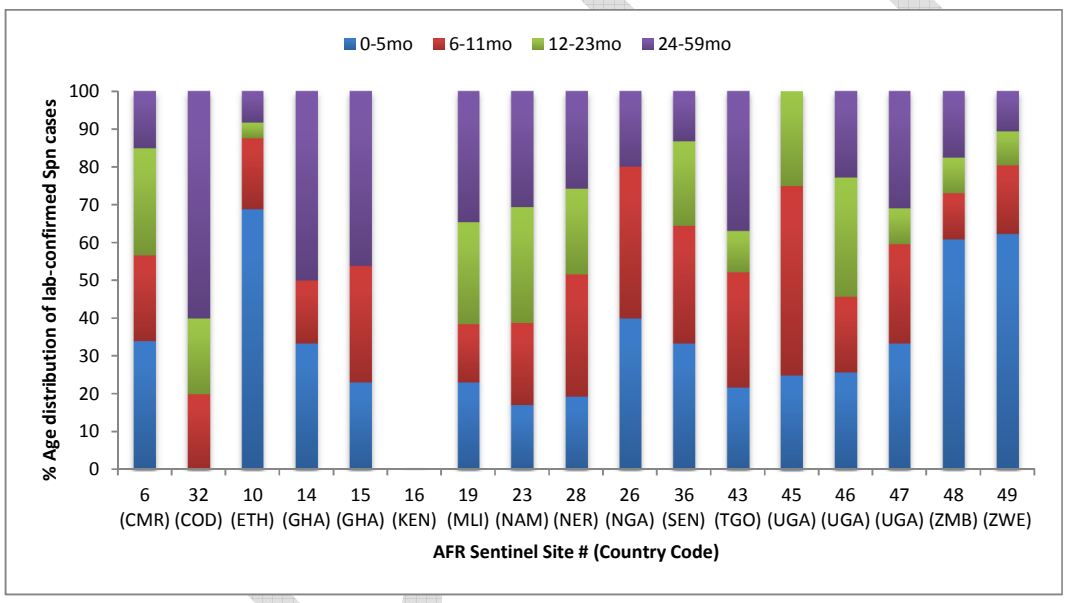


Figure 26. Age distribution of Nm in AFR

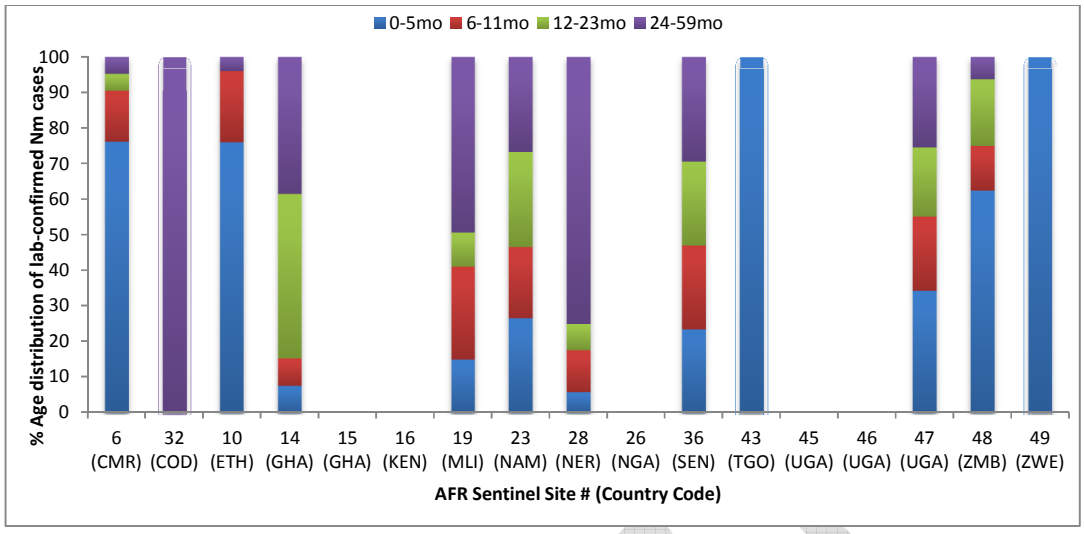


Figure 27. Age distribution of Hi in EMR

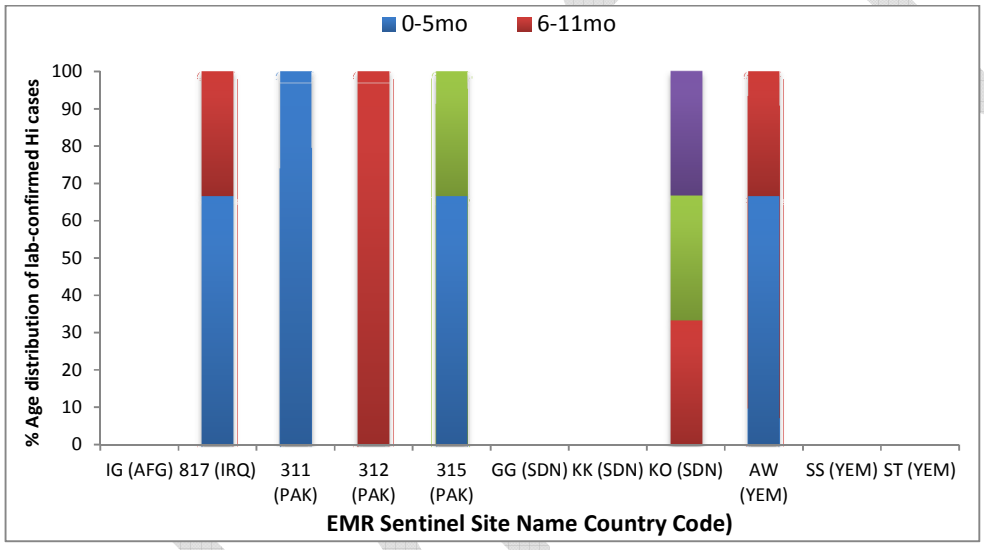


Figure 28. Age distribution of Spn in EMR

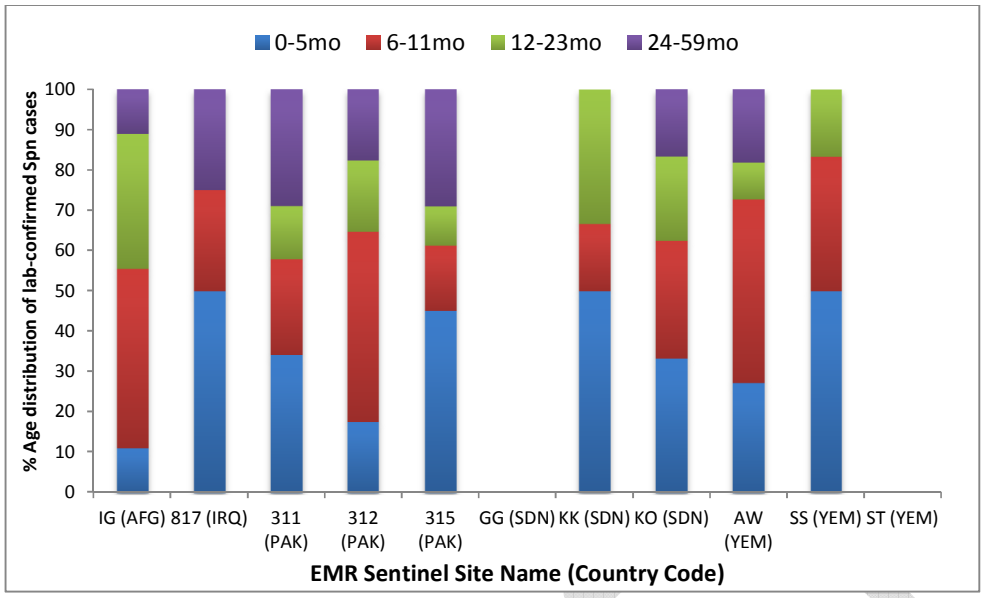


Figure 29. Age distribution of Nm in EMR

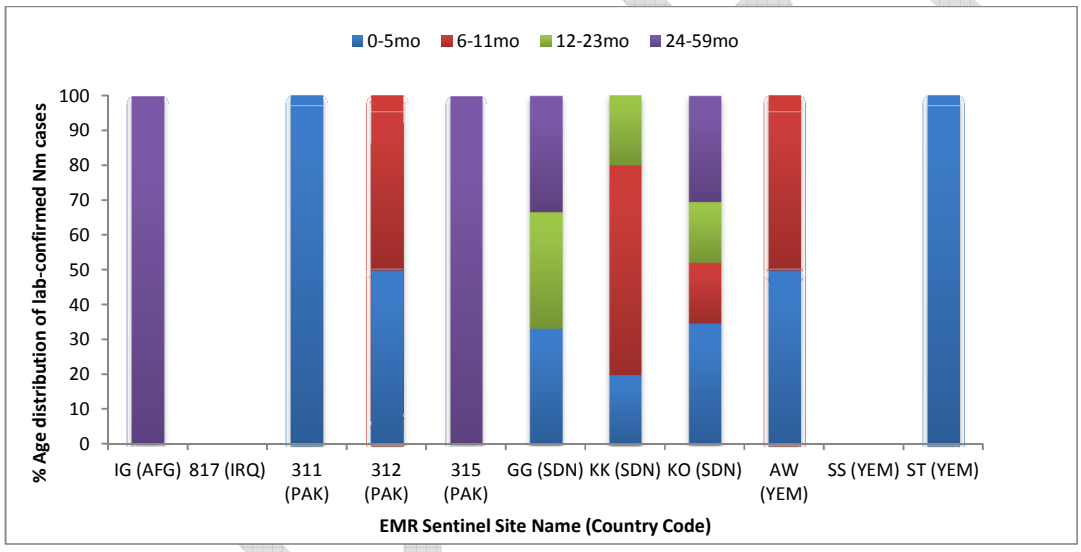


Figure 30. Age distribution of Hi in WPR

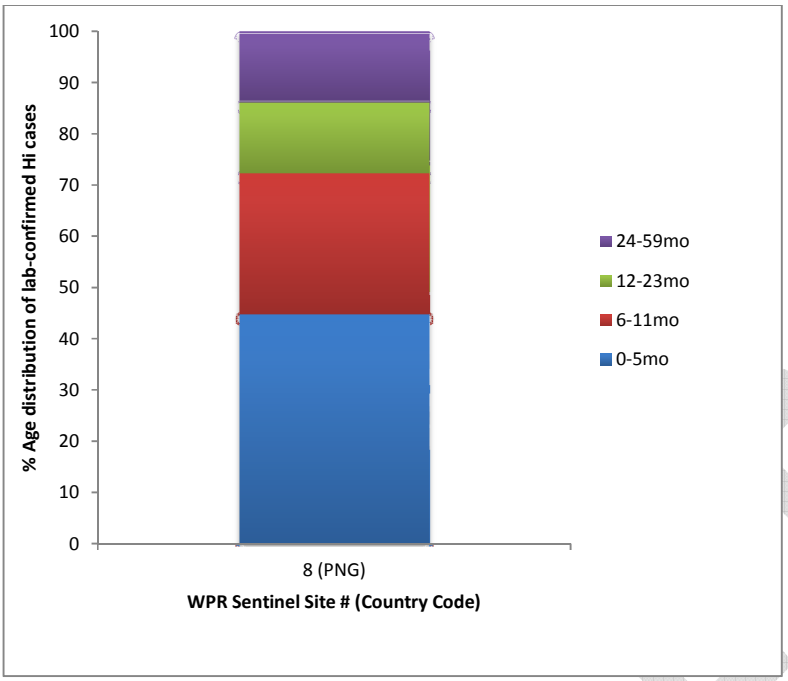


Figure 31. Age distribution of Spn in WPR

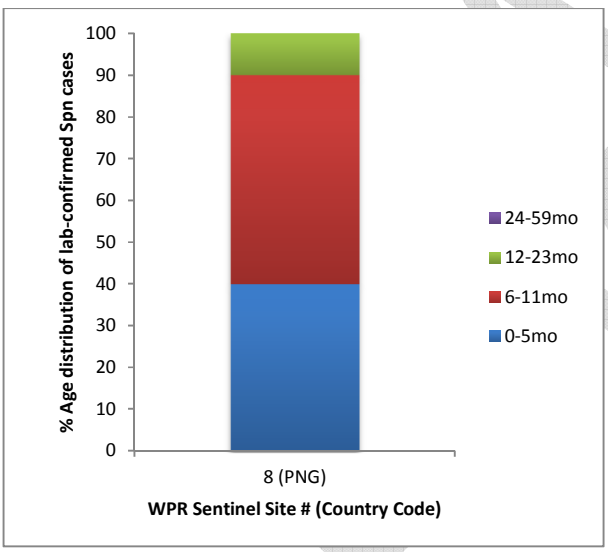
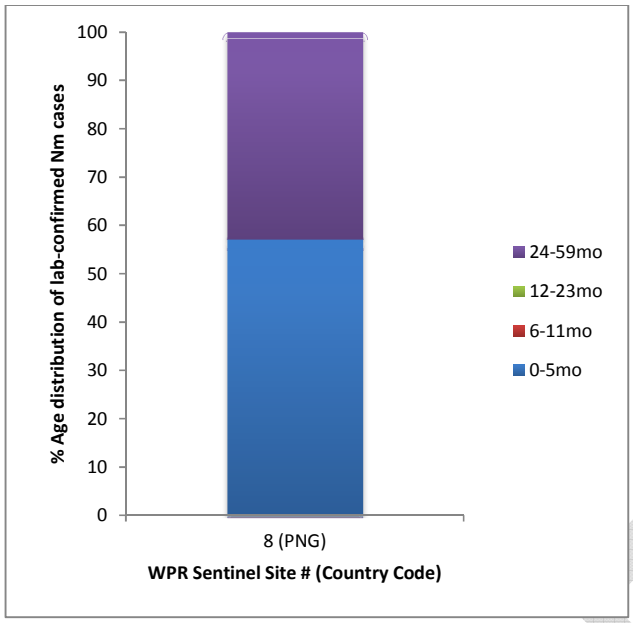


Figure 32. Age distribution of Nm in WPR



Percent Probable bacterial meningitis due to Hi, Spn, Nm organisms

The proportion of causative pathogens of meningitis were examined among PBM cases. Spn was found to be the major organism causing 12.2% (range, 0-61.5%) of PBM cases, followed by *Nm* (3.9%; range, 0-48.8%) and *Hi* (1.7%; range, 0-23.1%) (Table 5). The high percentage of Nm identified in PBM cases at certain sentinel sites in AFRO and AMRO (Figure 20, 21) could be attributed to meningitis outbreaks occurring at these locations.

Table 6. Summary of probable meningitis cases due to Hi, Spn or Nm in category "A" sites, 2010-2012

Region	# of sites that meet criteria	Total # of suspected meningitis cases	Total # of probable meningitis cases*	Total # of probable meningitis cases due to Hi, Spn, or Nm	Mean % probable meningitis cases due to organisms (range)		
					Hi	Spn	Nm
AFR	17	19,294	2,314	497	2.2 (0, 6.4)	12.4 (0, 31.0)	6.9 (0, 48.8)
AMR	---	---	---	---	---	---	---
EMR	11	9,414	1,206	80	0.4 (0, 5.2)	5.5 (0, 17.8)	0.7 (0, 40.0)
EUR	---	---	---	---	---	---	---
SEAR	5	10,783	1,135	242	1.4 (0, 23.1)	18.9 (6, 61.5)	1.0 (0, 15.4)
WPR	1	268	71	21	12.7	11.3	5.6

Total	***34***	***39,759***	***4,726***	***840***	***1.7 (0, 23.1)***	***12.2 (0, 61.5)***	***3.9 (0, 48.8)***

Figure 33. Percent PBM due to Hi, Spn and Nm in AFR

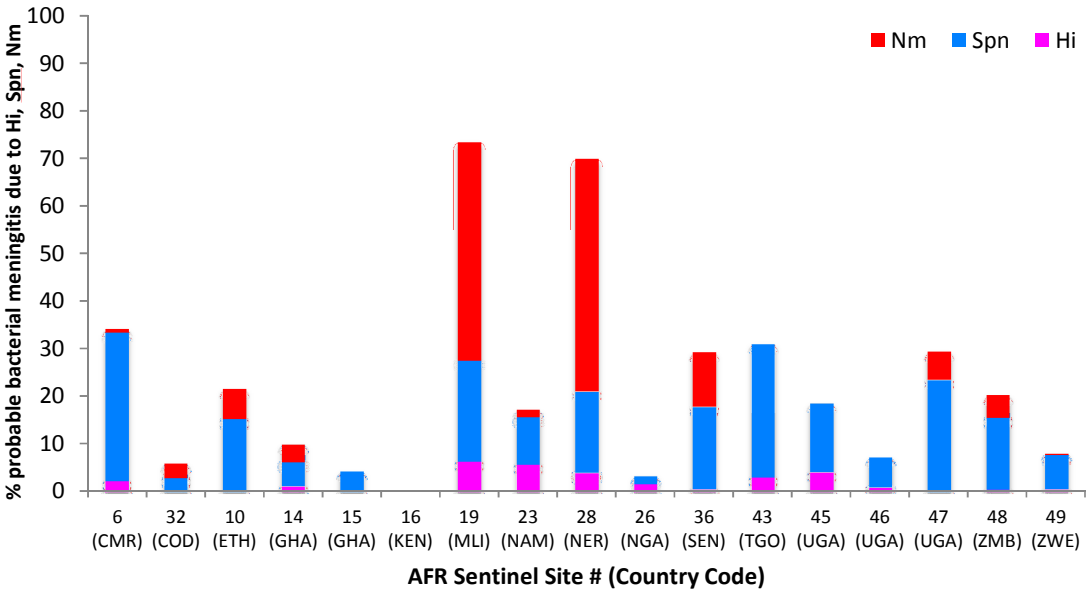


Figure 34. Percent PBM due to Hi, Spn and Nm in EMR

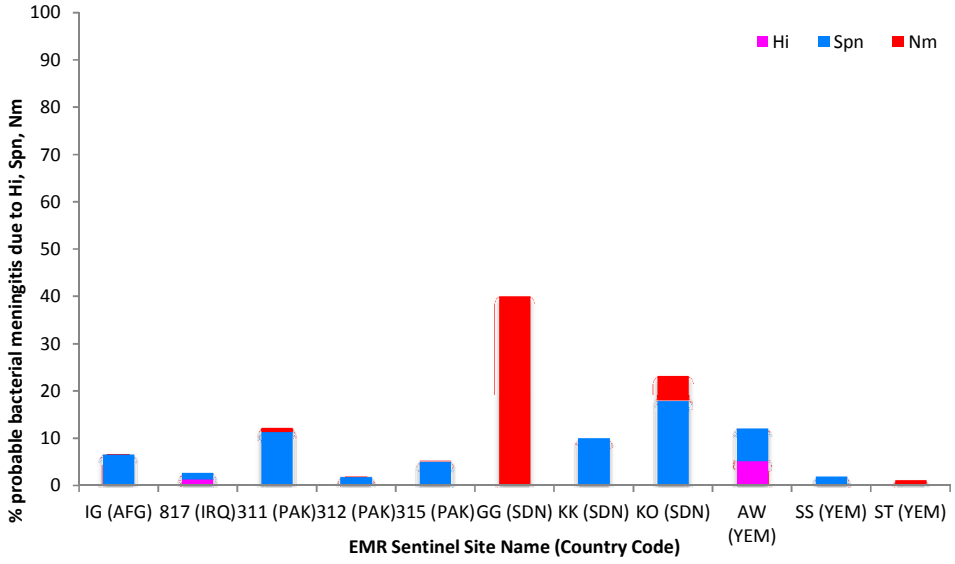


Figure 35. Percent PBM due to Hi, Spn and Nm in SEAR

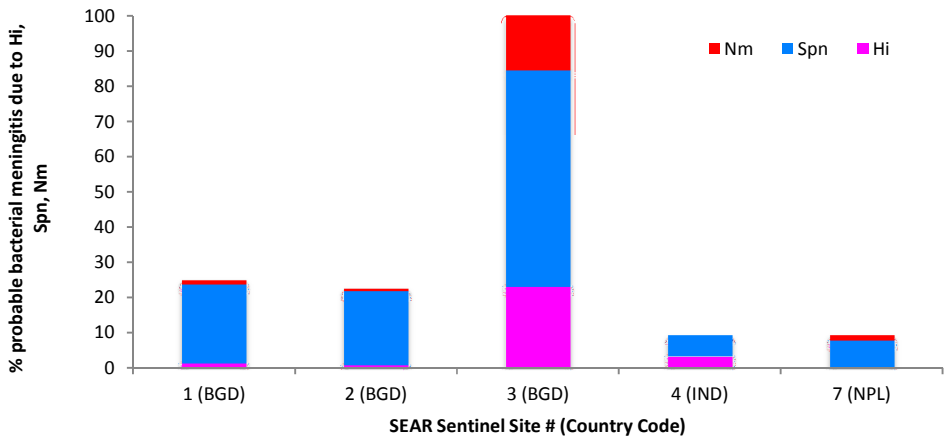
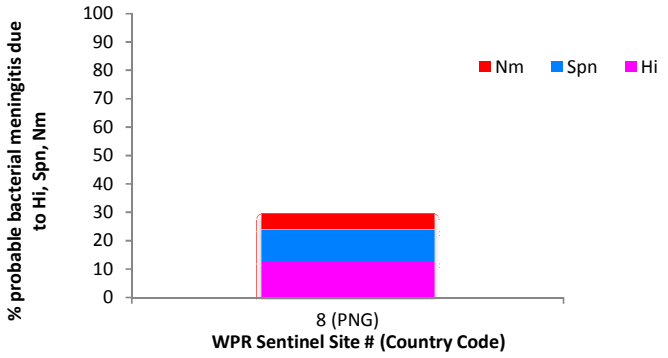


Figure 36. Percent PBM due to Hi, Spn and Nm in WPR



Percent lab-confirmed cases from suspected meningitis cases with an LP

Table 7. Summary of laboratory-confirmed cases from suspected meningitis cases with an LP in category "A" sites, 2010-2012

Region	*# of sites that meet criteria*	*# of suspected meningitis cases that had an LP performed*	*Total # of suspected meningitis cases with Hi, Spn, or Nm detected by a lab method*	*Mean % (range) lab-confirmed cases from suspected meningitis cases with an LP*		
				Hi	*Spn*	*Nm*
AFR	*17*	*19,150*	*815*	*0.4 (0, 2)*	*2.4 (0, 9.1)*	*1.5 (0, 15.7)*
AMR	*---*	*---*	*---*	*---*	*---*	*---*
EMR	*11*	*7,323*	*129*	*0.2 (0, 1.2)*	*1.3 (0, 3.1)*	*0.3 (0, 2.8)*
EUR	*---*	*---*	*---*	*---*	*---*	*---*

SEAR	***5***	***6,455***	***---***	***---***	***---***	***---***
WPR	***1***	***268***	***40***	***7.5***	***5.6***	***1.9***
Total	***34***	***33,196***	***973***	***0.4 (0, 7.5)***	***2.1 (0, 9.1)***	***1.2 (0, 15.7)***

Figure 37. Percent of laboratory-confirmed cases due to Hi, Spn and Nm in AFR

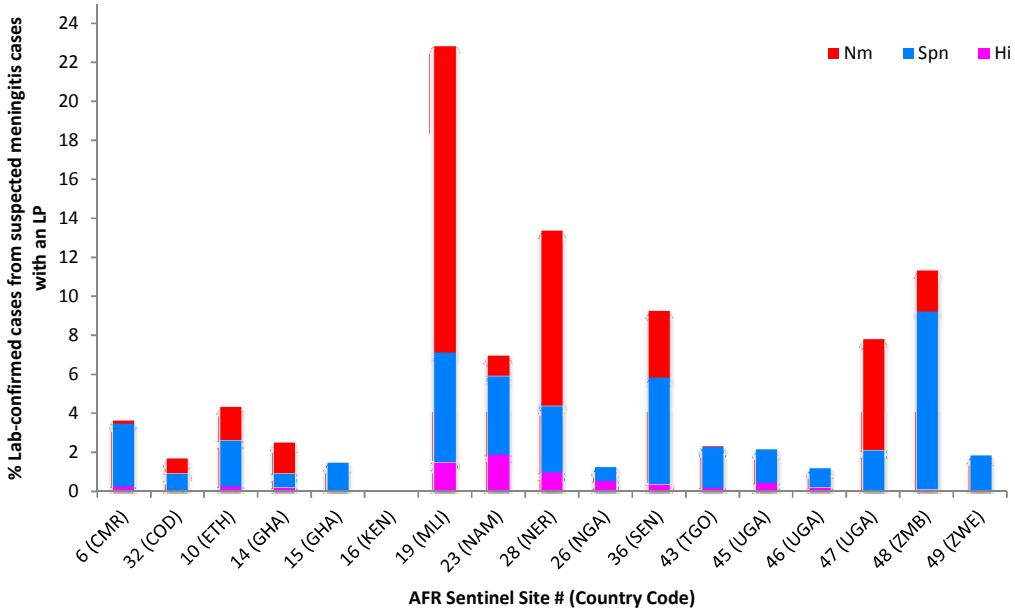


Figure 38. Percent of laboratory-confirmed cases due to Hi, Spn and Nm in EMR

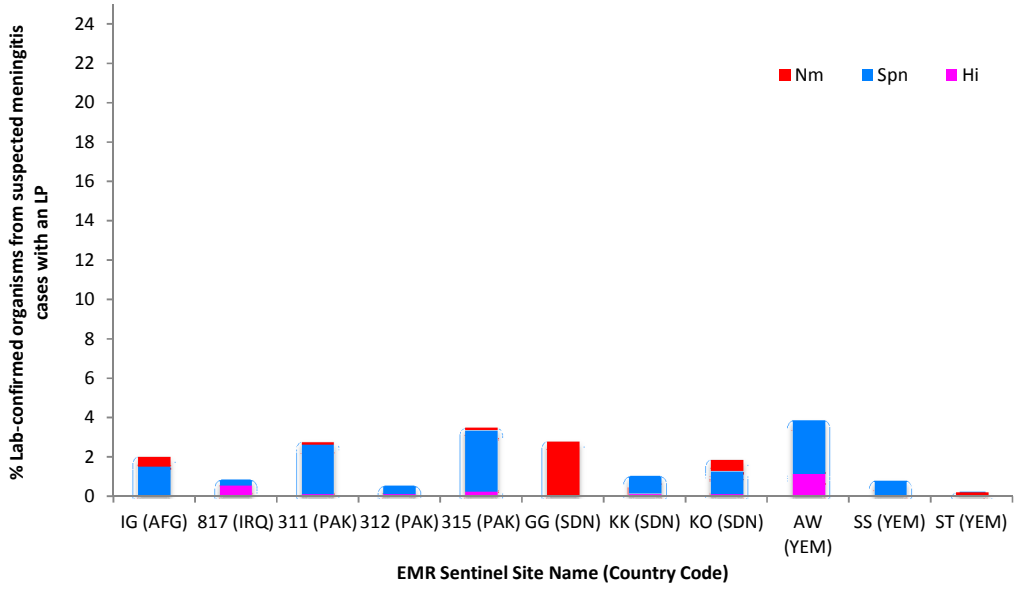
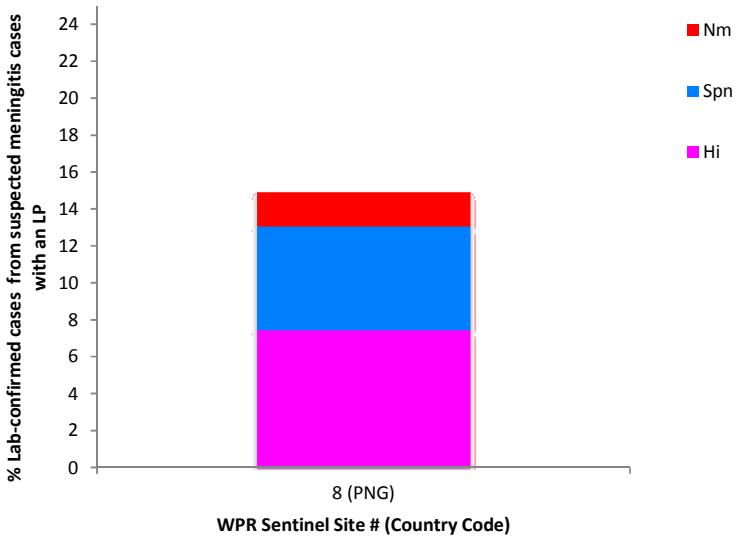


Figure 39. Percent of laboratory-confirmed cases due to Hi, Spn and Nm in WPR



Percent culture-positive suspected meningitis cases with VPD organisms detected by culture

Suspected meningitis cases that returned a result on culture, which was positive for vaccine-preventable disease (VPD) organisms, Hi, *Spn* and Nm, were surveyed across regions. Similar to aforementioned observations, Spn was found to be the major organism in 65.1% (range, 0-100%) of suspected meningitis cases, followed by Nm (24.4%; range, 0-100%) and Hi (10.5%; range, 0-66.6%) (Table 7). The high percentage of Nm identified in suspected meningitis cases at certain sentinel sites in AFRO and AMRO (Figure 27, 28) could be the result of meningitis outbreaks occurring at these locations.

Table 8. Summary of culture-positive suspected meningitis cases with VPD organisms detected in category "A" sites, 2010-2012

Region	*# of sites that meet criteria*	*Total # of suspected meningitis cases*	*Total # of suspected meningitis cases with a positive culture*	*Mean % (range) culture-positive suspected meningitis cases with organism detected by culture*		
				Hi	*Spn*	*Nm*
AFR	*17*	*19,294*	*471*	*10.4 (0, 50.0)*	*62.8 (0, 100.0)*	*26.8 (0, 77.8)*
AMR	*---*	*---*	*---*	*---*	*---*	*---*
EMR	*11*	*9,414*	*112*	*8.9 (0, 66.6)*	*73.2 (0, 100.0)*	*17.9 (0, 100.0)*
EUR	*---*	*---*	*---*	*---*	*---*	*---*
SEAR	*5*	*10,783*	*---*	*---*	*---*	*---*
WPR	*1*	*268*	*19*	*21.1*	*73.7*	*5.3*
Total	*34*	*39,759*	*602*	*10.5 (0, 66.6)*	*65.1 (0, 100.0)*	*24.4 (0, 100.0)*

Figure 40. Percent of culture-positive cases due to Hi, Spn and Nm in AFR

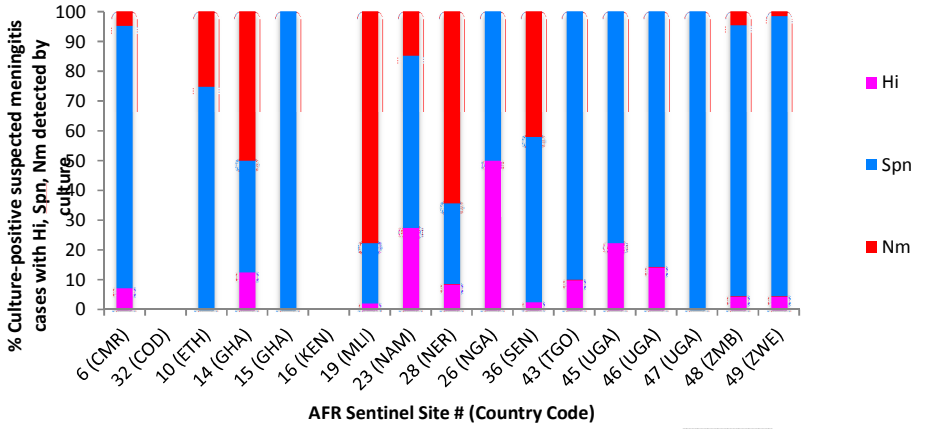


Figure 41. Percent of culture-positive cases due to Hi, Spn and Nm in EMR

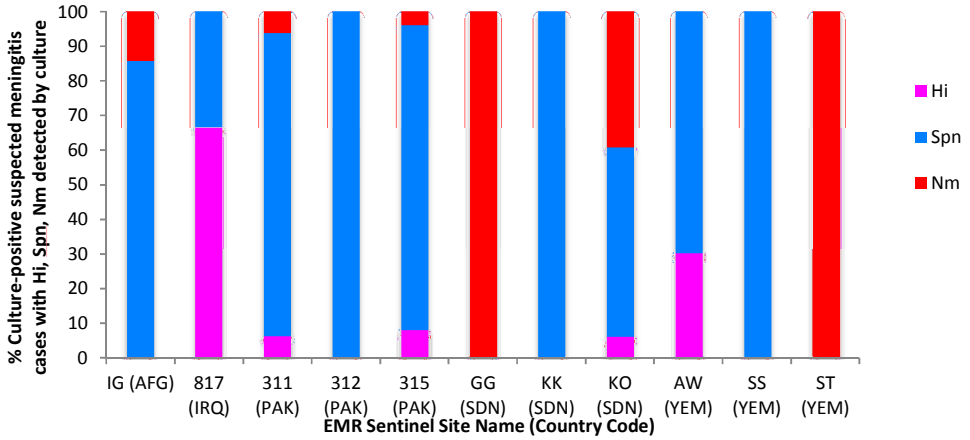
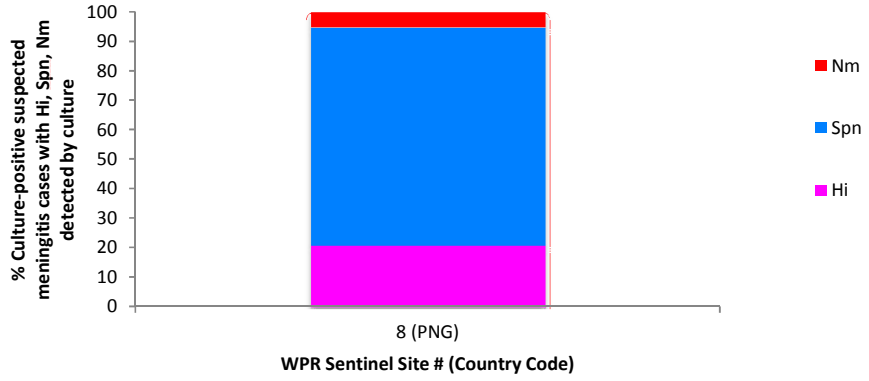


Figure 42. Percent of culture-positive cases due to Hi, Spn and Nm in WPR



Percent Binax positive for Spn from suspected meningitis cases with an LP

In order to improve the yield of detection for Spn, the Binax test was introduced and piloted at the AFRO regional reference laboratory in 2012. Only 0.3% (range, 0-1.8%) of suspected meningitis cases with an LP performed were tested positive for Spn by Binax (Table 8).

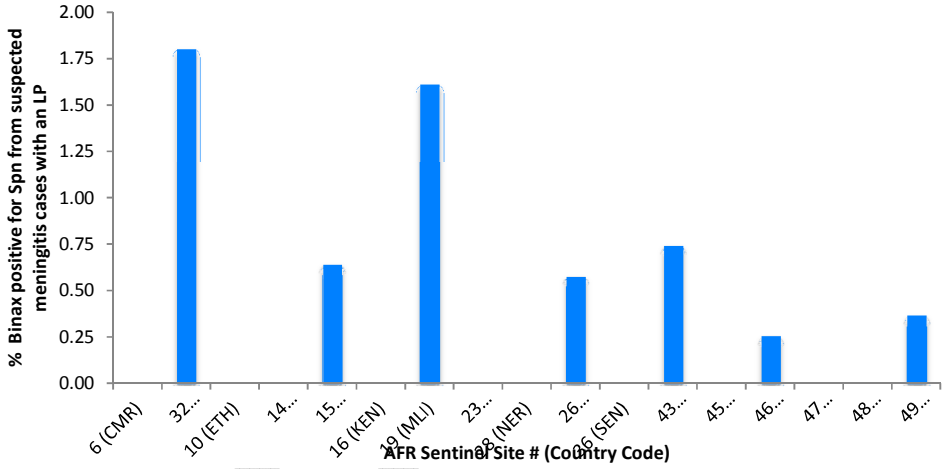
Table 9. Summary of Binax-positive for Spn from suspected meningitis cases with an LP in category "A" sites, 2012

Region	# of sites that meet criteria	# of suspected meningitis cases that had an LP performed	Total # of suspected meningitis cases tested with Binax	Mean % (range) Binax positive for Spn from suspected meningitis cases with an LP
AFR	*17*	*6,061*	*464***	*0.3 (0, 1.8)*
AMR	*---*	*---*	*---*	*---*
EMR	*11*	*2,541*	*---*	*---*
EUR	*---*	*---*	*---*	*---*
SEAR	*5*	*1,356*	*---*	*---*
WPR	*1*	*121*	*---*	*---*
Total	*34*	*10,079*	*464*	*0.3 (0, 1.8)*

* Binax result values are not available for 2010 and 2011 for AFR; All table data is for 2012 only

** Total # of suspected meningitis cases tested with Binax is 466 cases from 2010-2012 for AFR

Figure 43. Percent ofbinax-positive cases in AFR



Percent Latex positive for Hi, Spn, Nm organisms from suspected meningitis cases with an LP

The rapid diagnostic latex agglutination test was utilized to detect VPD organisms in suspected meningitis cases who had an LP performed. Spn was found to be the major organism for 1.2% (range, 0-7.0%) of suspected meningitis cases, followed by Nm (0.7%; range, 0-11.2%) and Hi (0.1%; range, 0-5.6%) as detected by the latex agglutination test (Table 9).

Table 10. Summary of Latex-positive for Hi, Spn or Nm from suspected meningitis cases with an LP in category "A" sites, 2010-2012

Region	# of sites	# of suspected meningitis	Total # of suspected	Mean % (range) latex positive for organisms from suspected meningitis

	that meet criteria	cases that had an LP performed	meningitis cases tested with latex	cases with an LP		
				Hi	Spn	Nm
AFR	17	19,150	1,513	0.1 (0, 0.9)	1.1 (0, 7.0)*	0.7 (0, 11.2)
AMR	---	---	---	---	---	---
EMR	11	7,323	3	---	---	---
EUR	---	---	---	---	---	---
SEAR	5	6,455	---	---	---	---
WPR	1	268	32	5.6	4.5	1.9
Total	34	33,196	1,548	0.1 (0, 5.6)	1.2 (0, 7.0)	0.7 (0, 11.2)

Figure 44. Percent of latex-positive cases due to Hi, Spn and Nm in AFR

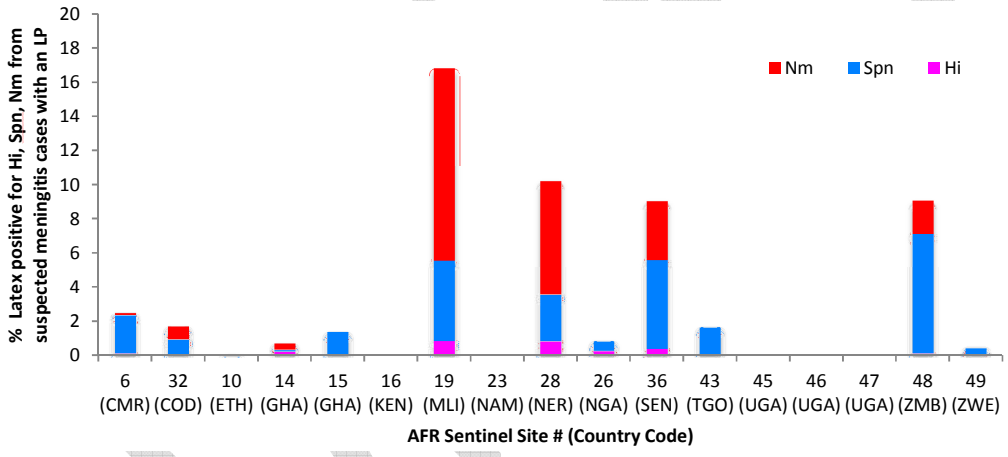
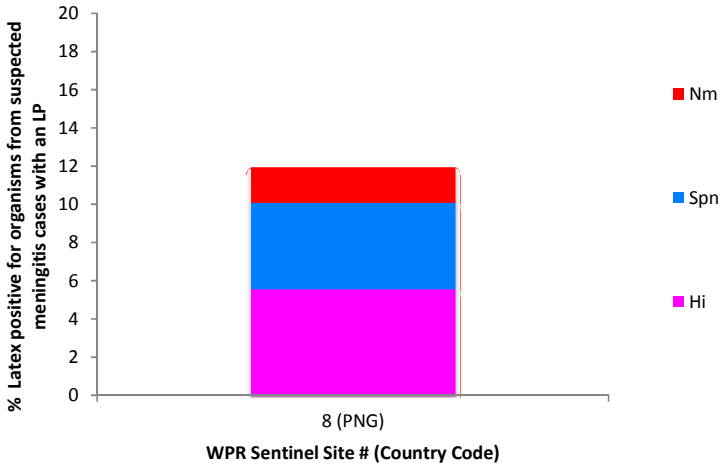


Figure 45. Percent of latex-positive cases due to Hi, Spn and Nm in WPR



Percent PCR positive for Hi, Spn, Nm organisms from suspected meningitis cases with an LP

PCR was employed in 2 regions, AFR and EMR, during the period 2010-2012, to detect VPD organisms from suspected meningitis cases who had an LP performed. 0.3% (range, 0-2.5%) of suspected meningitis cases had Spn detected by PCR, which was similar for Nm (0.3%; range, 0-8.9%), while 0.1% of cases (range, 0-1.4%) had Hi detected by PCR (Table 10).

Table 11. Summary of PCR-positive for Hi, Spn or Nm from suspected meningitis cases with an LP in category "A" sites, 2010-2012

Region	# of sites that meet criteria	# of suspected meningitis cases that had an LP performed	Total # of suspected meningitis cases tested with PCR	Mean % (range) PCR positive for organisms from suspected meningitis cases with an LP		
				Hi	Spn	Nm
AFR	17	19,150	862	0.1 (0, 1.4)	0.3 (0, 2.5)**	0.3(0, 8.9)
AMR	---	---	---	---	---	---
EMR	11	7,323	308	0.05	0.15 (0, 0.44)	0.01 (0, 0.04)
EUR	---	---	---	---	---	---
SEAR	5	6,455	---	---	---	---
WPR	1	268	---	---	---	---
Total	34	33,196	862	0.1 (0, 1.4)	0.3 (0, 2.5)	0.3 (0, 8.9)

* PCR data for AFR is only available for 2011-2012

** For Comparison with Binax data: Year 2012 Mean % PCR positive for Spn from suspected meningitis cases with an LP for AFR region is 0.6

Figure 46. Percent of PCR-positive cases due to Hi, Spn and Nm in AFR

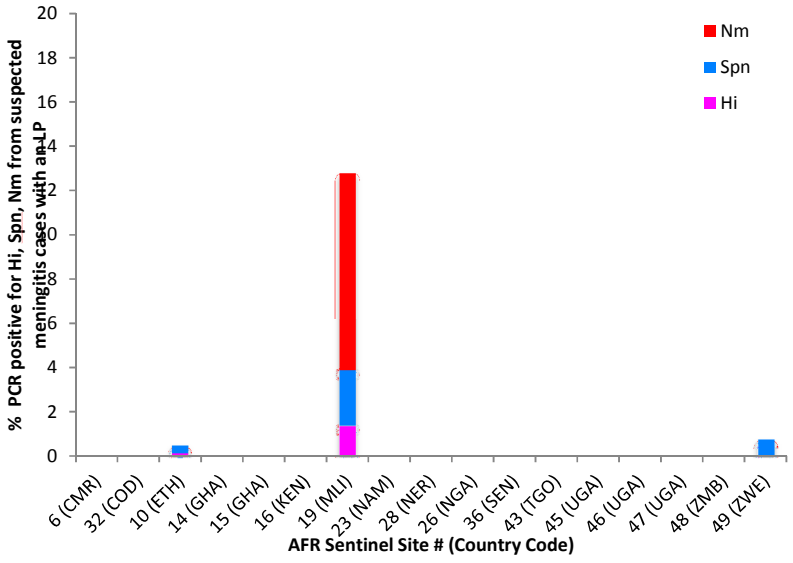
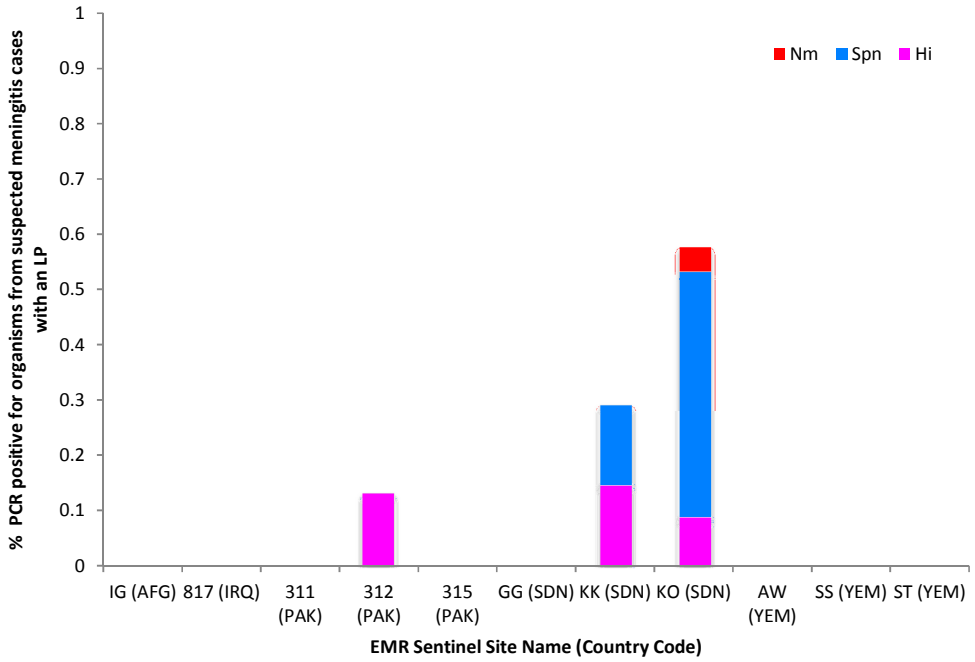


Figure 47. Percent of PCR-positive cases due to Hi, Spn and Nm in EMR



Percent of suspected meningitis cases of known outcome that died (CFR)

The percentage of suspected meningitis cases with known outcome who died (i.e. case fatality rate) of meningitis among suspected meningitis cases across all regions was 3.8% (mean, 4.6%; range, 0-100%) (Table 11). The AFR region was observed to have a higher CFR compared to the other regions.

Table 12. Summary of suspected meningitis cases with a known outcome that died (CFR) in category "A" sites, 2010-2012

Region	# of sites that meet criteria	Total # of suspected meningitis cases	Total # of meningitis cases of known outcome	Total # of meningitis deaths	Mean % of meningitis deaths of known outcome	Median % of meningitis deaths of known outcome	Range % of meningitis deaths of known outcome
AFR	*17*	*19,294*	*13,164*	*981*	*7.5*	*7.6*	*(0, 100.0)*
AMR	*---*	*---*	*---*	*---*	*---*	*---*	*---*
EMR	*11*	*9,414*	*6,771*	*127*	*1.9*	*1.2*	*(0, 8.4)*
EUR	*---*	*---*	*---*	*---*	*---*	*---*	*---*
SEAR	*5*	*10,783*	*10,188*	*290*	*2.8*	*2.8*	*(1.3, 3.5)*
WPR	*1*	*268*	*---*	*---*	*---*	*---*	*---*
Total	*34*	*39,759*	*30,123*	*1,398*	*4.6*	*3.8*	*(0, 100.0)*

Figure 48. Case fatality rate of suspected meningitis cases in AFR

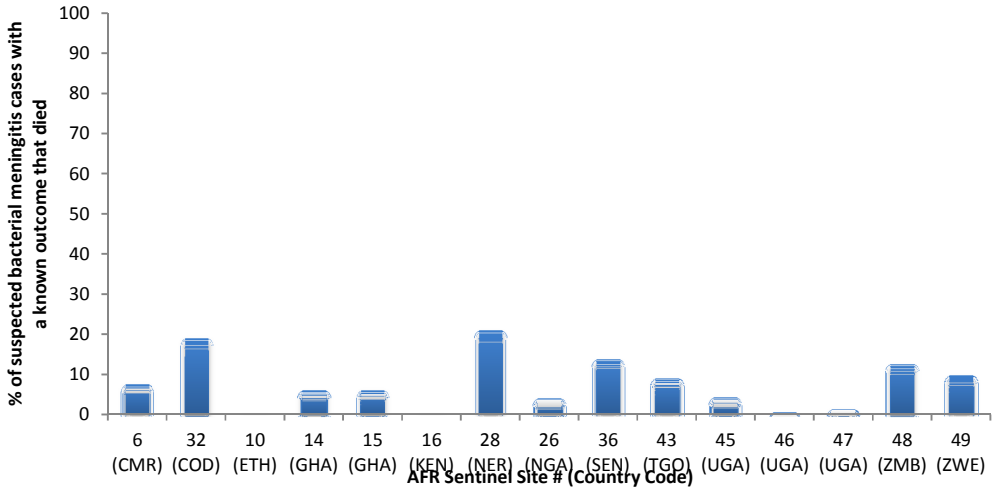


Figure 49. Case fatality rate of suspected meningitis cases in EMR

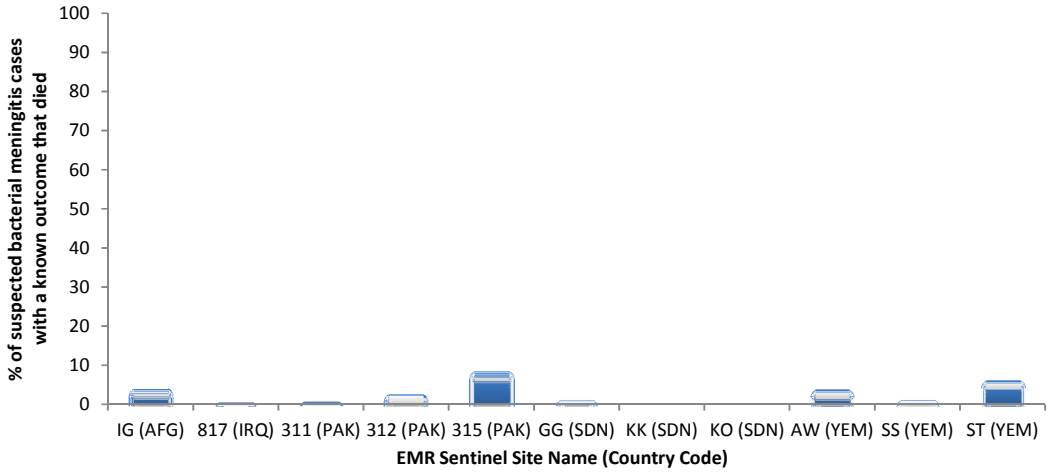
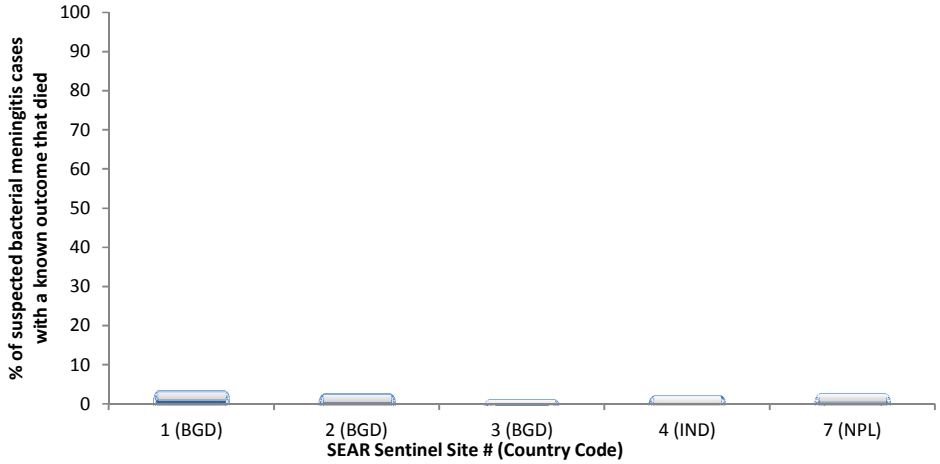


Figure 50. Case fatality rate of suspected meningitis cases in SEAR



Assess disease trends over time

Monthly distribution of suspect and probable meningitis cases, 2010-2012

The monthly distributions of suspected and probable meningitis cases were studied at each sentinel site over the period of 2010-2012. This would allow the elucidation of seasonal trends, and possibly the impact of introductions of vaccine and/or other public health interventions at these sentinel sites. Missing gaps for certain months have prompted the implementation of zero reporting by sentinel sites in 2014, so as to better discriminate between real changes and artifacts of the surveillance system.

Figure 51. Monthly distribution of suspected and probable meningitis cases in AFR (Site #23, NAM)

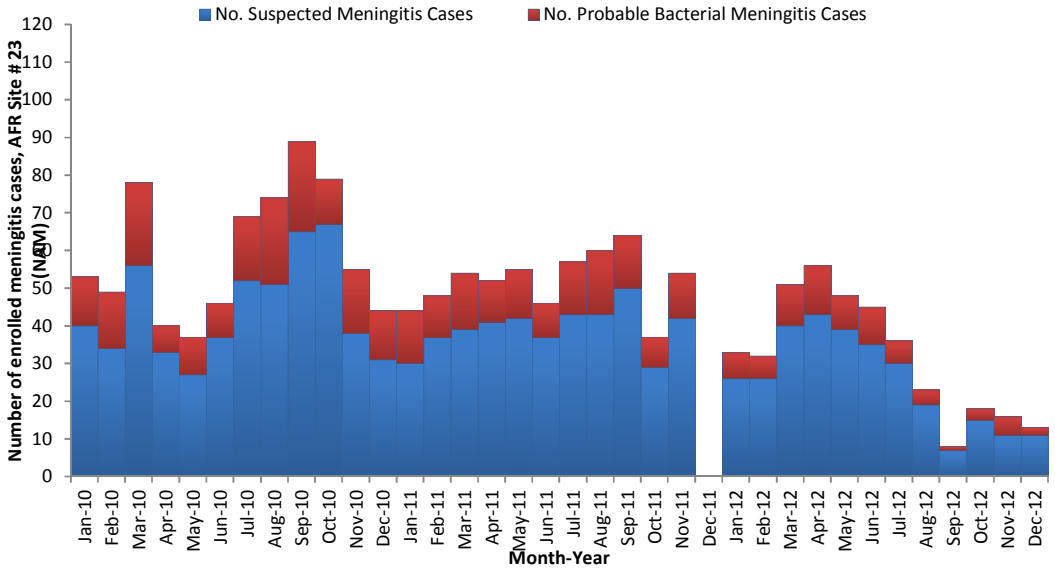


Figure 52. Monthly distribution of suspected and probable meningitis cases in AFR (Site #49, ZWE)

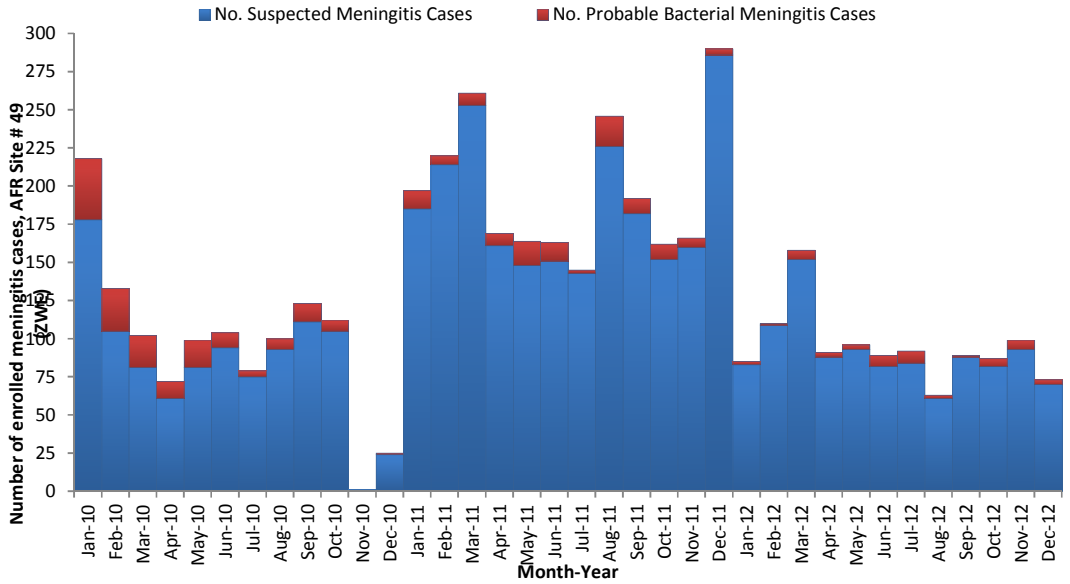


Figure 53. Monthly distribution of suspected and probable meningitis cases in EMR (Site #315, PAK)

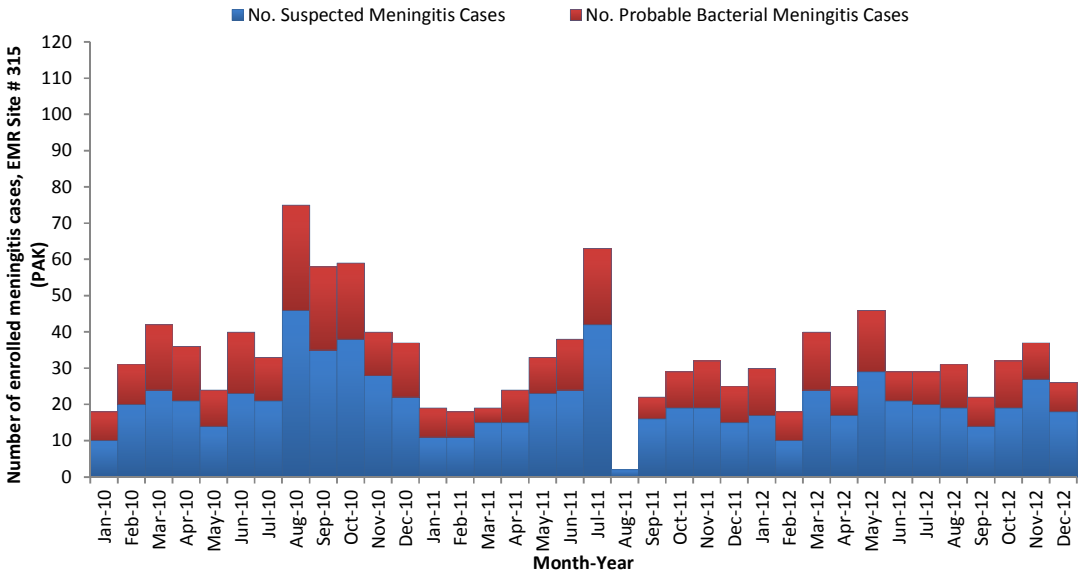


Figure 54. Monthly distribution of suspected and probable meningitis cases in EMR (Site KO, SUD)

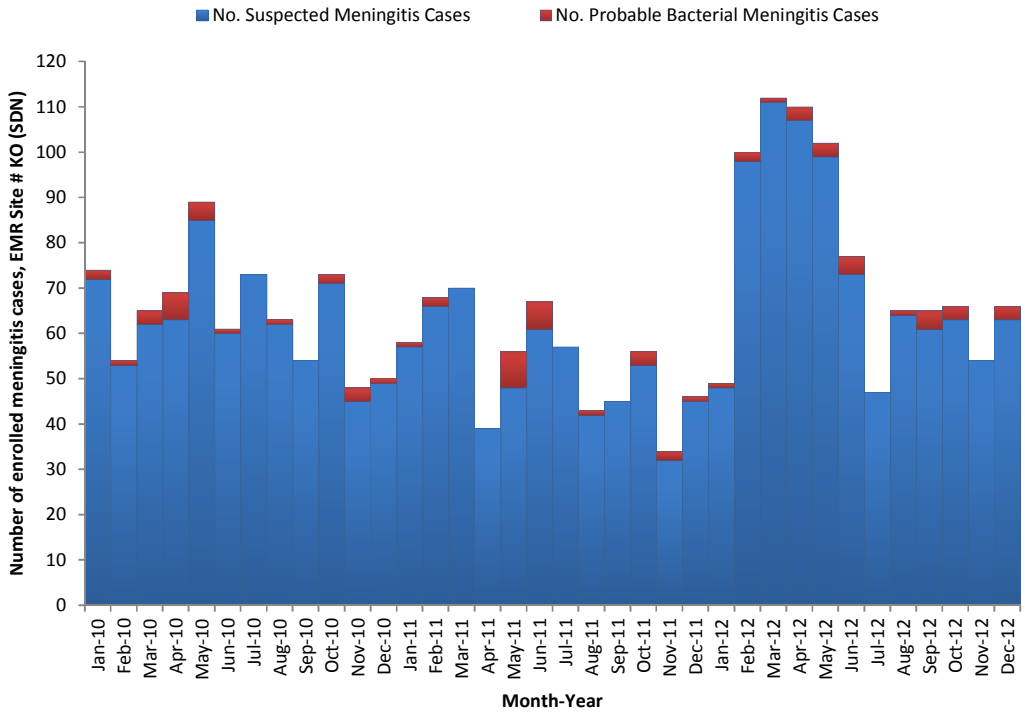
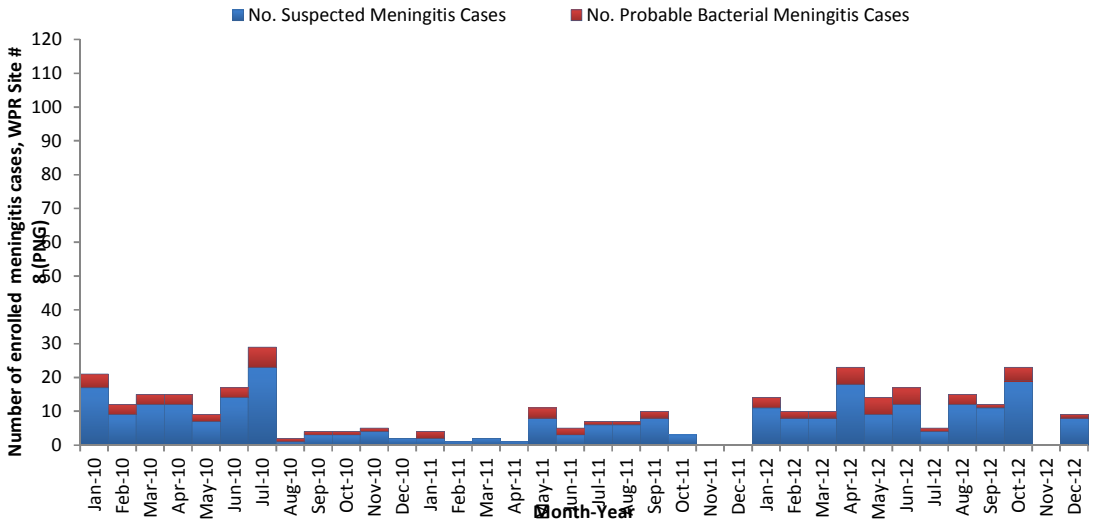


Figure 55. Monthly distribution of suspected and probable meningitis cases in WPR (Site #8, PNG)



Monthly distribution of suspected meningitis cases with lab-confirmed Hi, Spn, Nm, 2010-2012

The monthly distributions of suspected meningitis cases with lab-confirmed Hi, Spn, Nm organisms were examined annually over the period of 2008-2012 for each sentinel site. The seasonal nature of some of these pathogens could be observed at certain sites, and possibly the impact of introductions of vaccine and/or other public health interventions at these sentinel sites as well.

Figure 56. Monthly distribution of laboratory-confirmed meningitis cases in AFR (Site #23, NAM)

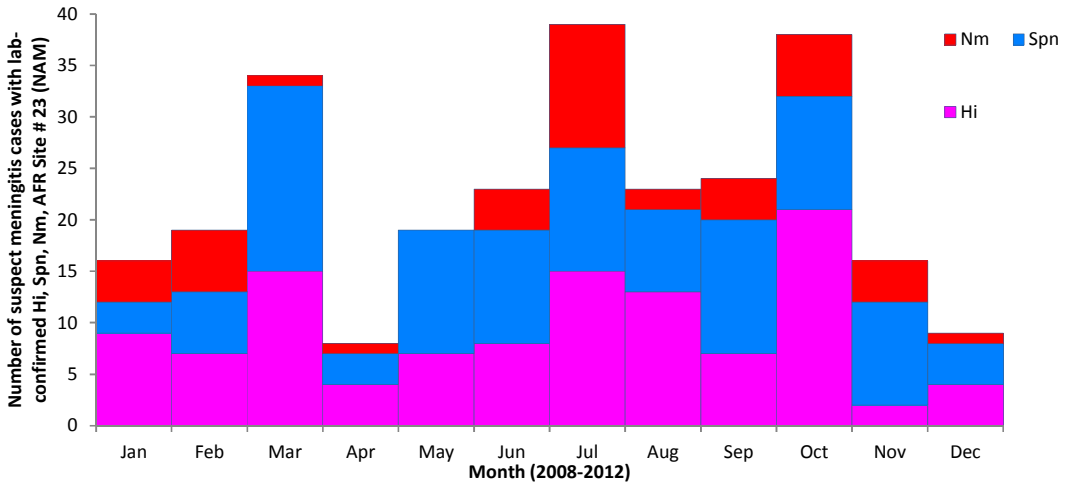


Figure 57. Monthly distribution of laboratory-confirmed meningitis cases in AFR (Site #49, ZWE)

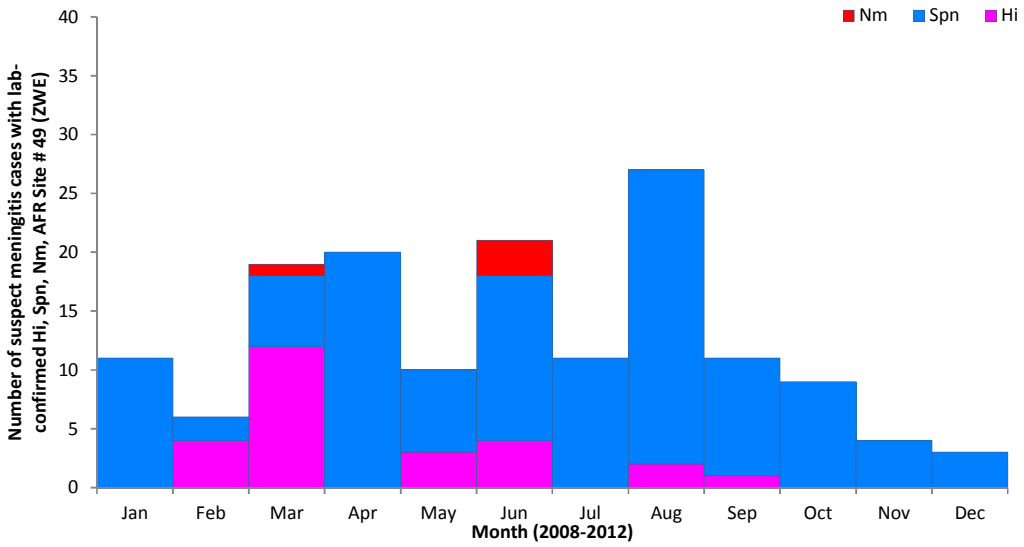


Figure 58. Monthly distribution of laboratory-confirmed meningitis cases in EMR (Site #315, PAK)

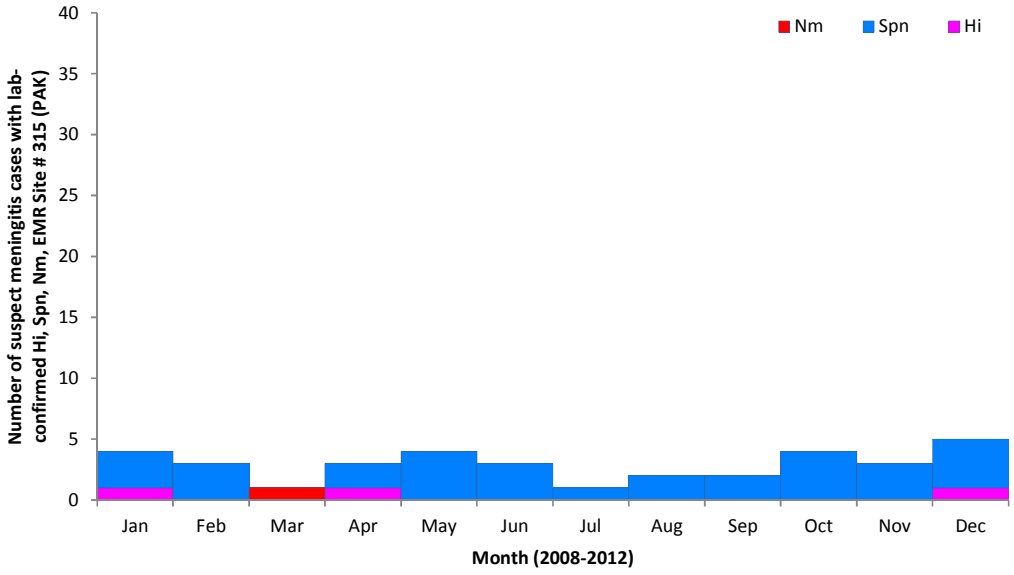


Figure 59. Monthly distribution of laboratory-confirmed meningitis cases in EMR (Site KO, SDN)

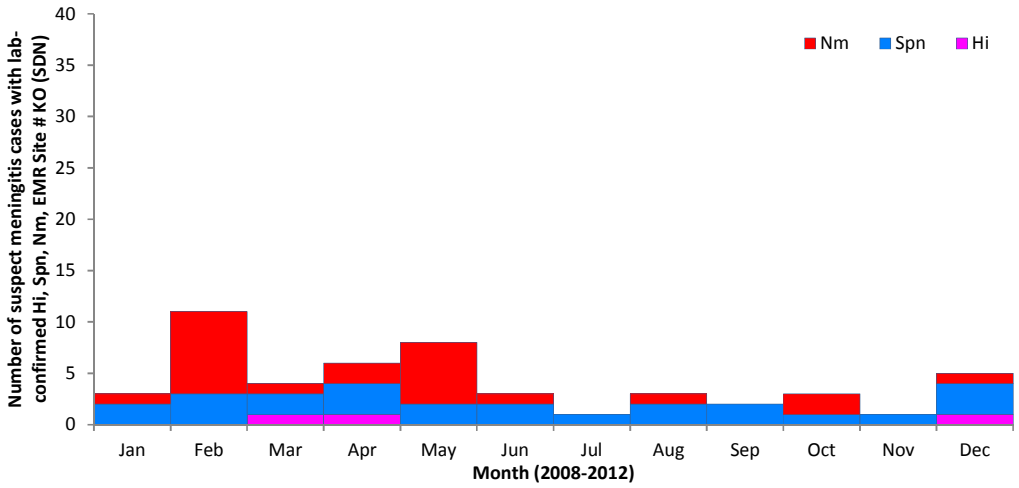
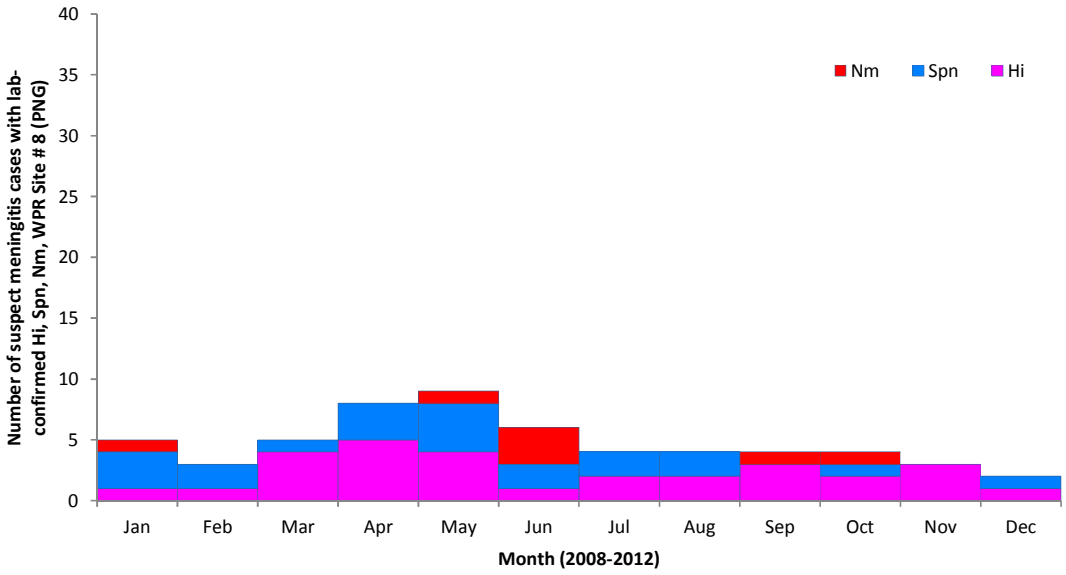


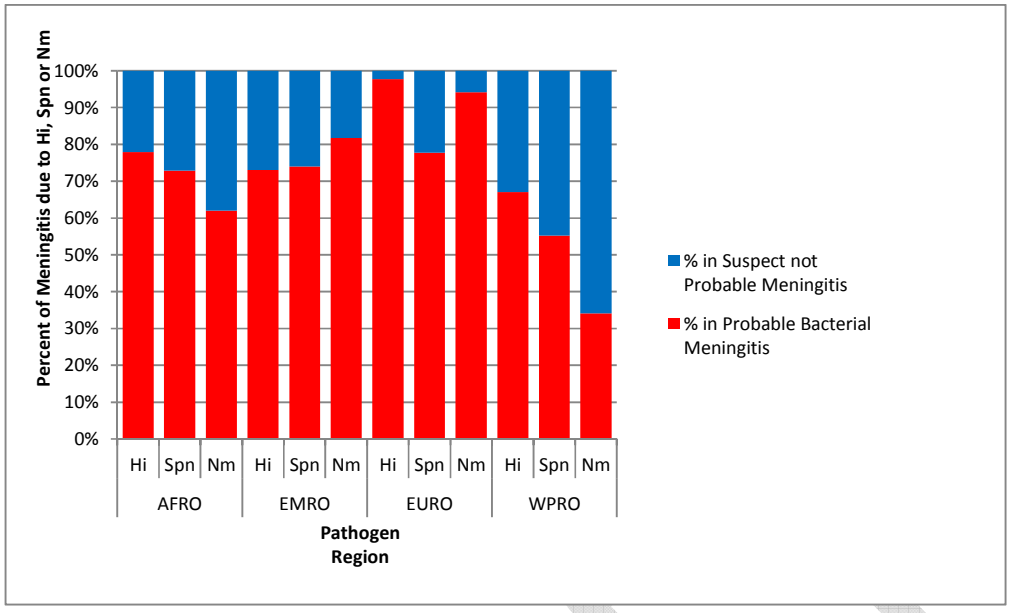
Figure 60. Monthly distribution of laboratory-confirmed meningitis cases in WPR (Site #8, PNG)



Lab confirmed cases : Percent Hi, Spn and Nm found in Probable or Suspect not Probable Meningitis

The percent of lab confirmed pathogens in cases categorized as probable bacterial meningitis and suspect not probable meningitis cases was analyzed for the years 2008-2012 in the four regions with case-based data. The cases in this analysis did not include those that did not have data to categorize probable bacterial meningitis status. The percent of pathogens found was consistently higher in cases that were categorized as probable meningitis, except for Nm in WPRO where less than 40% of lab-confirmed Nm cases were in probable meningitis cases.

Figure 61. The percent of lab confirmed pathogens in probable versus suspect not probable meningitis cases.



Serotype and Serogroup Data, Meningitis surveillance, 2010-2012

The IB-VPD surveillance network aims to determine the serotype / serogroup of all identified bacterial pathogens. The following figures present data for selected WHO Regions, stratified by vaccine use at the country level.

Figure 62. Distribution of Spn serotypes in AFRO in countries where PCV is not in use, 2010-2012

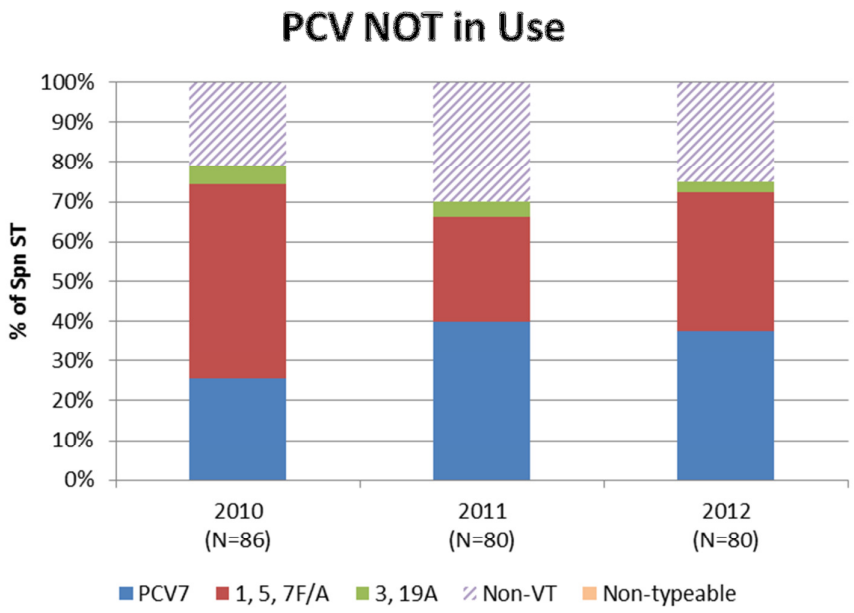


Figure 63. Distribution of Spn serotypes in AFRO in countries where PCV is in use

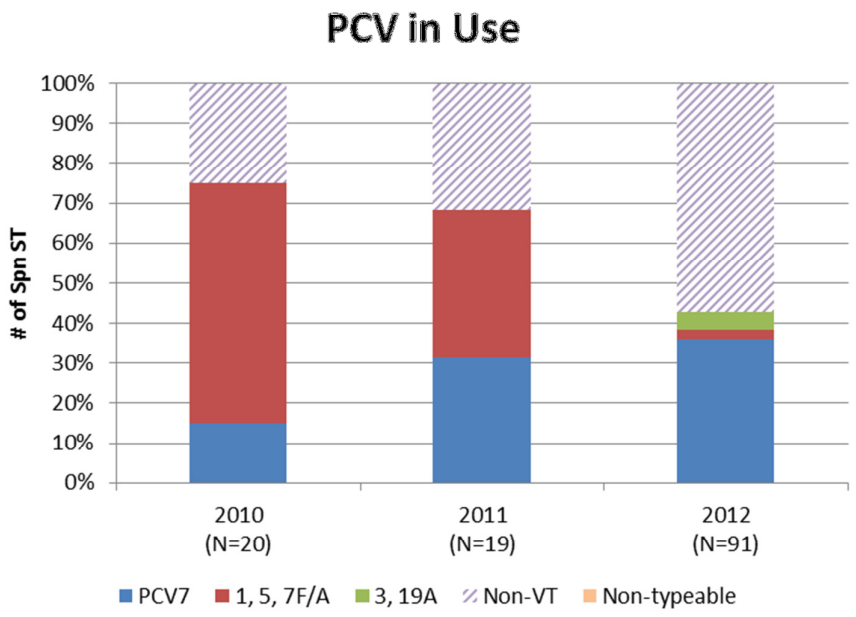
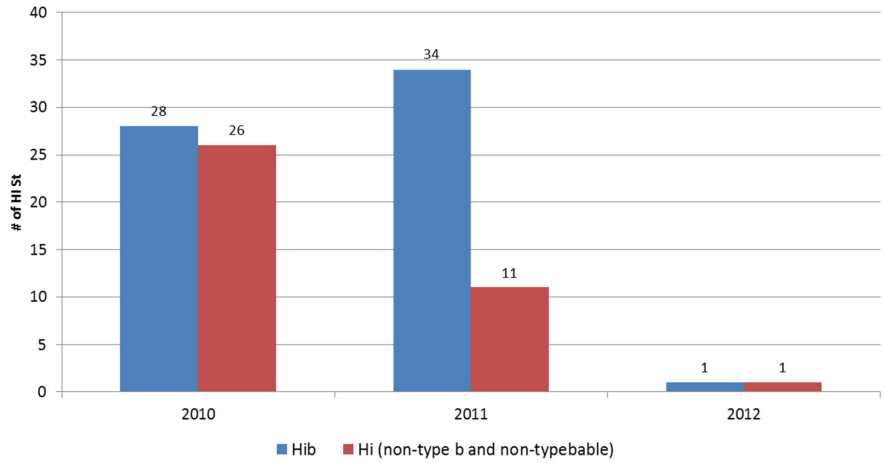


Figure 64. Distribution of Hi Serotypes in AMR Countries with Hib Vaccine Introduced



3. RV SURVEILLANCE NETWORK DATA ANALYSES

METHODS

Components of the RV surveillance network data analyses included assessments of the following:

Category	Data analysis components
Surveillance site data collection and management	• 6 performance indicators • Monthly reporting status • Completeness of reported data
Rotavirus epidemiology	• Rotavirus hospitalizations by age group • Rotavirus case fatality • Rotavirus seasonality
Rotavirus disease trends pre/post-vaccine introduction	• Numbers and % of rotavirus hospitalizations pre- and post-vaccine introduction in countries with sufficient surveillance data
Studies using WHO-coordinated surveillance network data (*available in section 6*)	• Literature review for studies of rotavirus disease burden and vaccine impact from network sentinel sites • Review of completed, ongoing, and planned vaccine impact studies using network sentinel sites

Source of surveillance data

In the fourth quarter of 2013, WHO HQ requested that the ROs submit sentinel site-level rotavirus surveillance data reported to each RO during 2008-2012. Once received, staff at WHO HQ entered these data into the WHO HQ RV surveillance database.

Diarrhea and rotavirus hospitalizations and laboratory data

Data received from the ROs contained sentinel site-level data on the following nine monthly or annual indicators, which are usually reported to WHO HQ in aggregate form by country:

Indicator	Description
1	No. of acute diarrhea hospitalizations in children <5 years eligible for enrollment
2	No. of children meeting the case definition that were enrolled with a case report form (CRF) completed and specimen collected
3	No. of total eligible enrolled (with CRF and specimen collected) acute diarrhea cases that were tested
4	No. of eligible enrolled acute diarrhea cases that tested positive for rotavirus among cases who stool specimen tested
5	No. of laboratory positive rotavirus patients who died
6	No. of cases with stool specimens collected within 2 days of admission
7	No. of stool specimens that arrived at the laboratory for enzyme-linked immunosorbent assay (ELISA) testing
8	No. of received specimens that are ELISA tested in the site laboratory

9 No. of sites that report according to the agreed timeline for that site

Data on these indicators allow for calculation of the rotavirus surveillance performance indicators. Also submitted were laboratory data on rotavirus genotyping.

Determination of inclusion sites

Overall reporting by sentinel surveillance sites during 2008-2012 was assessed. However, as the strategic review was to focus on 'sites most likely to have accomplished the original 2008 surveillance tasks most completely,' only sites that met the following reporting and testing criteria were included in subsequent data analyses:

- Reported ≥10 months of data per year for 2011 and 2012
- Tested ≥100 specimens per year for 2011 and 2012

Data analyses

All analyses were stratified by WHO region and GAVI funding eligibility. As per surveillance network protocol, any country eligible for GAVI support at the start of the WHO-coordinated rotavirus surveillance network has remained eligible for GAVI support; this includes countries that have graduated from GAVI eligibility.

Performance indicators. Rotavirus surveillance performance indicators were calculated for all sites that met the reporting and testing inclusion criteria previously described. The performance indicators calculated were the following:

Performance indicator	Target
% of children meeting the case definition that were enrolled with a case report form completed and specimen collected	80%
% of eligible enrolled acute diarrhea cases that tested positive for rotavirus among cases who had stool specimens tested	20%
% of cases with stool specimens collected with 2 days of admission	90%
% of collected stool specimens that arrive at the laboratory for ELISA testing	95%
% of received specimens that are tested in the site laboratory	90%
% of rotavirus positive (ELISA confirmed) specimens sent to the Regional Reference Laboratory (RRL) that are confirmed positive by the RRL	80%

Monthly reporting status. The percentage of sites reporting data for each month during 2011-2012 was determined for both sites that met reporting and testing criteria and those that had reported any data during 2011-2012.

Rotavirus hospitalizations by age group. The average percentage of eligible enrolled acute diarrhoea cases that tested positive for rotavirus during 2011-2012 was calculated for each age group. Age groups reported to WHO HQ are the following:

Region(s)	Age groups reported

AFR, EMR, EUR, SEAR WPR	0-5 months
	6-11 months
	12-23 months
	24-59 months
	All ≤59 months
AMR	0-11 months
	12-23 months
	24-59 months
	All ≤59 months

Rotavirus case fatality. The average annual percentage of rotavirus positive cases that died was calculated. The age stratification of the total number of cases who died was also assessed.

Rotavirus seasonality. The numbers of rotavirus positive and negative cases and the percentage of rotavirus positive acute diarrhea cases were calculated to assess rotavirus seasonality by region. Given different patterns of seasonality previously reporting in the African Region, rotavirus seasonality was assessed further by the following African sub-regions: West, Central, East, and South.

Rotavirus disease trends pre- and post-vaccine introduction. Rotavirus disease trends pre- and post-vaccine introduction were assessed for two countries for which at least two years of baseline (i.e., pre-vaccine introduction) surveillance data and one year of post-vaccine introduction surveillance data were available during 2008-2012. These countries were Guatemala and Sudan.

SUMMARY OF FINDINGS

Sentinel site reporting and inclusion criteria

During 2008-2012, 265 sites in 67 countries reported any rotavirus surveillance data to WHO, as per the reporting requirements for the strategic review. Applying the reporting and testing inclusion criteria previously described 79 sites in 37 countries were included in the data analyses; 63 of these sites were in 32 GAVI-eligible countries (Table 1). Thirteen of the 37 countries have introduced rotavirus vaccines into their national immunization programmes; 1 country has introduced rotavirus vaccine regionally.

Table 13. Countries and sentinel sites meeting reporting and testing criteria, 2011-2012

Region	# Countries	# (%) GAVI-Eligible Countries	# Sites	# (%) GAVI-Eligible Sites
AFR	13	13(100%)	15	15(100%)
AMR	5	2 (40%)	22	9 (41%)
EMR	4	3 (75%)	12	10 (83%)
EUR	6	6 (100%)	9	9 (100%)

SEAR	3	3 (100%)	5	5 (100%)
WPR	6	5 (83%)	16	15 (94%)
Total	**37**	**32 (86%)**	**79**	**63 (80%)**

Surveillance site data collection and management

Performance indicators

For the percentage of children meeting the case definition that were enrolled with a case report form (CRF) completed and specimen collected, by report, regions varied in their methodology for determining the number eligible and for sampling acute diarrhea cases for testing (Table 2).

Table 14. Percent of eligible children enrolled per month (target >80%) - all inclusions sites, 2011-2012

Region	# sites	Total # eligible	Total # enrolled	Mean %	Median %	Range
AFR	15	14 371	13 568	95%	100%	25%-150%
AMR	22	34 118	14 988	55%	59%	0-100%
EMR	12	18 640	15 642	87%	100%	0-100%
EUR	9	16 951	16 921	100%	100%	86%-100%
SEAR	5	4430	3777	89%	90%	0-186%
WPR	16	15 253	7301	55%	34%	0-186%
Total	**79**	**103 763**	**72 197**	**77%**	**93%**	**0-186%**

For all remaining performance indicators, most regions met the performance indicator targets, although performance did vary by site, as indicated by the ranges seen by region (Tables 3-7). Results did not vary greatly by GAVI funding eligibility status, so results for all inclusion sites presented.

Table 15. Percent of enrolled acute diarrhoea cases that tested rotavirus positive per month (target >20%) - all inclusion sites[1], 2011-2012

Region	# sites	Total # tested	Total # rota(+)	Mean %	Median %	Range
AFR	15	13 132	5398	42%	40%	13%-74%
AMR	22	14 988	4054	24%	24%	4%-63%
EMR	12	14 844	5110	36%	33%	10%-74%
EUR	9	16 918	6007	35%	33%	6%-55%
SEAR	5	3749	1634	49%	49%	26%-65%
WPR	16	11 722	5404	42%	43%	14%-64%
Total	**79**	**75 353**	**27 607**	**36%**	**34%**	**4%-74%**

[1]No values calculated for certain sites in AFR (4), AMR (8) and SEAR (5 – 2012 only) due to lack of reporting # cases w/ stool specimens collected w/in 2d of admission

Table 16. Percent of enrolled cases with stool specimen collected within 2 days of admission per year (target: >90%) - all inclusion sites[1], 2011-2012

Region	# sites	Total # enrolled	Total # specs in 2d	Mean %	Median %	Range
AFR	15	13 570	9781	96%	97%	72%-100%
AMR	22	14 988	10 993	100%	100%	100%
EMR	12	15 642	14 101	93%	95%	0-137%
EUR	9	16 921	16 762	99%	100%	94%-100%
SEAR	5	3777	1912	95%	95%	89%-100%
WPR	16	12 271	11 237	90%	95%	51%-100%
Total	**79**	**77 169**	**64 786**	**95%**	**98%**	**0-137%**

[1]No values calculated for certain sites in AFR (4), AMR (8) and SEAR (5 – 2012 only) due to lack of reporting # cases w/ stool specimens collected w/in 2d of admission; no values calculated for EUR as specimens for all sites sent to referral lab for testing

Table 17. Percent of stool specimens that arrive at the lab for testing per year (target >95%) - all inclusion sites[1], 2011-2012

Region	# sites	Total # enrolled	Total # specs at lab	Mean %	Median %	Range
AFR	15	13 570	9948	98%	100%	78%-100%
AMR	22	14 988	10 993	100%	100%	100%
EMR	12	15 642	15 414	101%	100%	76%-139%
EUR	9	16 921	NA	NA	NA	NA
SEAR	5	3777	1976	99%	100%	96%-100%
WPR	16	12 271	11 603	92%	100%	46%-100%
Total	**79**	**77 169**	**49 934**	**98%**	**100%**	**46%-139%**

[1]No values calculated for certain sites in AFR (4), AMR (8) and SEAR (5 – 2012 only) due to lack of reporting # stool specimens arriving at lab; no values calculated for EUR as specimens for all sites sent to referral lab for testing

Table 18. Percent of received specimens that are tested per year (target >90%) - all inclusion sites[1], 2011-2012

Region	# sites	Total # specs at lab	Total # tested at lab	Mean %	Median %	Range
AFR	15	9948	9724	99%	100%	90%-101%
AMR	22	10 993	10 993	100%	100%	100%

EMR	12	15 414	4570	52%	68%	0-100%
EUR	9	NA	NA	NA	NA	NA
SEAR	5	1976	1631	56%	35%	205-100%
WPR	16	11 603	11 721	107%	100%	75%-215%
Total	**79**	**49 934**	**38 639**	**89%**	**100%**	**0-215%**

[1]No values calculated for certain sites in AFR (4), AMR (8) and SEAR (5 – 2012 only) due to lack of reporting # stool specimens arrived and tested at lab; no values calculated for EUR as specimens for all sites sent to referral lab for testing

Table 19. Percent of rotavirus positive specimens confirmed by the RRL per year (target >80%) - all inclusion countries[1], 2011-2012

Region	# countries	Total # received by RRL	Total # confirmed by RRL	Mean %	Median %	Range
AFR	12	2359	1535	68%	88%	10%-100%
AMR	4	397	NA	NA	NA	NA
EMR	1	304	NA	NA	NA	NA
EUR	6	1245	1214	97%	98%	91%-101%
SEAR	3	NA	NA	NA	NA	NA
WPR	6	2496	2492	96%	100%	64%-101%
Total	**32**	**6801**	**5241**	**82%**	**98%**	**10%-101%**

[1]Only country-level data available. AFR – 1 country excluded due to lack of data in 2012; AMR/EMR without total no. confirmed by RRL; SEAR – no data for 2012

Monthly reporting status

Overall, the monthly percentage of inclusion sites with data available during 2011 and 2012 was ≥89%. For the majority of months, 99%-100% of sites had data that was reported to WHO HQ. Of those regions with sites that did not provide data for all months, data were missing over various months. Results did not differ greatly by GAVI eligibility status.

Figure 65. Monthly reporting status in all regions

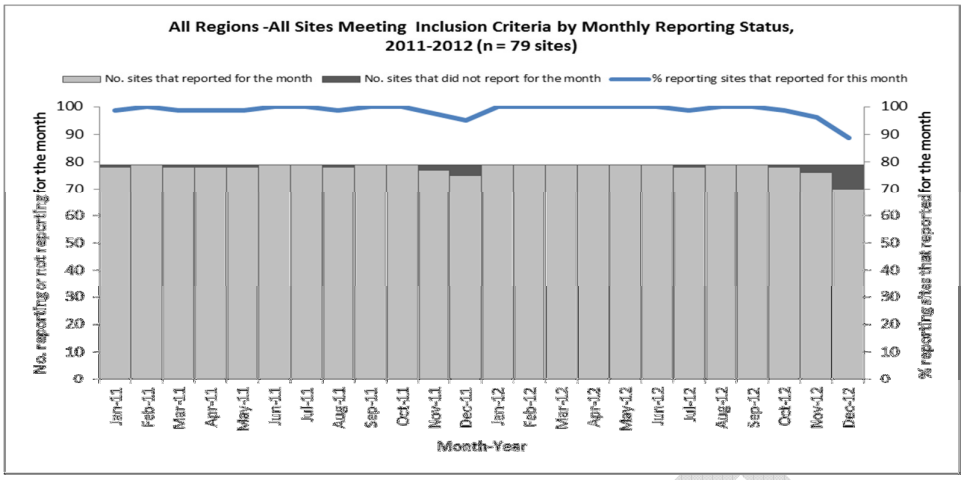


Figure 66. Monthly reporting status in AFR

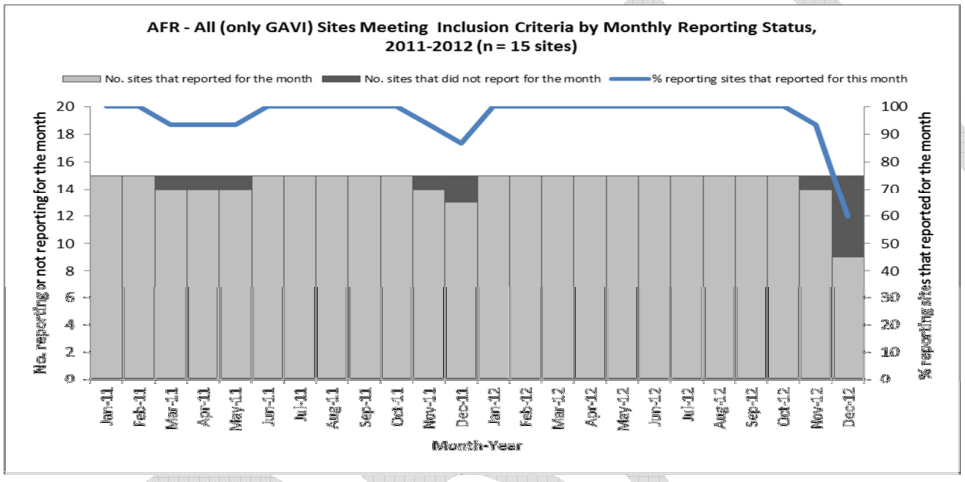


Figure 67. Monthly reporting status in AMR

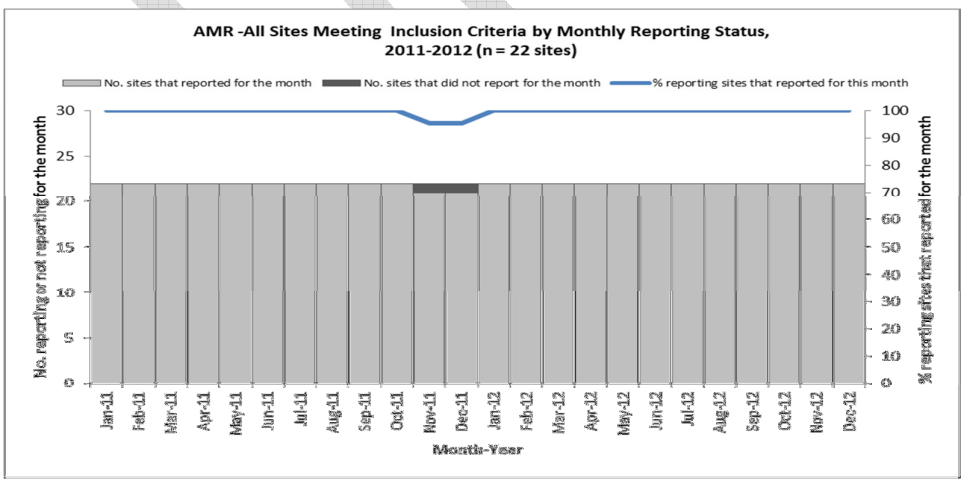


Figure 68. Monthly reporting status in EMR

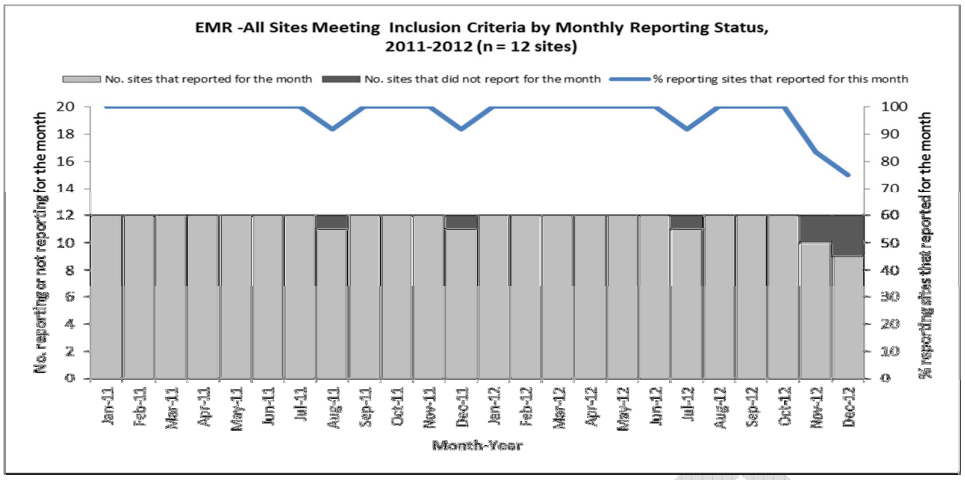


Figure 69. Monthly reporting status in EUR

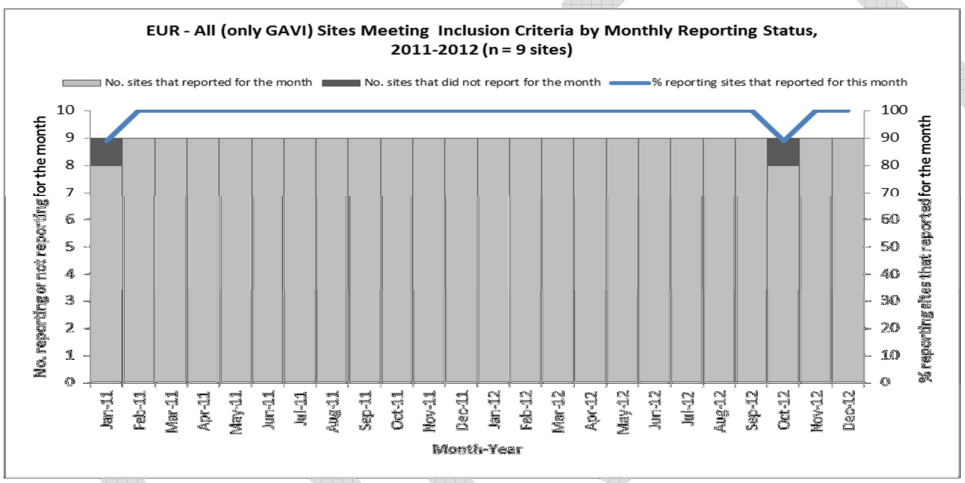


Figure 70. Monthly reporting status in SEAR

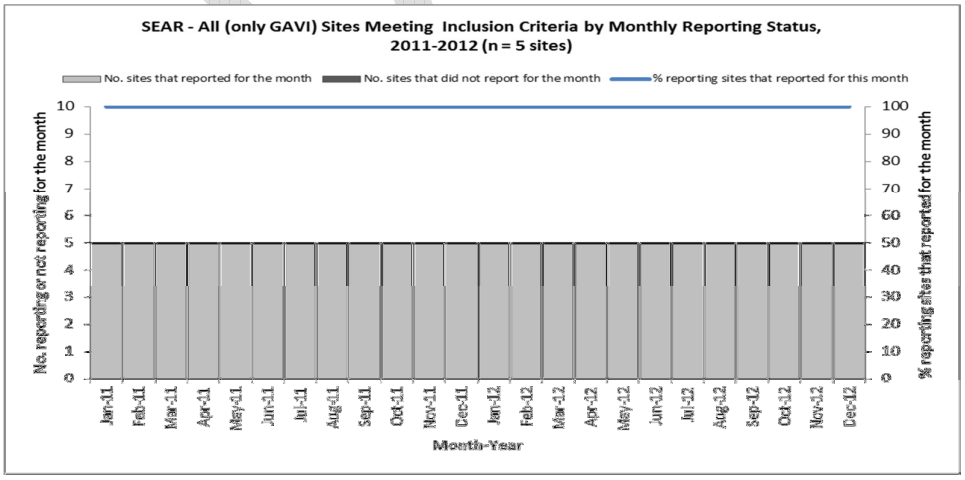
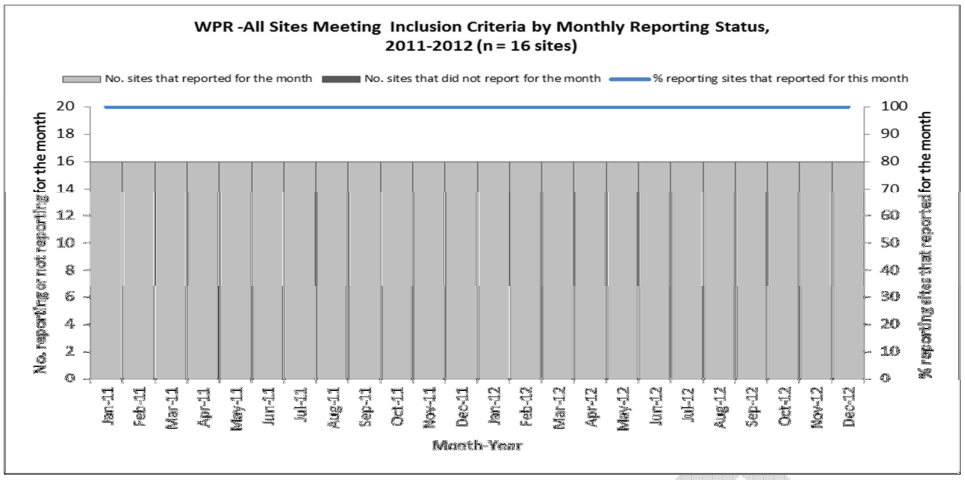


Figure 71. Monthly reporting status in WPR



Rotavirus epidemiology

Rotavirus hospitalizations by age group

The total numbers and mean percentage of diarrhoea hospitalizations due to rotavirus by age group are shown in Tables 8 and 9. Percentages varied by region, with AMR reporting the lowest rates and SEAR reporting the highest rates of rotavirus hospitalizations. Percentages also varied slightly between age groups within each region.

Table 20. Number of diarrhoea hospitalizations due to rotavirus per year, by age group - all inclusion sites, 2011-2012 (AMR reports for age group 0-11 months rather than 0-5 and 6-11 months)

Region	# sites	0-5m		6-11m		12-23m		24-59m		All ≤59m	
		# tested	# pos	# tested	# pos	# tested	# pos	# tested	# pos	# tested	# pos
AFR	15	2856	1311	5234	2427	3678	1355	1364	305	13 132	5398
AMR	22		5677	1265		4044	1107	2187	757	14 988	4054
EMR	12	2982	1113	5335	2027	4491	1458	2036	512	14 844	5110
EUR	9	1497	348	3583	1225	5646	2199	6113	2,206	16 918	6007
SEAR	5	349	168	792	466	1061	505	486	133	3749	1634
WPR	16	2185	775	4486	2151	3710	1965	1298	503	11 722	5404
All	**79**	**9869**	**3715**	**19 430**	**8296**	**22 630**	**8589**	**13 484**	**4416**	**75 353**	**27 607**

Table 21. Mean percent of diarrhoea hospitalizations due to rotavirus per year, by age group - all inclusion sites (AMR reports for age group 0-11 months rather than 0-5 and 6-11 months)

Region	# sites	0-5m		6-11m		12-23m		24-59m		All ≤59m	
		Mean %	Range	Mean %	Range	Mean %	Range	Mean %	Range	Mean %	Range
AFR	15	47%	(14-77)	45%	(19-77)	40%	(13-71)	28%	(6-86)	42%	(13-74)

AMR	22	18% (3-58)				23%	(3-60)	32%	(0-60)	24%	(4-63)
EMR	12	37%	(5-77)	37%	(11-75)	36%	(6-73)	30%	(3-83)	36%	(10-74)
EUR	9	23%	(9-47)	33%	(7-54)	38%	(7-61)	32%	(3-59)	35%	(6-55)
SEAR	5	48%	(32-66)	58%	(43-70)	52%	(30-80)	35%	(8-60)	49%	(26-65)
WPR	16	33%	(5-67)	43%	(13-67)	48%	(18-68)	36%	(10-70)	42%	(14-64)
All	**79**	**37%**	**(5-77)**	**42%**	**(7-77)**	**38%**	**(3-80)**	**32%**	**(0-86)**	**36%**	**(4-74)**

Rotavirus case fatality

Sixty-five deaths among rotavirus positive cases were reported by all sites during 2011-2012. The majority of deaths were reported by AFR and AMR (Table 10).

Table 22. Mean percent of diarrhoea hospitalizations due to rotavirus per year, by age group - all inclusion sites, 2011-2012 (AMR reports for age group 0-11 months rather than 0-5 and 6-11 months)

Region	# sites	Total # rota pos	Total # rota deaths	Mean %	Median %	Range
AFR	15	5398	30	2.3%	1.9%	0.4%-5.9%
AMR	22	7142	21	0.2%	0	0-4.5%
EMR	12	5110	5	0.1%	0	0-0.9%
EUR	9	12 014	3	0.3%	0.3%	0.1%-0.5%
SEAR	5	1634	2	0.4%	0	0-1.1%
WPR	16	5404	4	0.1%	0	0-1.6%
Total	**79**	**36 702**	**65**	**0.4%**	**0**	**0-5.9%**

Age group distribution of the reported deaths shows that the majority of death occurred among children 0-11 months of age (Table 11):

Table 23. Age distribution of rotavirus deaths - all inclusion sites, 2011-2012 (AMR reports for age group 0-11 months rather than 0-5 and 6-11 months)

Age group	No. of deaths	% total rotavirus deaths
0-5m	15	23%
6-11m	27	42%
0-11m	3	4%
12-23m	16	25%
24-59m	4	6%
Unknown	0	0
Total	**65**	**100%**

Rotavirus seasonality

Rotavirus seasonality differed by region (Figures 8-13) and by AFR sub-region (Figures 14-17). Seasonal peaks were seen in more obviously in AMR, EUR, WPR and the AFR South sub-region.

Figure 72. Rotavirus seasonality in AFR

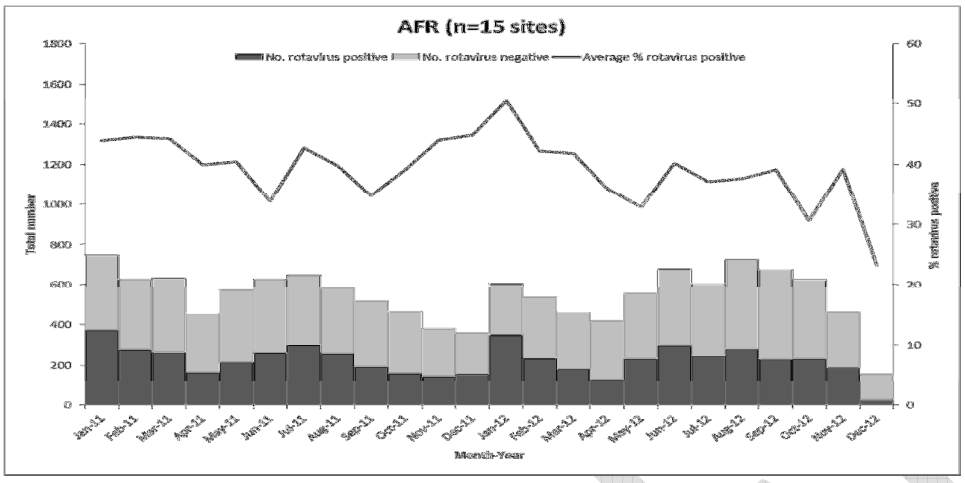


Figure 73. Rotavirus seasonality in AMR

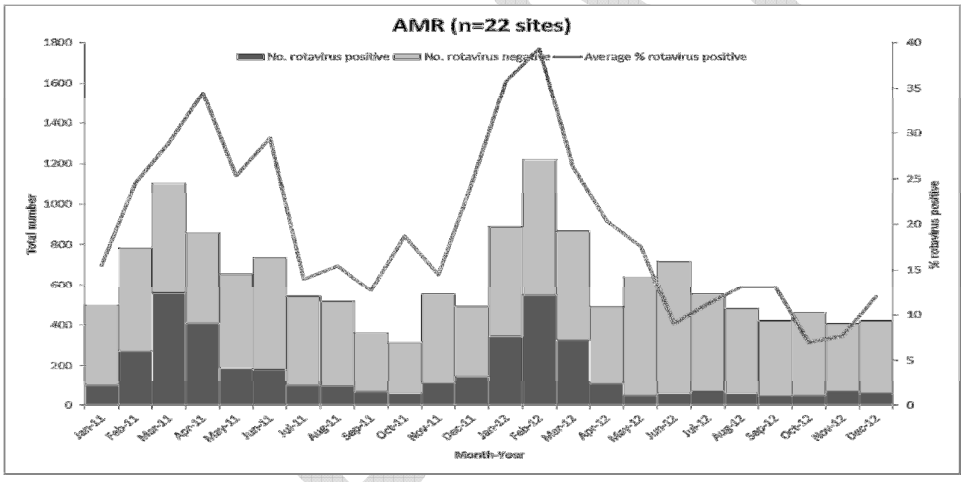


Figure 74. Rotavirus seasonality in EMR

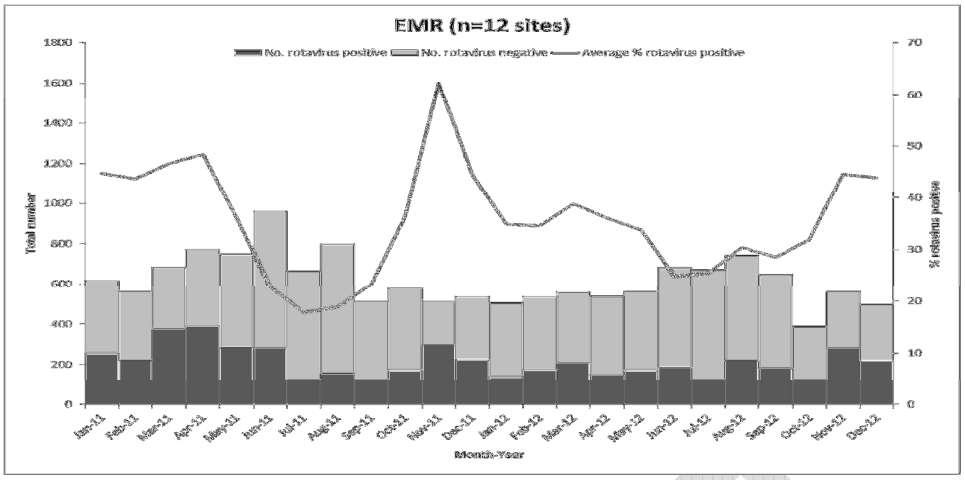


Figure 75. Rotavirus seasonality in EUR

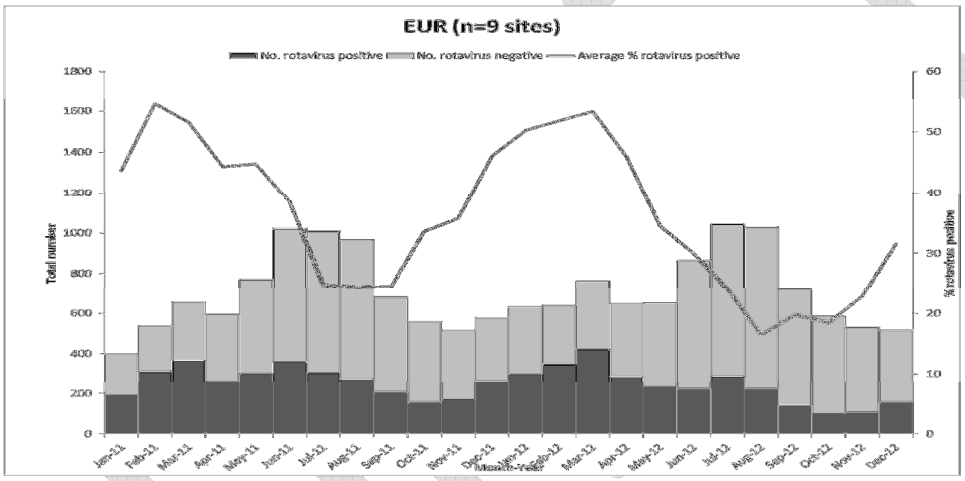


Figure 76. Rotavirus seasonality in SEAR

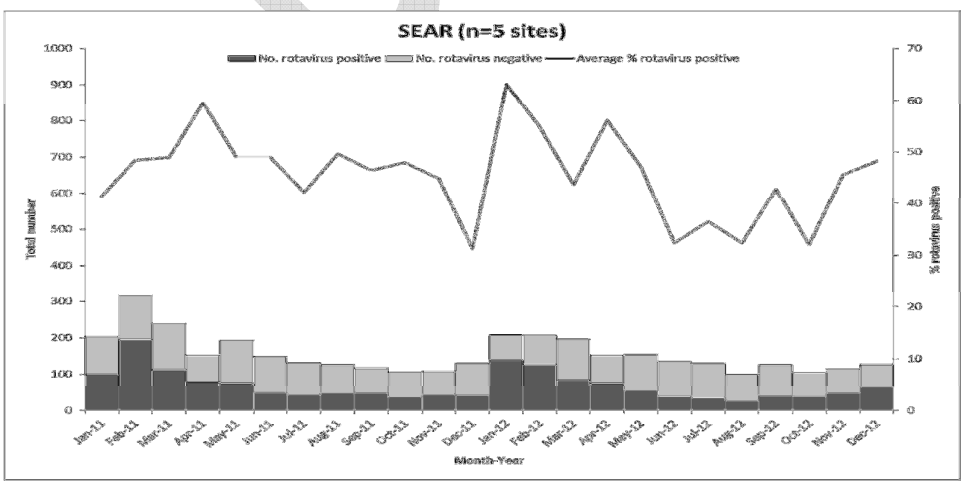


Figure 77. Rotavirus seasonality in WPR

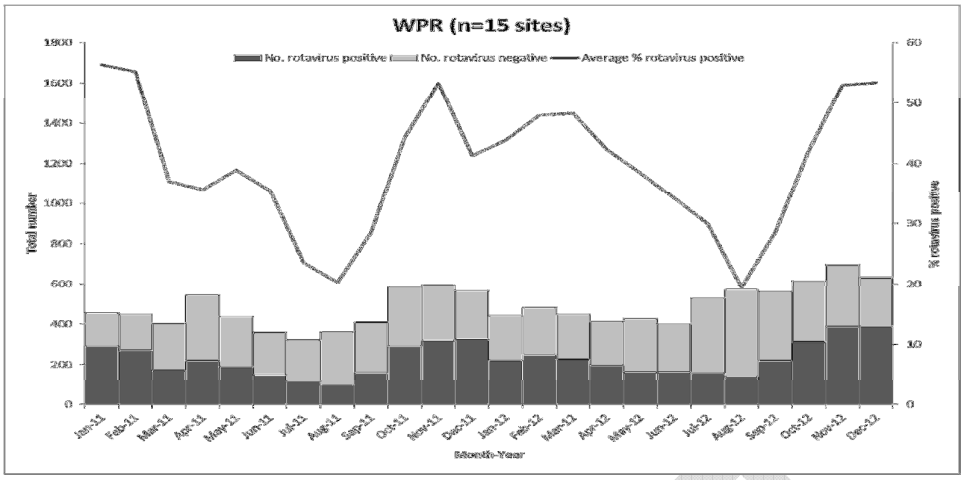


Figure 78. Rotavirus seasonality in AFR West - includes Ghana, Guinea Bissau, Nigeria, Senegal and Togo

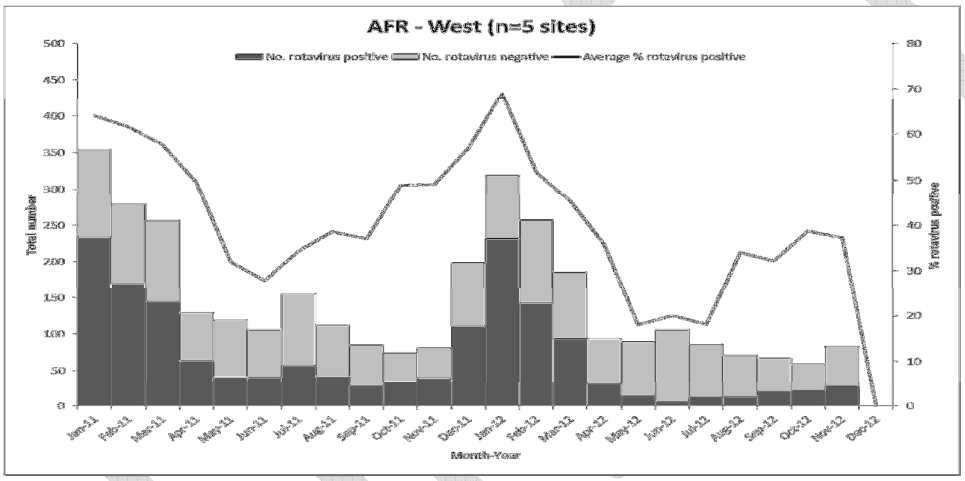


Figure 79. Rotavirus seasonality in AFR Central - includes Cameroon and the Democratic Republic of the Congo

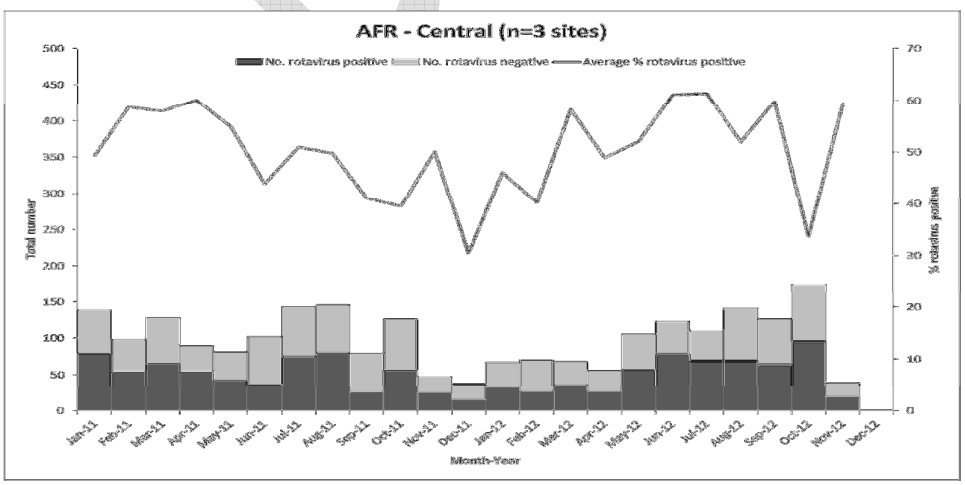


Figure 80. Rotavirus seasonality in AFR East - includes Ethiopia, Kenya, Rwanda and Uganda

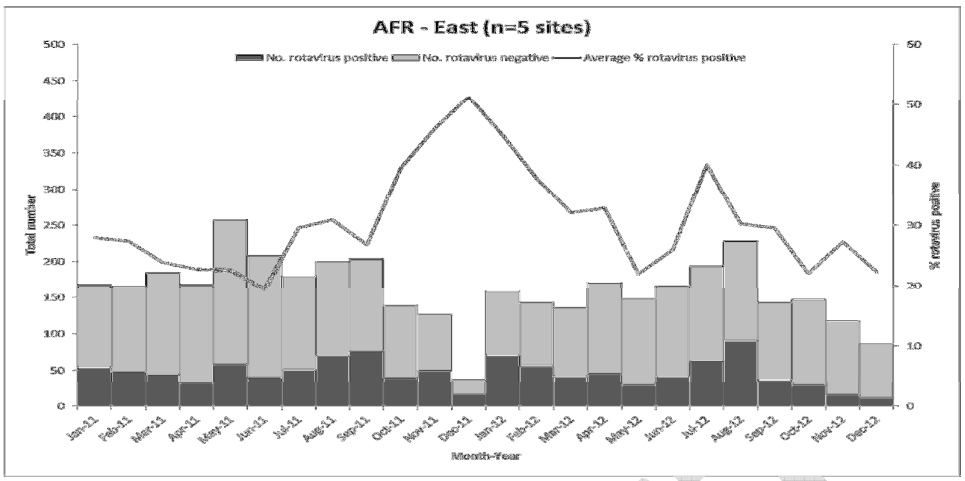
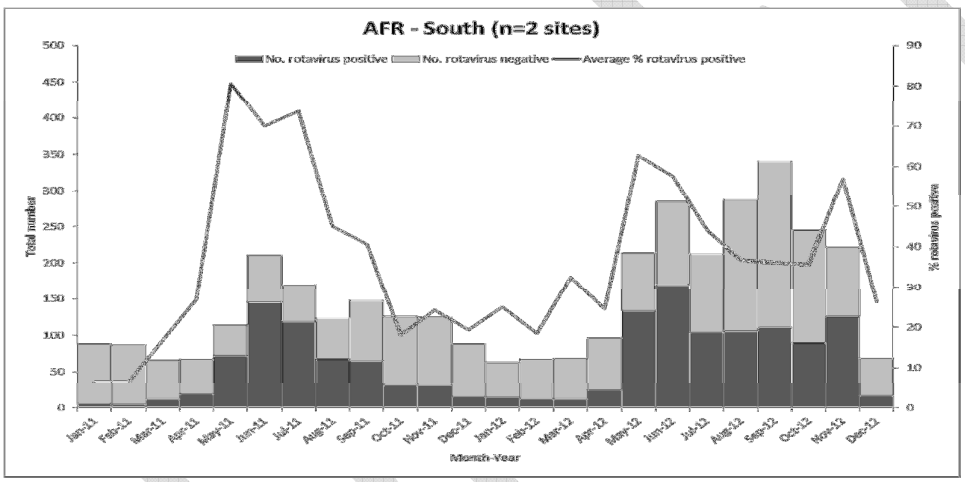


Figure 81. Rotavirus seasonality in AFR South - includes Zambia and Zimbabwe



Rotavirus disease trends pre- and post-vaccine introduction

Guatemala and Sudan were the two countries with sites meeting reporting and testing criteria and with at least two years of baseline and one year of post-vaccine introduction surveillance data during 2008-2012. Guatemala introduced rotavirus vaccine in February 2010; Sudan introduced in July 2011. Diarrhoeal and rotavirus disease trends are shown in Figures 18 and 19 and for pre- and post-vaccine introduction years (vaccine introduction year excluded) in Tables 14 and 15.

Guatemala

Figure 82. Total number and average percent rotavirus positive children hospitalized with diarrhoea, 3 sentinel surveillance sits, Guatemala – 2008-2012

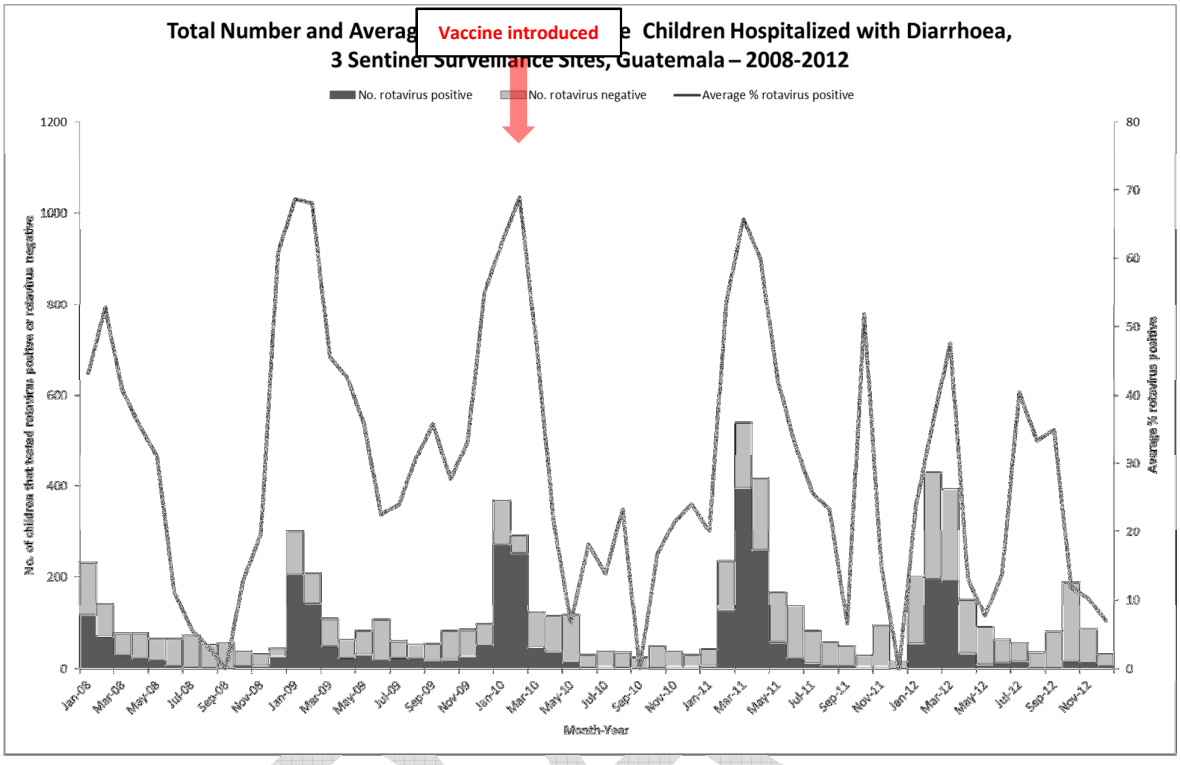


Table 24. Total number and average percent rotavirus positive children hospitalized with diarrhoea, 3 sentinel surveillance sites, Guatemala – 2008-2012

Diarrhoea hospitalizations[1]	2008-2009 mean	2011	2012
Diarrhoea cases tested	1123	1866	1807
Rotavirus positive cases	461	893	545
Average % rotavirus positive	42%	49%	28%

[1]Totals and % by age group could not be calculated due to lack of age group-specific data

Sudan

Figure 83. Total number and average percent rotavirus positive children hospitalized with diarrhoea, 5 sentinel surveillance sites, Sudan - 2008-2012

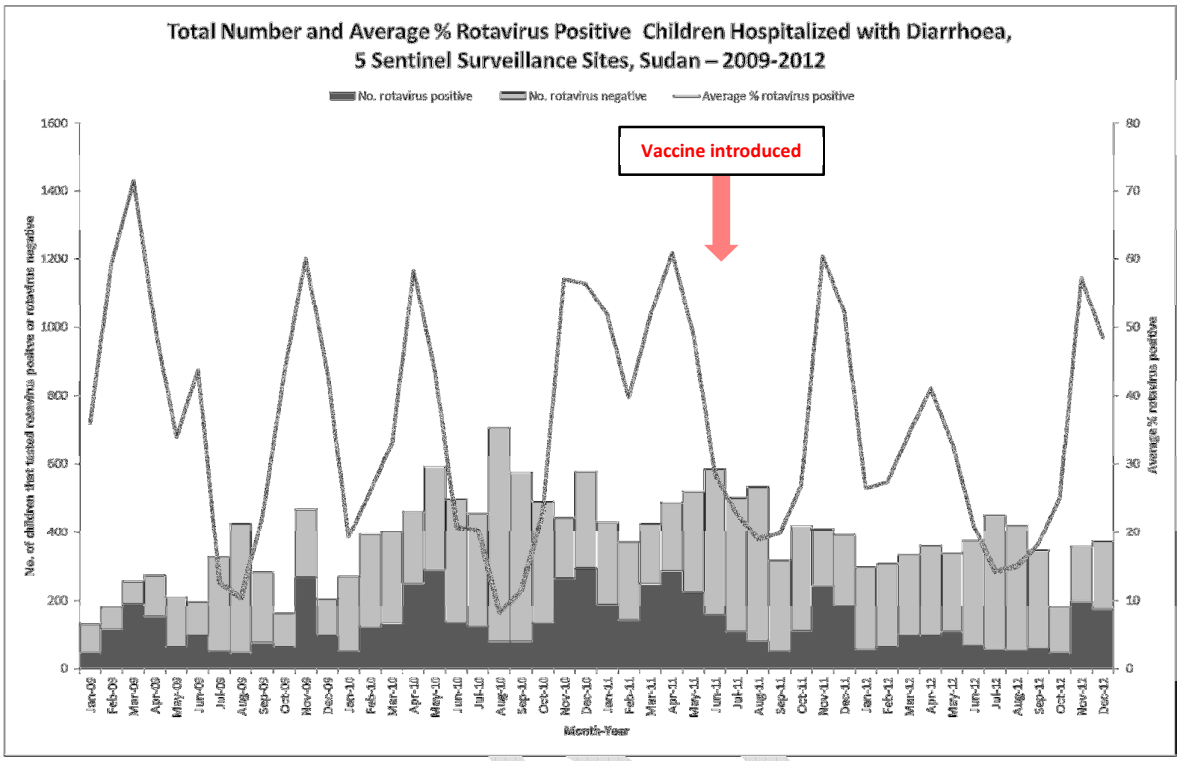


Table 25. Total diarrhoea and rotavirus positive cases reported by 5 sentinel surveillance sites, Sudan - pre- and post-rotavirus vaccine introduction in 2011

Diarrhoea hospitalizations	2009-2010 mean	2012
Diarrhoea cases tested		
0-5m	4499	4145
6-11m	804	562
12-23m	1778	1351
24-59m	1354	1630
All ≤59m	564	602
No. (mean %) rotavirus positive cases		
0-5m	1604 (36%)	1078 (30%)
6-11m	300 (38%)	154 (30%)
12-23m	674 (38%)	399 (31%)
24-59m	464 (35%)	401 (30%)
All ≤59m	166 (30%)	124 (25%)

Rotavirus Genotype Distribution

The genotype distribution of Rotavirus was analyzed globally and by region for the years 2009-2012.

Figure 84. Global rotavirus genotype distribution

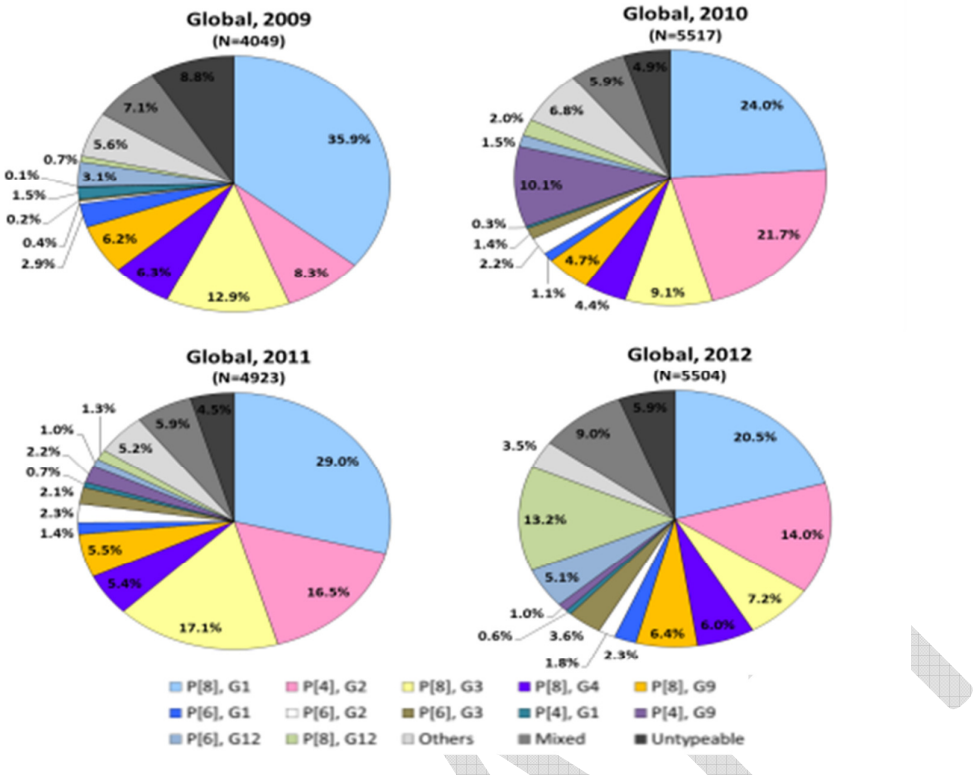


Figure 85. Rotavirus genotype distribution in AFR

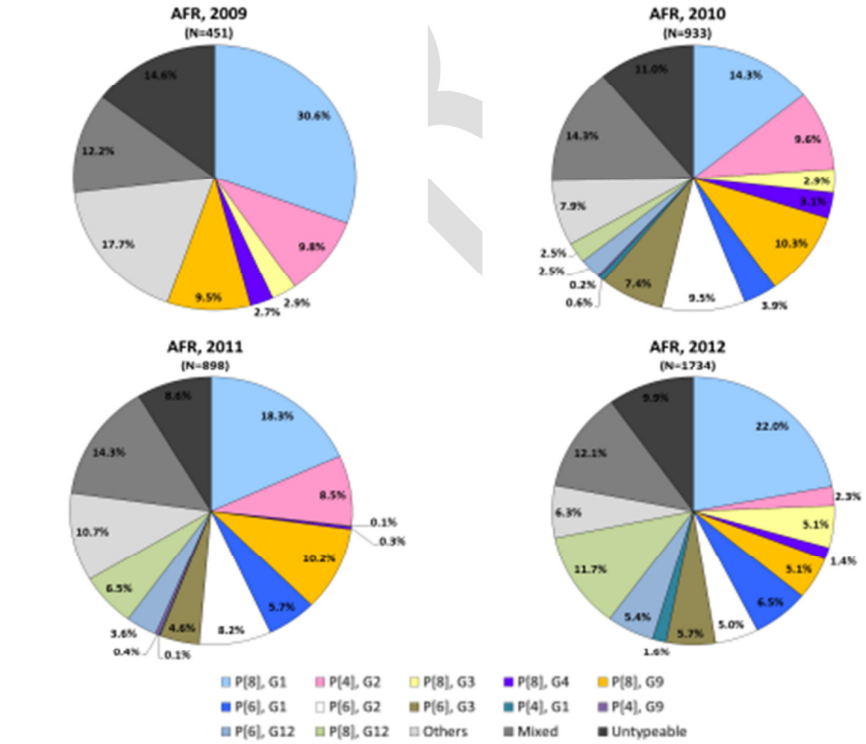


Figure 86. Rotavirus genotype distribution in AMR

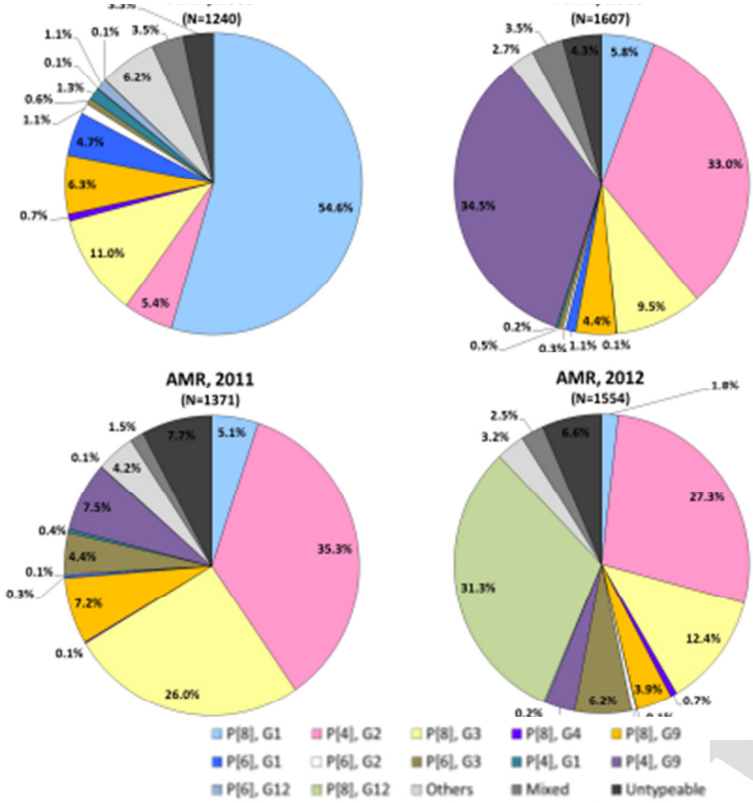


Figure 87. Rotavirus genotype distribution in EMR

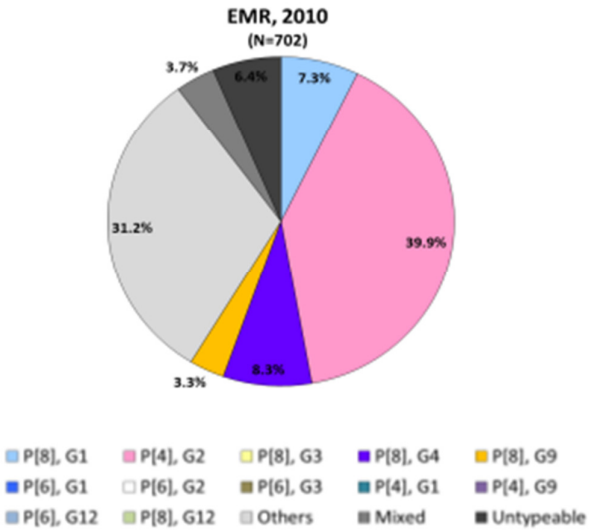


Figure 88. Rotavirus genotype distribution in EUR

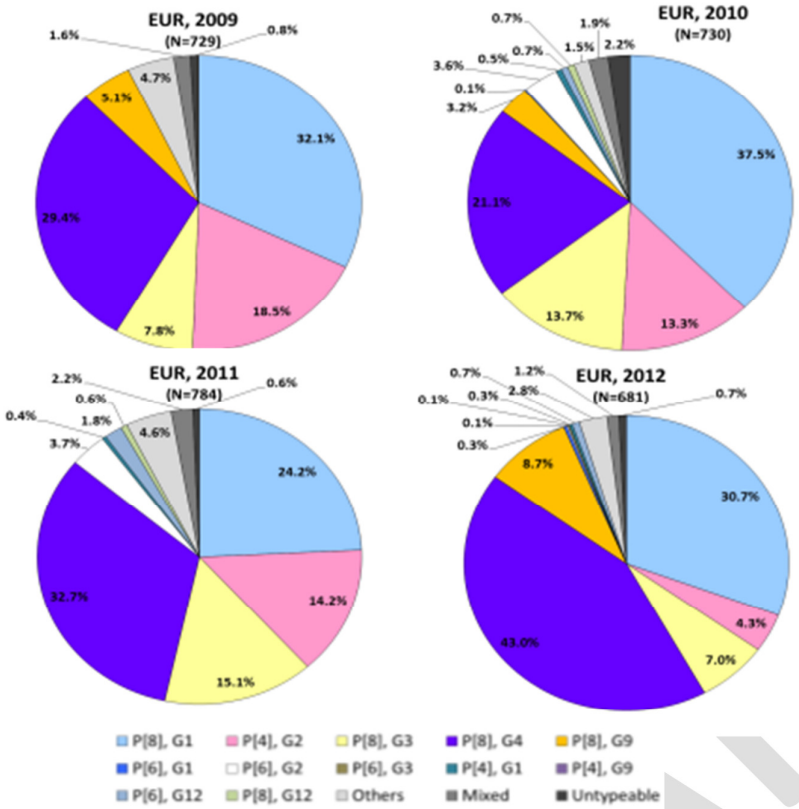


Figure 89. Rotavirus genotype distribution in SEAR

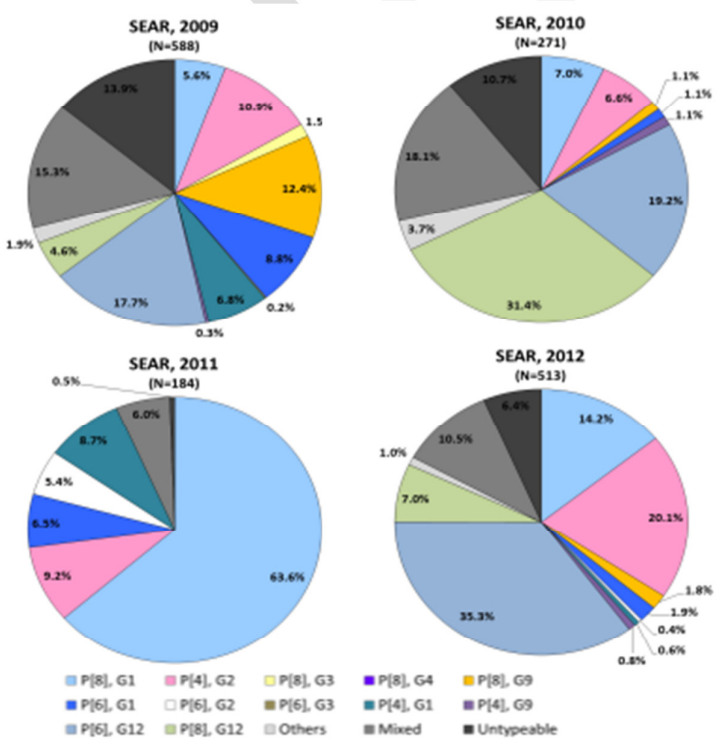
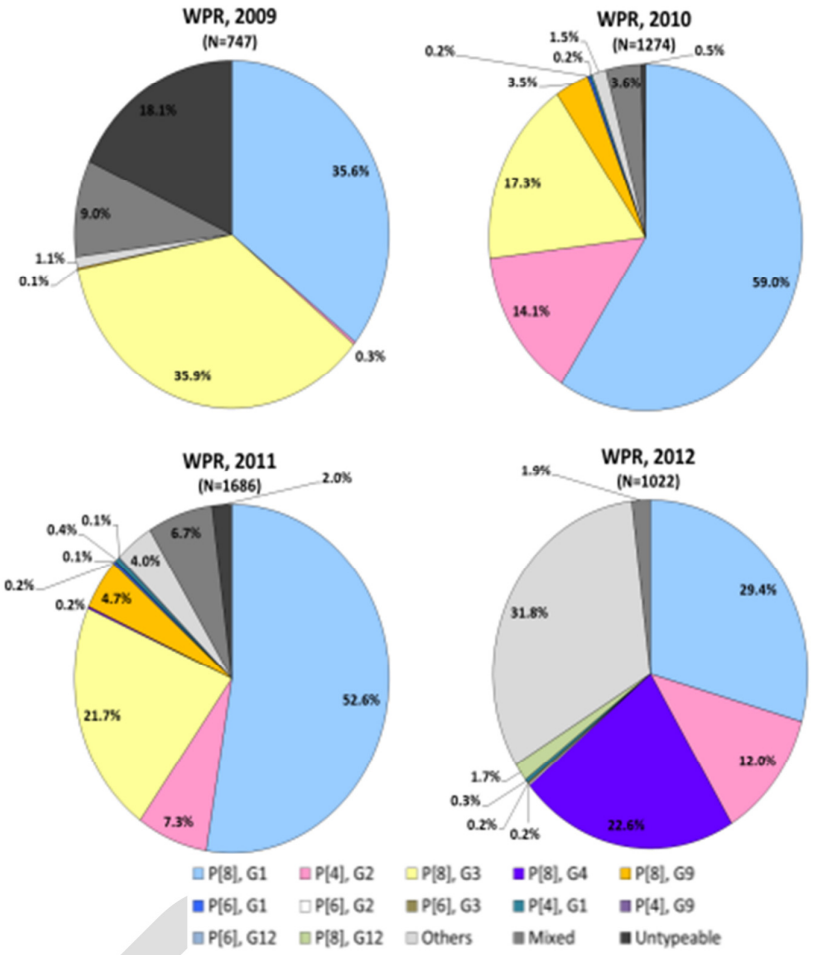


Figure 90. Rotavirus genotype distribution in WPR



4. IB-VPD AND RV LABORATORY NETWORKS REVIEW

A review of the global IB-VPD and RV laboratory networks was conducted by an independent consultant. The conclusions and recommendations from the independent consultation were discussed at the strategic review meeting and are provided in this section of the report. Additional details for the summary provided here may be found in the more detailed report from Dr. Ray Sanders.

METHODS

An analysis was made of the major components and outputs of the Global IB-VPD and RV Laboratory Networks according to a series of questions posed by the Global Programme. Questions were framed with reference to the original programme objectives and the 2008 proposals for data collection, analysis and sharing. These questions were:

1. Are the IB-VPD and RV laboratory networks supporting the surveillance systems in the most effective/efficient manner?
2. Are the Regional Reference Laboratories performing effectively and appropriately?
3. Are participating sites meeting global standards for quality assurance, proficiency testing, and SOPs?
4. Do the IB-VPD and RV networks link with other existing laboratory networks for viral and bacterial diseases?
5. Did the genotype and serotype data generated by the IB-VPD and RV networks address the 2008 objectives, as outlined in the data analysis plan including the list of activities for the laboratory?
6. Are laboratory data components complete and of high-quality?

Information for the review was gathered through access to documents available at WHO HQ and on the WHO HQ website, interviews with WHO HQ programme staff, and documentation provided by WHO ROs and available on WHO RO websites. In June 2013, WHO HQ sent structured requests to each WHO RO to provide detailed information on the nature and performance of the regional surveillance systems in place. The requests included structured questions on laboratory training, activities and monitoring together with questions on laboratory data collection analysis and dissemination. Information provided in the responses from the ROs was used for the review. Given acute time limitations, Regional Laboratory Coordinators were not contacted further during the review process.

Due to the time restriction and the limited opportunity for RO comment there was a strong bias towards viewing the networks from the perspective of WHO HQ, since that was the source of the majority of information used for the review. Where possible and appropriate attempts were made to reflect information provided directly and indirectly from the WHO ROs and the GRLs and RRLs, but the perspective remains predominantly that of the global programme and the laboratory networks viewed from the global position.

SUMMARY OF FINDINGS

Based on results of the analysis, a summary of the main findings to the key questions posed by the Global Programme are provided in Table 26:

Table 26. Review of the global IB-VPD and RV laboratory networks - main findings

Question	Main Findings
1. Are the IB-VPD and RV laboratory networks supporting the system in the most effective/efficient manner?	• Neither network presently can be described as supporting the system in the most effective/efficient manner, however… ○ Much has been achieved over the past 5 years, but the networks remain in a state of development ○ Important steps have been taken to

	strengthen national and regional laboratory capacities, improve laboratory quality and performance, and establish functional international networks ○ Both networks provide technical information that may be influential in developing vaccine policies ○ The RV network is closer to achieving effective support of the system (laboratory components are more compatible with those of existing polio and measles/rubella networks) – now capable of demonstrating vaccine impact on disease burden ○ The quality and quantity of technical support provided through the laboratory technical working groups (TWGs) and WHO are outstanding ○ Support for developing external quality assessment (EQA) and quality control (QC) programmes and standard operating procedures (SOPs), improving laboratory testing sensitivity and specificity, and rationalizing reporting processes has been exemplary ○ WHO has been effective in providing and contributing to technical guidance of the laboratory networks, but provision of overall management and oversight could be improved ○ The 2 global laboratory networks are effectively super-networks of the 6 regional networks – each regional network has characteristics that are region-specific. A detailed understanding of these characteristics the conditions under which the networks operate would allow WHO HQ to manage the global networks more effectively
2. Are the Regional Reference Laboratories (RRLs) performing effectively and appropriately?	• There is variation in the level of network involvement, but in general, available evidence suggests that all RRLs are performing appropriately ○ Although a tiered or hierarchical laboratory structure can work effectively, RRLs often do not appreciate the additional administrative, supervisory, quality management and training responsibilities expected of them when they agree to participate in the network ○ If RRLs agree to undertake activities such as monitoring and implementing QA/QC programmes; providing technical support National Laboratories (NLs), sentinel hospital laboratories, and the WHO surveillance programme; and conducting research aimed

	at improving or developing methods of diagnoses and pathogen characterization, they often lack the staffing levels and financial resources necessary

3. Are participating sites meeting global standards for quality assurance, proficiency testing, and SOPs?	• With 131, participating laboratories in the IB-VPD network and 153 laboratories in the RV network, it is unlikely that all meet required standards
	  ○ Both networks remaining in a state of development, and there has been improvement in the past 3 years
	  ○ On-site laboratory assessment tools have been developed and are being used, but limited evidence of their effectiveness was provided for this review
	  ○ A potential problem anticipated is that responsibility for assessing sentinel/national laboratories fall on the RRLs, which may stretch the available resources of the RRLs and RO staff to comprehensively and frequently review all laboratories
	  ○ Comprehensive on-site assessment of RRLs is underway, and should not overtax available resources

Question	Main Findings
4. Do the IB-VPD and RV networks link with other existing laboratory networks for viral and bacterial diseases?	• Available evidence suggests that both networks link with other laboratory networks to a greater or lesser extent ○ In several regions, the IB-VPD network has maintained links to the bacteriological surveillance networks from which it evolved. ○ The RV laboratory has made use of potential synergies with the WHO polio and measles/rubella laboratory networks, particularly in terms of training, but this probably could be done more often ○ In AFR, the policy to establish integrated surveillance for communicable diseases has achieved a good level of success, and both IB-VPD and RV networks are integrated with the regional system ○ Due to time restrictions and lack of information at the global level, this review has not considered antimicrobial susceptibility (AMS). However, there is evidence that several of the regional IB-VPD laboratory networks participate in AMS surveillance networks and provide valuable information
5. Did the genotype and serotype data generated by the IB-VPD and RV networks address the 2008 objectives, as outlined in the data analysis plan including the list of activities for the laboratory?	• Genotype and serotype data generated from 2009-2011 failed to address the 2008 objectives. However, a detailed analysis of 2012 data is underway, and the results may go some way towards meeting the 2008 objectives ○ Given the level of achievement in the networks' development over the past 5 years, if more effective participatory management and oversight is provided by WHO, both networks likely will address the 2008 objectives in the near future ○ Some incompatibilities exist between the laboratory networks envisaged in 2008 and the current networks – 2008 objectives assumed that 'classic' sentinel surveillance with a small number of sites producing high quality data would be conducted; the current networks have characteristics that are intermediate between true sentinel surveillance and population-based surveillance – this indeterminacy may place stress on the laboratory networks
6. Are laboratory data components complete and of high-quality?	• The laboratory data components are not universally complete and of high quality ○ Serotype/serogroup and genotype data received by WHO HQ is likely of high quality, but the quality of data with reference to the

programme objectives is unknown since there is no indication of the isolate source, site of initial testing, or any history of specimen/isolate processing - receipt of case-based data at the Global level would overcome these doubts

- The fidelity with which laboratory data is entered into the reporting system and the degree to which all required data is provided is inadequate – this is a problem of network management and oversight that can be overcome to some extent by ensuring strict linkage between laboratory data and clinical/epidemiological data

CONCLUSIONS AND RECOMMENDATIONS OF THE INDEPENDENT CONSULTATION

Conclusions

- Both laboratory networks have made huge advances in strengthening national and regional laboratory capacities, standardization of laboratory testing, improving laboratory quality and performance, and establishing functional international networks. Both remain in a state of development. Of the 2 laboratory networks, the RV network is significantly closer to achieving effective support of the surveillance programme.
- Shortcomings in performance of the 2 laboratory networks are not due to lack of technical support. While WHO has been very effective in providing and contributing to technical guidance of the laboratory networks, provision of overall management and oversight could be improved.
- In general, available evidence suggests that all network Regional Reference Laboratories RRLs are performing appropriately, but a more detailed review of the regional networks may reveal issues that have not be detected in this overview.
- With 131 participating laboratories in the IB-VPD network and 153 laboratories in the RV network it is unlikely that all meet required standards, and evidence from analysis of reported data, regional reports and discussions at technical meetings suggest that failure to meet standards is an on-going problem. Development and roll-out of the global EQA programmes, development of regional and global QC guidelines and development and distribution of generic SOPs are all appropriate technical responses to improving laboratory quality.
- Detailed genotype and serotype data generated from 2009 to 2011 failed to address the original 2008 objective of monitoring disease trends and genotype/serotype distribution over time. However, a detailed analysis of the 2012 data may go some way towards meeting those objectives.
- Incompatibilities exist between the data-generating laboratory networks envisaged in 2008 and the networks evident in 2013. The 2008 objectives appear to assume that the sentinel surveillance conducted will depend on a small number of sites producing high quality data. Although the term ‘sentinel surveillance’ is used to describe the activities of both the IB-VPD and RV surveillance networks, for several participating countries the surveillance activities have characteristics that are intermediate between true sentinel surveillance and

population-based surveillance. This indeterminacy places stress on the laboratory networks as they are attempting to provide the level of quality of performance associated with sentinel surveillance while also providing the flexibility and scope of population-based surveillance.

- The laboratory data components are not universally complete and of high quality. While it is highly likely that the serotype/serogroup and genotype data received by WHO HQ is of itself high quality, as there is no indication of the source of the isolate, the site of initial testing, or any history of processing of the specimens/isolates, the quality of the data with reference to the programme objectives must be in doubt. The fidelity with which laboratory data is entered into the reporting system and the completeness of reporting is inadequate.

Key Recommendations

1. **Networks size and surveillance function:** Incompatibilities exist between the current networks size, in terms of number of participating laboratories, and availability of resources to support, monitor and maintain those laboratories. A rationalization process is required to more closely match networks size with expected surveillance outputs and the level of resources available.

    a. In-depth regional reviews of laboratory networks function and output are required in each of the WHO regions to identify region-specific issues and provide appropriate evaluations. The reviews should document laboratory performance, output and resource requirements for each laboratory in the regional network together with regional network coordination and management, performance and network resource requirements. These reviews should be under the direction of the Global Laboratory Coordinator with support from the Regional Laboratory Coordinators, Global Reference Laboratory and selected Regional Reference Laboratory staff.

    b. Following regional review, where appropriate and possible, the number of participating network laboratories should be reduced to more closely match programme capacity to fully support and supervise these laboratories to an extent that guarantees confidence in reported laboratory results.

    c. For participating laboratories in Member States that have established *de facto* population-based surveillance using multiple 'sentinel' sites, the programme should determine if this form of surveillance is appropriate to achieving programmatic objectives. If this form of surveillance is not considered technically appropriate within resource limitations, steps should be taken to reallocate programme resources more effectively. Great care must be taken, however, to maintain the laboratory networks within existing regional programme and initiative structures rather than establishing separate, vertical programmes.

2. **Networks coordination and management:** Coordination and performance management of the laboratory networks by WHO at global and regional levels have not matched the level of provision of technical support and guidance, and urgently need to be strengthened.

    a. The roles and responsibilities of WHO Regional and Global Laboratory Coordinators should be reviewed and revised, within the bounds of existing job descriptions, to place more emphasis on active management of network performance. The roles and responsibilities of the Global Laboratory Coordinator must be clearly distinguished

from those of Regional Laboratory Coordinators to reflect the additional functions associated with coordinating and monitoring the distinctive regional networks.

b. Support and encouragement should be provided to the WHO Global and Regional Laboratory Coordinators to play more active participatory roles in the routine management of the networks. Every opportunity should be taken for the coordinators and key Regional and Global Reference Laboratory staff to meet to discuss and resolve laboratory network issues.

c. Appropriate tools exist for the on-site assessment of participating laboratories from sentinel site hospital to Regional Reference Laboratory levels. Greater use should be made of these assessment tools, and every effort should be made to assess every participating laboratory at least once each year. These assessments should be regarded as a component of an external quality assurance programme and conducted in addition to any external quality assessment (proficiency testing).

3. **Reporting and data management:** A primary programmatic objective is to provide detailed and accurate information on the aetiologic agents associated with specific disease presentations, including detailed characterization according to serotype/serogroup or genotype. While the technical capacity to achieve this objective exists in both Global networks, the information management systems are failing to provide accurate and complete data for full analysis and monitoring of progress towards achieving programme objectives.

   a. To encourage more accurate systematic reporting from WHO regions to WHO Headquarters, the frequency of reporting serotype/serogroup and genotype data should be increased from the current annual reporting of aggregate data to at least 6-monthly reporting of aggregate data. This should be complemented by more frequent feedback of global analysis results to the Regional Offices and to participating laboratories.

   b. To more accurately monitor progress towards achieving programme objectives, Regional Offices should provide case-based data on all pathogen-positives to WHO Headquarters on a quarterly or 6-monthly basis, whichever is appropriate to their regional reporting schedules. This should be conducted in addition to routine reporting of aggregate data. If WHO Regional Offices are constrained in their capacity to fully analyze laboratory-based data from their regional networks, case-based data on all reported cases (including pathogen negatives) could be forwarded to WHO Headquarters following consultation.

   c. Greater emphasis should be placed on the global requirement for all reported laboratory results to be unequivocally linked to case and epidemiological information. If necessary additional support should be provided to the regions to establish routine information management systems capable of meeting this requirement.

5. DATA LANDSCAPE ANALYSIS

To enhance data management processes around collection, analysis and interpretation of surveillance information related to vaccine preventable diseases, a data landscape analysis was conducted by an independent consultant with the following objectives:

1. To perform a landscape analysis of the overall data management process at WHO HQ and each RO.
2. To propose a structure and management system overview for future New and Underutilized Vaccines Implementation (NUVI) data surveillance

Additional details for the summary provided in this report may be found in the more detailed report from Mr. Dave Jackson.

METHODS

Network overview

The timeline of the evolution of the global IB-VPD and RV networks was reviewed. This included four key time periods: 1) ADIP managed networks (pre-2008), 2) the October 2008 Data Standardization Meeting, 3) the September 2010 Indicator Review Meeting and Update, and 4) post-September 2010.

Data submission templates review

All versions of the standardized WHO HQ Excel data submission templates were reviewed and assessed for data management issues.

Overview of network participants

There has been no formal documentation outlining all participating sentinel sites and countries for each RO in the surveillance networks. Interviews were held with each RO and documents available at WHO HQ were consolidated to create a database to track sentinel sites and their various levels of participation within the network.

Data flow

Interviews were held with key members of the WHO HQ team as well as key members at each of the six ROs to assess the flow of data through the surveillance networks. Each interview had three general focuses:

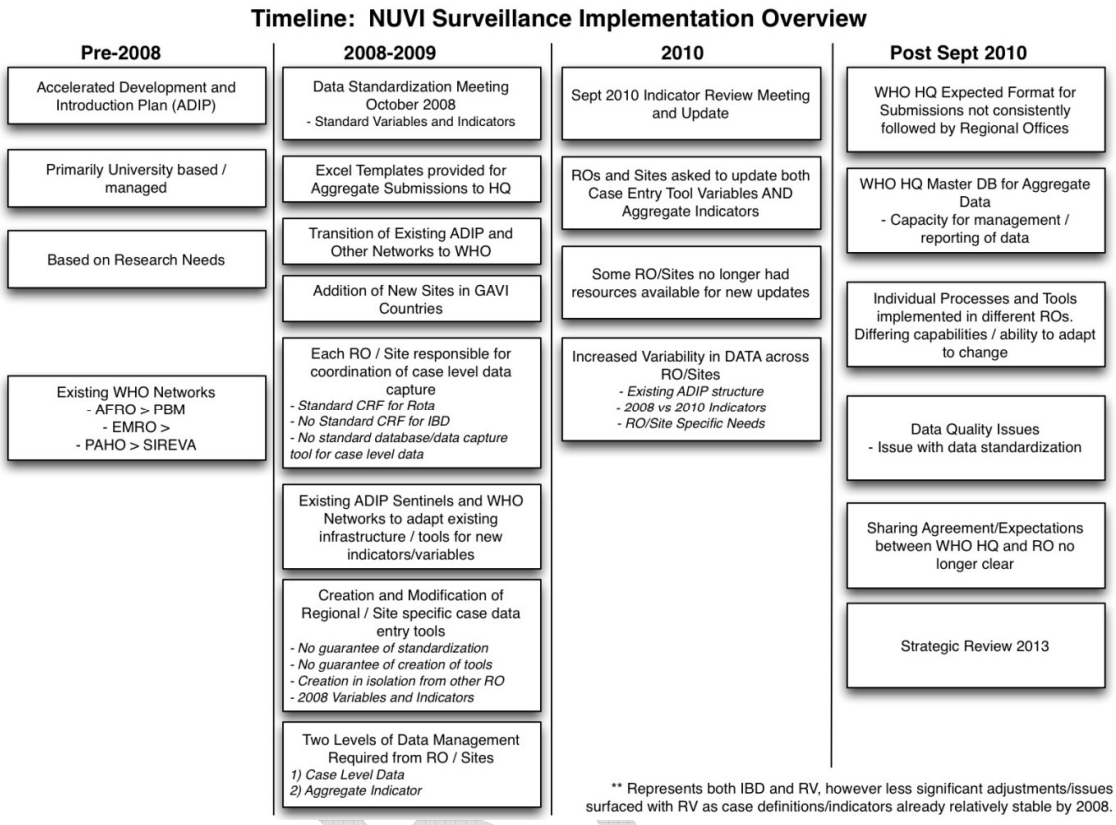
1. Actual data flow within the system
2. General overview of the environment in which the system operates
3. Lessons learned since 2008 implementation.

SUMMARY OF FINDINGS

Network overview

The following figure is an overview of IB-VPD and RV surveillance (aka NUVI surveillance) implementation during the four key time periods:

Figure 91. Timeline of IB-VPD and RV surveillance (aka NUVI surveillance) implementation



Data submission templates review

During the establishment of the global IB-VPD and RV surveillance networks, a decision was made for WHO HQ to receive aggregate data from each of the ROs using standardized Excel data submission forms – two epidemiology-focused forms (one for IB-VPD; one for RV) and two laboratory-focused forms (one for IB-VPD; one for RV). All ROs have been using these forms to report data to WHO HQ on a regular basis. However, three main issues were identified:

- **Issue 1: Consistency of use**
  A standard template has been provided to all of the ROs for data submission to WHO HQ. An issue faced by the ROs and by HQ has been the interpretation of the data that has been submitted or that was required to be submitted. Due to the variability in existing data sets from country to country, each RO may not consistently use the same data interpretations when populating the aggregate reports. This in turn results in inconsistencies in the data received at WHO HQ, resulting in difficulties pinpointing why the inconsistencies exist.

- **Issue 2: Template modifications by RO, country**

Another issue faced with the data submission templates has been changes made by the countries and ROs when submitting the templates. There have been instances where column headings have been changed or removed, once again resulting in data inconsistencies. Modifications to the submission templates have also resulted in an increased (and more manual) workload when processing the data.

- **Issue 3: Updates/changes to indicators and required variables**
  There has also been an issue where a change of data indicators and variables has necessitated a change to the submission templates. A formal change to the template can, in most part, be distributed to each of the participating sentinel sites without issue, however, the ability of each sentinel surveillance site to populate new variables and indicators may vary. With each change in the template, there is no guarantee that the new variables are part of the sentinel site datasets and also no guarantee that the sentinel sites have the resources to adjust their current data capture mechanisms / reporting systems.

Overview of network participants

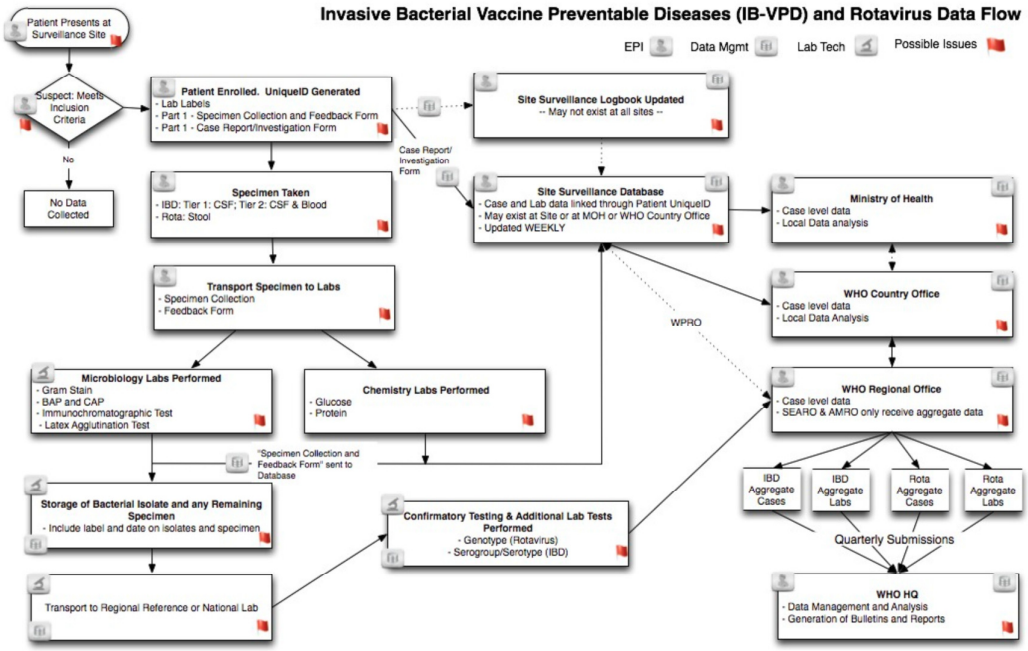
Review of the current surveillance networks revealed that there is no clear picture of all participating sites (based on data submissions). Furthermore, little is understood regarding the capacities and resources available at each sentinel surveillance site as there has been difficulty in management of quality improvement initiatives and accountability.

Data flow

Data flow within each region was examined in detail. The following is a summary of the main findings for the overall surveillance systems.

- **Actual data flow within the system**
  The general data flow in each RO is consistent across all six regional networks and is consistent with the expectations of HQ. Data capture occurs at a sentinel site; data are then sent to the country office, then RO, and finally HQ (Figure 93). The method in which the data is transferred and captured, however, is quite varied.

Figure 92. General data flow within the IB-VPD and RV surveillance networks and areas with possible issues



Specific issues noted include the following:

- *Case-based versus aggregate data:* Two of the ROs have opted to only collect aggregate data, while the other four collect case-based data from participating countries.
- *Standard paper case report form:* Every RO has implemented a standard paper case report form. However, each form may have been created in isolation from the other ROs. Each country and even site within each RO may have made modifications to the standard forms to allow for capture of other variables required for other studies.
- *Standard database/data collection tool:* Every RO has implemented some type of standard data collection tool. However, there is not any standardization across the tools. One RO uses a modified version of the HQ Excel Submission Template; one RO uses a combination of the HQ Excel Submission Template and a custom web entry tool; one RO uses an EPI info database; and three ROs use Access databases. All but one of the ROs has internal resources to maintain their current tools.

- **General overview of the environment**

  The data flow within the IB-VPD and RV surveillance systems is heavily affected by external factors and the environment in which the system is managed. Some of the major factors affecting the quality of data and general flow include the relationship with RRLs and the general availability of resources and funding:

  - *Relationship with Regional Reference Labs:* All but one of the ROs indicated that issues exist with test results data received back from the RRLs. Data received back from RRLs no longer contain unique patient identifiers and cannot be linked back to the original case data. Currently there is no formal agreement between the surveillance networks and the RRLs.
  - *Availability of Resources and Funding:* All of the ROs have expressed a concern with the current year-to-year funding allocation (allocation and disbursement of funds on an annual basis without commitment for future years). The year-to-year setup has caused

hesitation by countries to implement new systems or protocols. A few of the ROs have also indicated issues in maintaining and training quality staff as a result of inadequate funding. Additionally, site assessments and quality improvement initiatives have not been able to be performed regularly.

- **Lessons learned**
  The information gathered from the feedback and lessons learned by each of the regional offices and headquarters were used to generate a proposal for a future data management system. General system recommendations included the following:
    - Simplify and avoid redundancy
    - Have clear deliverables and standard participation agreements
    - Increase collaboration among ROs and RRLs
    - Improve data linkage and connectivity

CONCLUSIONS AND RECOMMENDATIONS OF THE INDEPENDENT CONSULTATION

The IB-VPD and RV surveillance networks have great potential to provide quality surveillance for IB-VPDs and rotavirus. The experience gained since 2008 and the data gathered as part of the 2013 Strategic Review has positioned the network to make crucial decisions related to the improvement of the network moving forward. Potential options for data flow/quality improvement can be separated into three main parts:

1. General System Recommendations;
2. RO Engagement / Involvement;
3. Proposal for Future Data Management System.

1. General system recommendations

There is a great deal of complexity in the IB-VPD and RV surveillance networks. The complexity comes not only from the actual epidemiologic surveillance required, but also as a result of the variability of requirements and resources across each regional office, country, and participating site. In order to attempt to manage this complexity, it is extremely important that there is a strong system to support the surveillance. Outlined below is a set of general recommendations.

- **Simplify and avoid redundancy**
  Many things can affect data quality within the network. However there are two major areas in which a level of control can be implemented: data type collected and data consolidation/merging.
    - Data type collected: Aggregate versus case-based. Currently, only aggregate data is being collected at two of the ROs and at HQ. The requirement for submission of aggregate data to HQ has both added workload to each of the regional offices as well as added complexity to the ability of HQ to interpret and understand the data. Data received in aggregate format requires a set of assumptions for interpretation, makes many analyses impossible and often requires additional effort by both HQ and each RO for clarifications. This can lead to the misinterpretation of results as well as potentially conflicting results between different levels within the network. Making case-based data available at all levels would increase the network's ability to perform meaningful analyses, and significantly minimize resource needs and time, as each

level would have the same data. The case-based data would allow for detailed analysis and the application of new algorithms in the interpretation of results. It would also allow for the conversations between HQ and RO to be focused more on the results and findings rather than the interpretations of the data entered.

- Data Consolidation /Merging: There is currently a high degree of manual data consolidation required at the headquarters level, in particular. Each data submission requires a database or dataset and each level to be consolidated into a larger database/dataset. Each time, there is a risk of possible issues or corruption to the data as well as time required by local resources to merge, clean, and verify the data. This process becomes even more complicated as each site may also be collecting other variables, outside of the variables required for IB-VPD and RV surveillance, within the same database. These additional variables may be important locally, however are outside of the scope of requirements for IB-VPD and RV surveillance and add complexity. In order to manage this, it is recommended that a semi-automated, centralized system be implemented. A recommendation for this system is provided in detail later in this report.

- **Clear deliverables and standard participation agreements**

A great deal of effort has been taken to put together deliverables and SOPs describing how the surveillance network works and what is required, however there does not appear to be a singular document or package that can be distributed to sentinel sites providing guidance as to "What does it mean to be a sentinel site" or "What is a required as a sentinel site". It is understood that there will be variability between countries and regional offices, there are certain elements that should remain consistent on all levels, including…

- Case definitions
- Data elements collected
- Submission Timelines
- Resources required / capacities (EPI, Lab, Data)

For areas that can be variable across countries and ROs, it is recommended that a template be provided which regional offices can modify. The template portion of the package could include items such as…

- Tools to be used (forms, databases, etc.)
- Publication and research guidelines
- Key contacts, locations, resources

As part of the distributed packages, a set of standard participation / information sharing agreements would be included. These agreements would need to be signed by any potential sites before formal participation in the network. This would allow for a clear establishment of accountability and ownership at the site levels.

It is important to allow for countries to manage their own surveillance, however, it is the responsibility of the surveillance network to ensure that surveillance is being done properly. Without establishing clear requirements for participation and clear accountabilities, the overall data quality is compromised.

- **Increased collaboration**
  The current setup of the network has provided ROs with core decision-making responsibilities regarding implementation, support and management of data surveillance. This is extremely important for continued success. However, in the network's current state, each RO is working in isolation from the other ROs. This has hindered the ability of each RO to share successes and strategies with one another and increases the chances of duplicated efforts and resources. It is recommended that regular meetings be convened with key people from each RO to discuss specific "focus" topics. Each focus could have monthly or quarterly teleconferences to discuss the various focus areas (i.e. Data Managers, Lab Coordinators, etc.).

  Another area where collaboration could be improved is with the RRLs. Currently, the RRLs operate independently from the surveillance network. It would be worthwhile to establish formal agreements and regular communications with key people at each RRL. These people could be invited to the regular teleconferences to allow for a better understanding of both what the network is trying to do and what issues are being faced.

- **Data linkage and connectivity**
  The quality of the surveillance of the data is improved with the ability to link to both internal (labs) and external (other surveillance networks) data sets. The data is also improved with the ability to look at the data over time. In order for either of these linkages to be successful, it is recommended that a standard be established for creation of a data linkage file. The purpose of a data linkage file would be to have a simple file that could be used to link multiple datasets. The file would contain only the elements required for linkage, and not any actual data elements. As data linkages are required, no modification would be required to be made to the processes or to the actual datasets to allow for linkage. The datasets would be able to be linked using the unique elements contained in the data linkage file. Some examples of variables that could be contained in the data linkage file…
    - Patient Health Number + Country
    - Database Unique Identifier
    - Lab Unique Identifier
    - Birthdate
    - Gender

The linkage file would be updated on a regular basis and would be maintained to ensure that the same patient can be tracked across time through different data submissions.

2. RO engagement/involvement/requested functionality

As part of the discussions with each of the ROs, questions were asked regarding thoughts and preferences in the possible development of future systems. These conversations were not comprehensive, but they provided some high level insight as to future requirements for system development. The following is a summary of needs/recommendations identified through these conversations:

- Clearly communicated objectives and requirements
    - Visible and accessible documentation/agreements

- Standardization of the way that information is requested → fields, indicators, etc. Very clearly defined deliverables
- Easily maintained tool which is compatible with standard of RO
    - RO IT/IS team involvement in specification development of future system for full Network
- Any data collected must be fully accessible to countries
    - Meaningful extrapolation of data
    - Ability to generate and interpret country level data and conduct own analyses
- Clearly communicated objectives and requirements
    - WHO funding is to support and provide mechanism to achieve objectives of surveillance – to help countries to be able to become independent in own surveillance and vaccine decision making
    - RO to be seen as a coordinator providing support, not as a driver.
- Long-term sustainability → year-to-year funding does not instill confidence to dedicate resources to building required infrastructure
- System for participating sentinel sites to clearly understand and formally agree/sign on to participate
- Any processed/reported data collected must be fully accessible to countries
    - Meaningful extrapolation of data
    - Ability to generate and interpret country level data and conduct own analyses

3. Proposal for future data management system

A future data management system for the IB-VPD and RV surveillance networks can take direct lessons from the Polio Surveillance Network as these networks have similar infrastructures and flows of data. The IB-VPD and RV networks may have more flexibility in developing an even more comprehensive system due to its smaller size and relatively new implementation (only since 2008). The following is a proposal for a data management system for the IB-VPD and RV surveillance networks and how each level of data flow is affected.

Overview

- **Centrally hosted master database at WHO HQ**
  This will allow for data access points and viewing tools to be branded with WHO logos and have accessible WHO website addresses.

- **Web based interface – two parts:**

  1. **Data uploads/entry** – participating sites will have the option to either upload a specific, standardized dataset or utilize a data capture tool:

     <u>Upload:</u> To accommodate for sites/countries that already have data management tools and processes in place, a web interface would be developed allowing for the upload of data from existing systems.
        - Existing tools would require modification to allow for an export of the specified dataset into the proper format for uploading.

- Web interface would perform a set of validations on the uploaded dataset to ensure data validity and consistency. Site/Country would receive immediate feedback as to requirements required for cleaning, etc.
- Upon completion of validation, system would require user confirmation and signoff before finalization of upload.
- Data uploaded to central, master database. Data would be automatically tagged and identified (Country, Site, etc.) based on user inputs.

Data capture tool: To accommodate for sites/countries that do not have existing data management tools in place, a basic web-based data capture tool would be provided for data entry.

- The data capture tool will provide the ability to enter ONLY the variables required for surveillance for IB-VPD and RV on a case-based level.
- Validation performed on data entry. Finalization of data submission cannot occur without signoff from data entry person.
- Accessible from any device with internet browsing capacity

2. **Data reporting** – a data portal view will be available for each level of data management (Site, Country, RO, HQ):
    - Dashboard view with quick reports regarding data submissions and generally desired reports. Ability to customize which reports are immediately seen.
    - Ability to view, filter and perform advanced searching on data
    - Ability to export data to a wide variety of formats for local level analysis and reporting
    - Portal available from any device or platform with Internet browsing capacity.

- **Data approval and review to start at country level moving to regional office and then to headquarters**
  The system would have a series of checks and balances integrated. Each submission would require a sign-off before becoming available for use by the next level surveillance level.
    - RO requires signoff by Country
    - HQ requires signoff by RO

Development Requirements / Considerations

- **Clearly defined dataset and variable requirements**
    - Sites, Countries, and ROs will continue to have additional data outside of what is required for IB-VPD and RV surveillance. This additional data can cause extra complexity and confusion in data management. To simplify the data management, validation and reporting process, ONLY the data variables specified for IB-VPD and RV surveillance will be captured in the new system.
    - The system will be initially developed based on the agreed upon set of variables for IB-VPD and RV. The capacity will exist to add additional variables, however no new variables will be added until adequate time/efforts have been made to ensure the system is functioning properly.

- **Comprehensive user management system and access rights**
    - An account management portion of the system is strongly recommended in order to control data inputs and quality. Accessing the system would require a secure login from an approved user.
    - User access rights would allow for system validation to ensure the user is submitting data from the expected site / region. Access rights would also ensure that each Site, Country, RO would only be able to see their own dataset.
    - User accounts would be assigned in the following manner:
        - HQ → Create/Manage accounts for RO
        - RO → Create/Manage accounts for Countries
        - Country → Create/Manage accounts for Sites
        - Site → Create/Manage accounts for Users
    - Proper allocation of accounts would allow for traceability, reporting and auditing of data uploads and data entries. Greater traceability allows for increased capacity for quality improvement.
    - All accounts would connect to an automated reminder system. The reminder system would be initiate automatic emails to the assigned user indicating a timeline for data submission. System reminders would continue to be sent to the user until either the user completes the submission or indicates why data will not be submitted (i.e. No surveillance done or no cases identified, etc.).

- **Data security and privacy**
    - A web interface will be established using the most secure web technologies and certificates
    - A system should be in place to allow for a secure connection to be confirmed at both the user and receiver levels.
    - An audit and system activity log should be in place to track all system activity. Space should be allocated to capture changes and allowance for restoration of data.

- **Data reporting requirements and logic**
    - A working group will need to be formed to discuss a standardized set of reporting to be integrated into the system. A set of logic for the reporting functionalities could be developed into the system to allow for future customization and dynamic reporting.
    - The system would be setup to allow for both standardized “1-click” type reporting as well as customizable ad-hoc reporting.
    - The system would allow for flexibility in data exports of all types for use in external data analysis software.

- **Provision of an Application Program Interface (API) and potential for future seamless integration.**
    - A set of APIs could be developed which would allow for a direct connection between existing systems and the central database. This would allow for an automatic sharing of data without the need for manual uploads. This would allow for real-time data surveillance and reporting for any connected systems.
    - APIs would also allow for the development of custom applications and reporting tools that could be distributed on mobile devices (iOS, Android, etc.)

- **System Accessibility for sites with Intermittent Internet Access**
    - Currently web technology that exists to allow for offline data entry, however some issues in implementation. This technology requires the most modern browsers, which unfortunately cannot be managed centrally. Sites with intermittent Internet access most likely do not have the most recent browser versions. Even with the most recent browsers, rules would also have to be defined in managing data syncing. Syncing can be very complex.

This proposal system would allow for consistent data management and reporting at every level of the IB-VPD and RV surveillance networks. Each site, country, and regional office would have access to the exact same data with a significantly decreased amount of time required for data processing and consolidation. The system would most importantly allow for countries to have full control over their data, while allowing for data to be reported regionally and at a global level.

6. USE OF SURVEILLANCE NETWORK DATA

One critical question during this review has been how the data generated by the IB-VPD and RV surveillance networks are used to inform and improve public health programmes. To assess how data generated by the surveillance networks are used, literature reviews, project reviews, and GAVI application reviews were conducted. ROs also were asked to provide feedback on surveillance data use by their regions and countries within each region. Additional country-level feedback is provided in the next section on country expert opinions.

STUDIES USING WHO-COORDINATED SURVEILLANCE NETWORK DATA

METHODS

A literature review of publications using WHO-coordinate surveillance network data was conducted with the following selection criteria:

- Publication included data from 2008 and later (but could also include pre-2008 data)
- Publication acknowledged WHO as a source of funding
- Publication was found in a peer-review journal indexed in PubMed

In additional to the literature review, subject matter experts and Regional Offices provided information on completed, ongoing, and planned vaccine effectiveness and impact evaluations using WHO surveillance platforms from 2008 to the present.

SUMMARY OF FINDINGS

Tables 27-29 summarize the publications and vaccine effectiveness and impact evaluations that have been completed, are in process, or are planned, using WHO surveillance platforms from 2008 to the present. Forty-two publications were listed in PubMed; 9 vaccine effectiveness and impact evaluations have been completed, are ongoing, or planned.

Table 27. Hib and PCV vaccine effectiveness and impact evaluations using WHO surveillance platforms, 2008 to present

Region	Country	Study Description	Status
AMR	Brazil	PCV effectiveness evaluation	?
AMR	Uruguay	PCV effectiveness evaluation	?
EMR	Multiple	Hib vaccine impact evaluations	Completed
SEAR	Bangladesh	PCV post-introduction impact evaluation	Ongoing
WPR	Cambodia	PCV impact evaluation	Planned
WPR	Fiji	PCV impact evaluation	Ongoing
WPR	Papua New Guinea	Hib vaccine impact evaluation	Completed
WPR	Papua New Guinea	PCV impact evaluation	Ongoing
WPR	Mongolia	PCV impact assessment	Planned

Table 28. Literature review summary - RV

Type of Study	Region	# Countries with Published Data	Countries
Disease Burden	AFR	8	Cameroon, Ethiopia, Ghana (2), Kenya, Tanzania, Uganda, Zambia, Zimbabwe
	AMR	12	Bolivia (2), Brazil, Columbia, Ecuador, El Salvador, Guatemala, Guyana, Honduras, Nicaragua, Paraguay, Peru, Venezuela
	EMR	5	Iraq, Jordan, Morocco, Oman, Tunisia
	EUR	1	Bulgaria
	SEAR	1	Nepal
	WPR	1	Papua New Guinea
Vaccine Impact and Effectiveness	AMR	5	Bolivia (2), Nicaragua, El Salvador (3), Honduras, Venezuela
Other	AFR	1	Uganda
	AMR	4	Bolivia, El Salvador, Honduras, Venezuela
	Global	1	
Network Summaries	Global	3	

Table 29. Rotavirus vaccine effectiveness and impact evaluations using WHO surveillance platforms, 2008 to present

Region	Country	Study Description	Status
AFR	Ghana	Vaccine effectiveness and impact evaluation	Ongoing
AFR	Kenya	Impact evaluation (trends in rate of rotavirus hospitalization)	Planned
AFR	Rwanda	Vaccine effectiveness and impact evaluation	Ongoing
AFR	Tanzania	Vaccine effectiveness and impact evaluation	Ongoing
AMR	Bolivia	Vaccine effectiveness	Completed
AMR	El	Vaccine effectiveness and impact evaluation	Completed

	Salvador		
AMR	Nicaragua	Vaccine Effectiveness	Completed
EUR	Armenia	Vaccine effectiveness and impact evaluation	Ongoing
EUR	Moldova	Vaccine effectiveness and impact evaluation	Ongoing

GAVI APPLICATIONS REVIEW

METHODS

The assessment of the use of surveillance data in GAVI Alliance applications for new vaccine support is part of a larger review of rotavirus and pediatric bacterial meningitis surveillance network performance, country-level opinions about the surveillance network, and the roles and responsibilities of WHO.

Data sources

Approved applications for *Haemophilus influenza b* (Hib), pneumococcal, and rotavirus vaccine introduction support submitted by countries eligible for GAVI support were accessed through the GAVI Alliance website at www.gavialliance.org.

Data extraction

Each application was reviewed to answer 7 questions (Table 1). Categorical answers (e.g., 1='yes', 2='no'), and a description and source(s) of data cited were recorded using a Microsoft Excel template:

Table 30. Questions for GAVI application data extraction

Question
1. Was the number of cases and/or deaths specified (for country or for their region)?
2. Was any country-level surveillance data cited?
3. Was the number of cases and/or deaths specified for this country?
4. Was the number of cases and/or deaths specified for their region?
5. Was the proportion of all disease that is covered by the serotypes in the vaccine specified for this country cited (this would reference local data, not regional estimates)?[1]
6. Was the proportion of all disease that is covered by the serotypes in the vaccine specified for the region cited?[1]
7. For any of the above disease burden estimates provided (regional or country-level), did they cite sources (published data)?

[1] Questions 5 and 6 applied only to pneumococcal vaccine applications since serotype replacement has been documented with pneumococcal vaccine use.

Country participation in the WHO-coordinated invasive bacterial-vaccine preventable diseases (IB-VPD) and rotavirus surveillance networks also was determined.

Data analysis

Analyses were conducted separately for Hib, pneumococcal, and rotavirus vaccine applications. For each vaccine type, the number and percentages of countries with data for each of the questions was summarized by whether or not the country participates in WHO-coordinated IB-VPD surveillance (for Hib and pneumococcal vaccine applications) or rotavirus surveillance (for rotavirus vaccine applications), by region, and by GAVI application year. Based on answers to the original seven questions, countries also were categorized as having cited WHO as a data source or not. Statistical analyses to determine a significant variation between application years, pre-/post-surveillance network establishment, and participating/non-participating surveillance countries were not conducted.

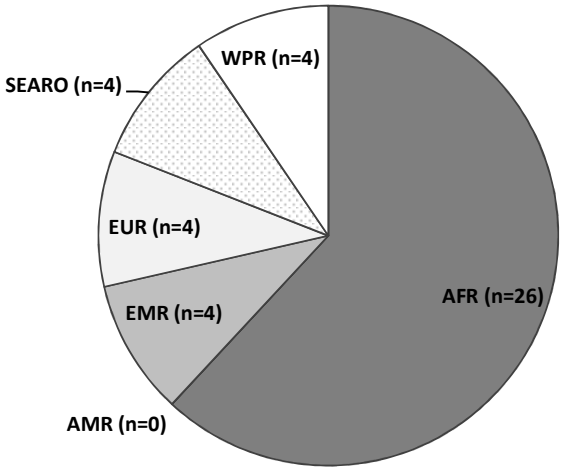
SUMMARY OF FINDINGS

Overall, most applications cited some country- or regional-level disease burden data. However, many did not cite a specific source or specific sources of data, so results presented below are limited by this.

Hib vaccine applications

From 2000-2012, 65 countries applied for GAVI support for Hib vaccine introduction activities – 42(65%) were from countries participating in WHO-coordinated IB-VPD surveillance; 23(35%) were from countries that do not participate in WHO-coordinated IB-VPD surveillance. The majority of applications from participating surveillance network countries were located in AFR (Figure 94).

Figure 93. Participating WHO-coordinated IB-VPD surveillance network countries that applied for GAVI support for Hib vaccine introduction, 2000-2012, by WHO region



Examining sources of data by GAVI application year, most applications by countries participating in WHO-coordinated surveillance cited at least one source of surveillance data (Figure 95). Most applications by countries not participating in WHO-coordinated surveillance also cited at least one source of surveillance data during years in which applications were submitted by these countries

(Figure 96). WHO was cited specifically as a data source in at least one or more of applications submitted each year during 2004-2011.

Figure 94. Sources of data from participating WHO-coordinated IB-VPD surveillance network countries, by Hib vaccine application year

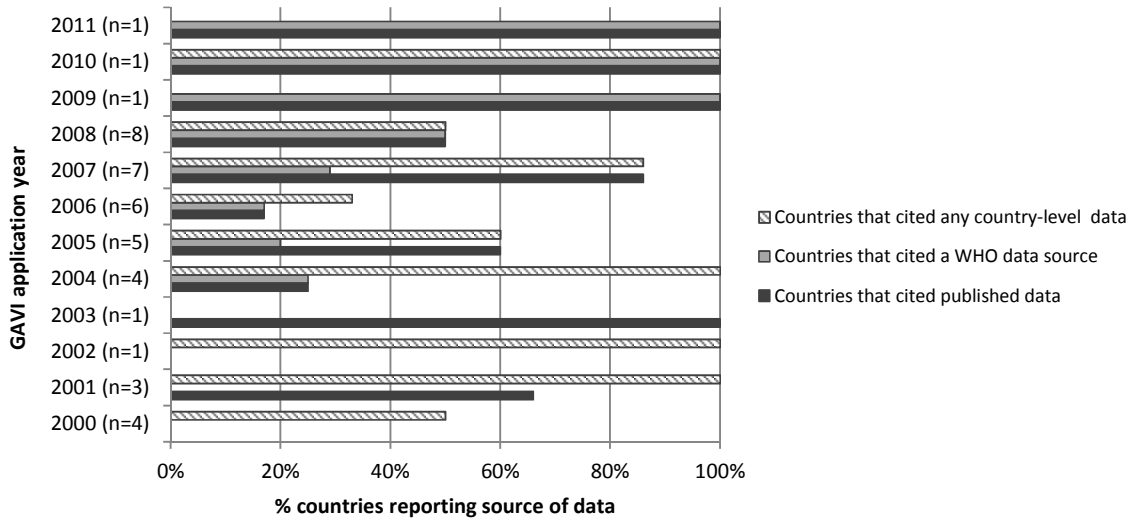
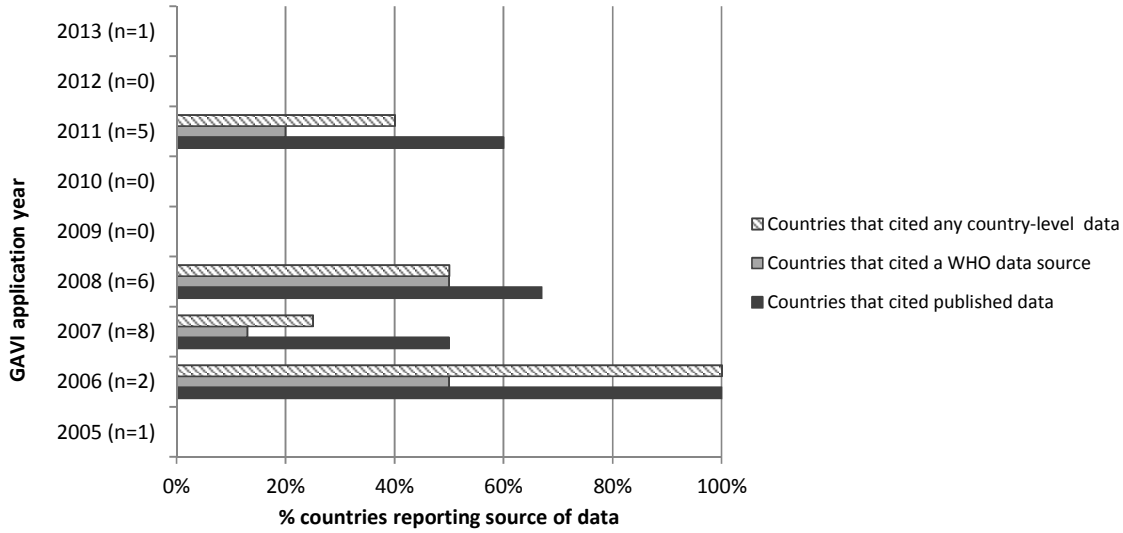


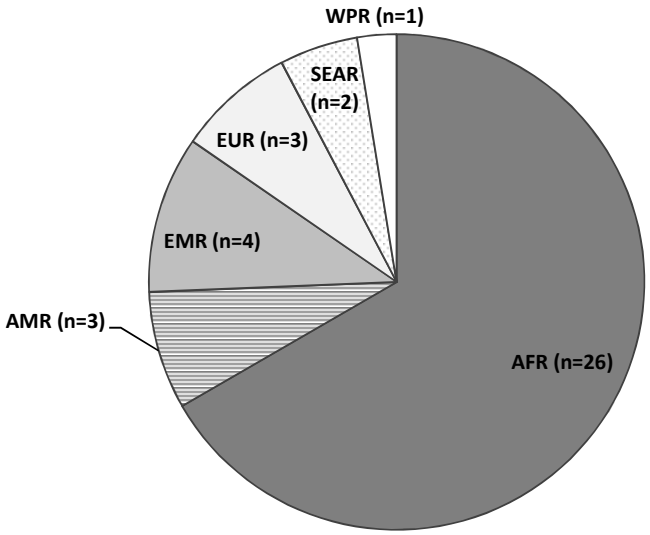
Figure 95. Sources of data from countries not participating in WHO surveillance, by Hib vaccine application year



Pneumococcal vaccine applications

From 2007-2012, 49 countries applied for GAVI support for pneumococcal vaccine introduction activities – 39(80%) were from countries participating in WHO-coordinated IB-VPD surveillance; 10(20%) were from countries that do not participate in WHO-coordinated IB-VPD surveillance. The majority of applications from participating surveillance network countries were located in AFR (Figure 97).

Figure 96. Participating WHO-coordinated IB-VPD surveillance network countries that applied for GAVI support for pneumococcal vaccine introduction, 2007-2012, by WHO region



Examining sources of data by GAVI application year, most applications by countries participating in WHO-coordinated surveillance cited at least one source of surveillance data (Figure 98). Many applications by countries not participating in WHO-coordinated surveillance also cited at least one source of surveillance data during years in which applications were submitted by these countries (Figure 99). WHO was cited specifically as a data source in one or more applications during each application year.

Figure 97. Sources of data from participating WHO-coordinated IB-VPD surveillance network countries, by pneumococcal vaccine application year

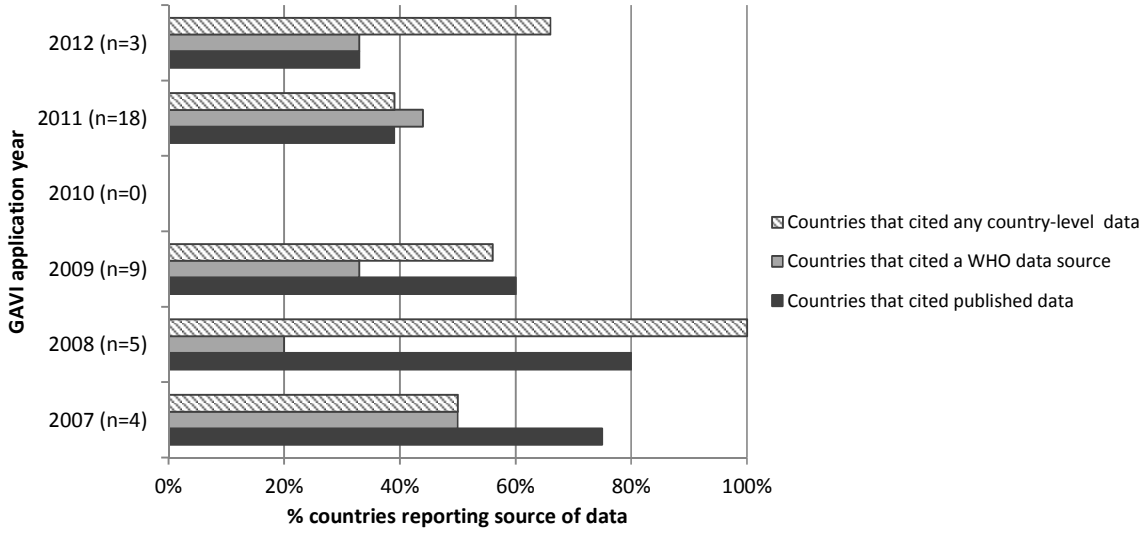
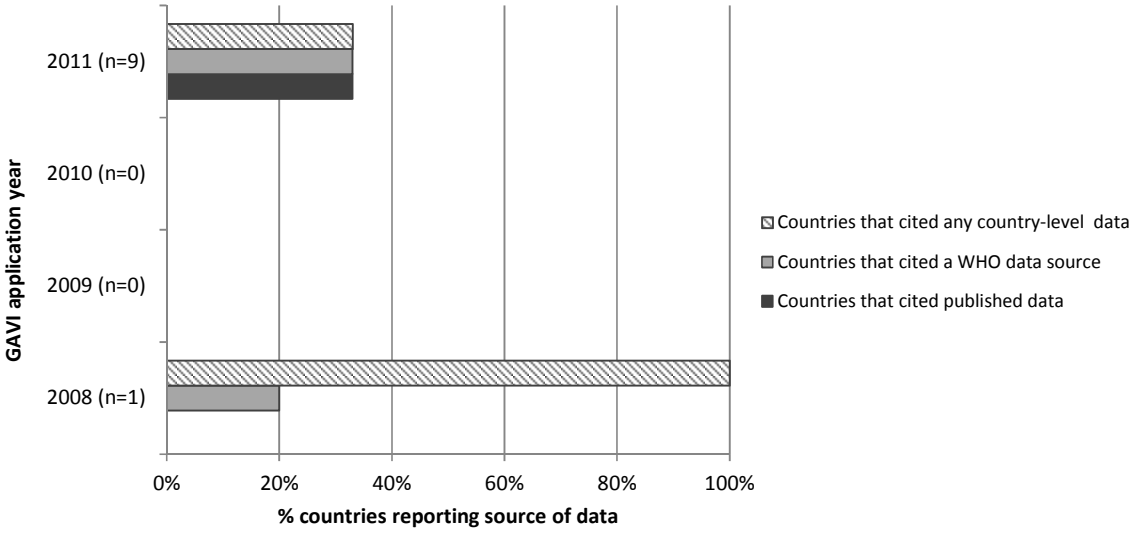


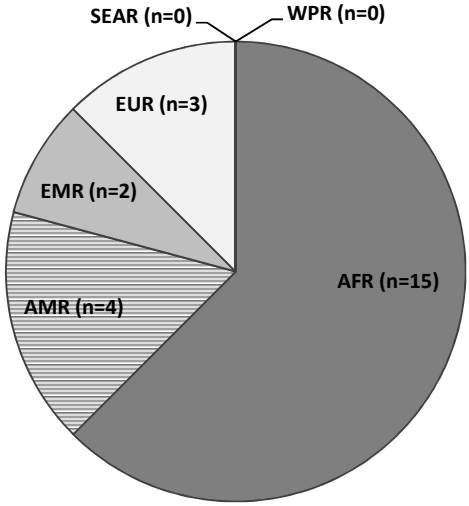
Figure 98. Sources of data from countries not participating in WHO surveillance, by pneumococcal vaccine application year



Rotavirus vaccine applications

From 2007-2012, 34 countries applied for GAVI support for pneumococcal vaccine introduction activities – 24(71%) were from countries participating in WHO-coordinated rotavirus surveillance; 10(29%) were from countries that do not participate in WHO-coordinated rotavirus surveillance. The majority of applications from participating surveillance network countries were located in AFR (Figure 100).

Figure 99. Participating WHO-coordinated rotavirus surveillance network countries that applied for GAVI support for rotavirus vaccine introduction, 2007-2012, by WHO region



Examining sources of data by GAVI application year, most applications by countries participating in WHO-coordinated surveillance cited at least one source of surveillance data (Figure 101). Most applications by countries not participating in WHO-coordinated surveillance also cited at least one

source of surveillance data during years in which applications were submitted by these countries; WHO was not cited specifically as a data source of any of these applications (Figure 102).

Figure 100. Sources of data from participating WHO-coordinated rotavirus surveillance network countries, by rotavirus vaccine application year

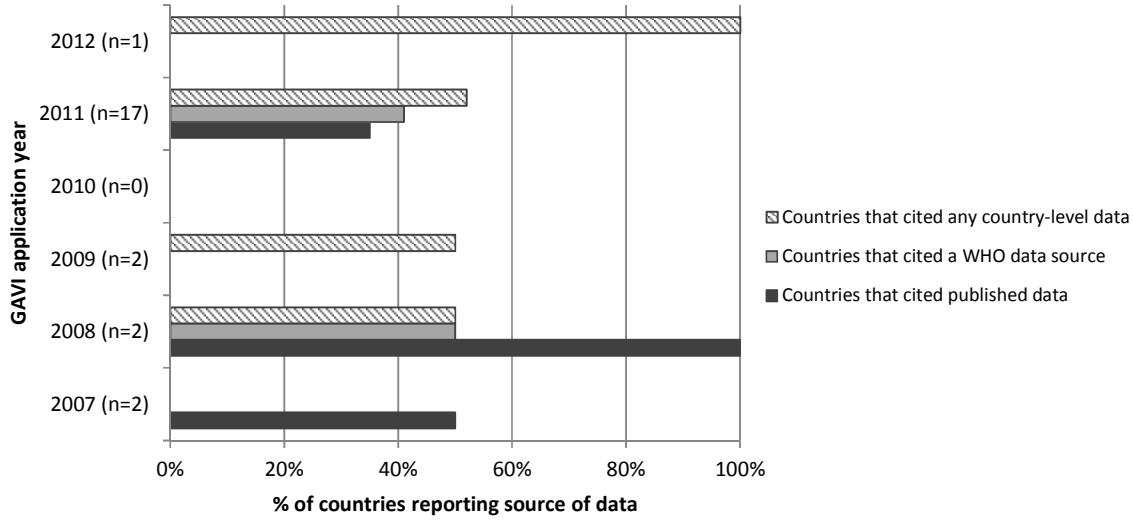
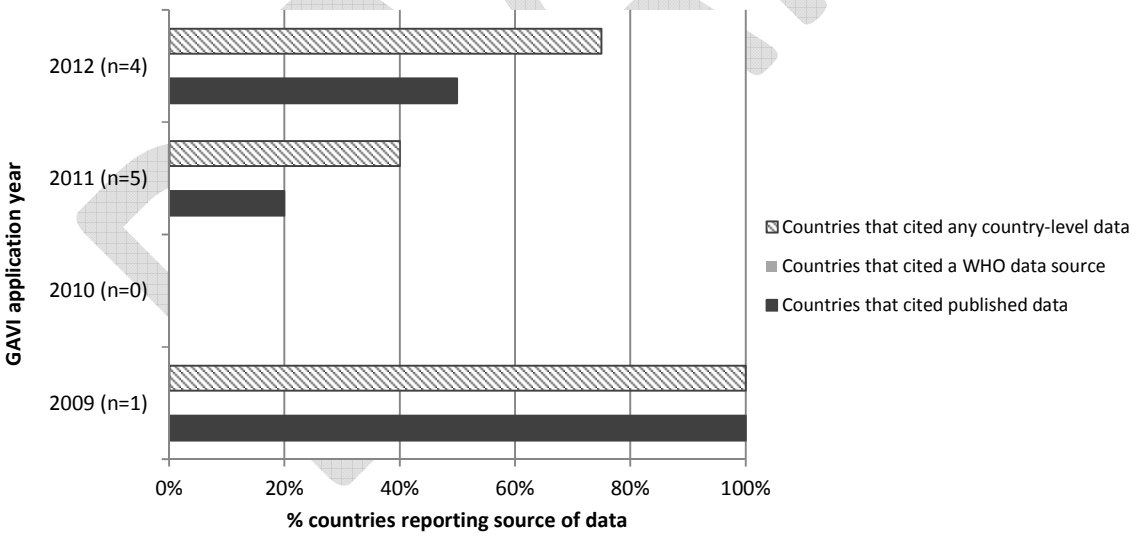


Figure 101. Sources of data from countries not participating in WHO surveillance, by rotavirus vaccine application year



ADDITIONAL REGIONAL OFFICE INPUT

IB-VPD and rotavirus surveillance coordinators at all Regional Offices were asked to provide feedback on a series of questions related to surveillance data use:

1. How have the data been used?
2. Have NITAGs and ICCs used the data?
3. Have vaccine introduction decisions been informed with the data?
4. Have data been included on GAVI applications?
5. Have there been any publications using the sentinel site information?
6. Have there been any publications including incidence data from sentinel sites?
7. Has there been any other information generating disease burden information?
8. Have data been shared with groups, such as pediatric societies?
9. Have there been additional requests for data from Ministries of Health?

Table 31 provides a summary of these answers and examples provided by the ROs:

Table 31. Summary of RO input regarding uses of surveillance network data

Question	Summary of RO answers	Examples
1. How have the data been used?	• Mentioned in GAVI applications • To provide disease burden trends • To inform vaccine introduction decisions • To conduct vaccine impact studies • For internal reports	• Mentioned in many GAVI applications from AFR • PCV10 vs. PCV13 selection (Bangladesh) • Rotavirus vaccine cost-effectiveness study (Azerbaijan) • Used for priority setting of new vaccines (Sri Lanka) • Used to inform NTAGI for PCV introduction (Nepal) • Rotavirus vaccine impact studies in AMR (Bolivia, El Salvador, Nicaragua), EMR (Sudan)
2. Have NITAGs and ICCs used the data?	• All ROs reported 'yes'	• EUR – NITAGs/ICCs have used the data to discuss introduction of rotavirus vaccine and PCV in all GAVI-eligible countries
3. Have vaccine introduction decisions been informed with the data?	• All ROs reported 'yes'	• EUR – MoHs made the decision whether to introduce rotavirus vaccine or PCV based on NITAG or Immunization Programme recommendations; epidemiology was the major factor that influenced MoH decisions to introduce new vaccines (e.g., rotavirus

		vaccine in Armenia, Moldova, Georgia, and Uzbekistan; PCV in Azerbaijan and Georgia)
4. Have data been included on GAVI applications?	• All ROs reported 'yes'	• AFR – many countries • AMR – Bolivia • SEAR – Sri Lanka, Bangladesh, Nepal • WPR – Papua New Guinea, Mongolia
5. Have there been any publications using the sentinel site information?	• Most ROs reported 'yes' • 2 ROs did not respond	• EMR - bacterial meningitis surveillance publication in *J Pediatr* 2013
6. Have there been any publications including incidence data from sentinel sites?	• 1 RO reported 'yes' • 5 ROs did not respond	• No specific example provided

Question	Summary of RO answers	Examples
7. Has there been any other information generating disease burden information?	• Impact studies • Information is generating estimates for disease burden in the country • (2 ROs responded)	• AFR – impact studies
8. Have data been shared with groups, such as pediatric societies?	• 5 ROs reported 'yes' • 1 RO did not respond	• No specific example provided
9. Have there been additional requests for data from Ministries of Health?	• 3 ROs reported 'yes' • 1 RO reported 'not yet' • 2 ROs did not repond	• EUR – MoH requested WHO support in building capacity of immunization personnel to do more advanced analysis • SEAR – Bangladesh EPI has consulted the surveillance sites; Sri Lanka uses the data when needed; Nepal site provides data to MoH as needed

7. MINISTRY OF HEALTH PERSPECTIVE

METHODS

Questionnaire

A structured questionnaire was administered to potential respondents during EPI Managers meetings in AFR, EMR, and WPR during 2012-2013. Completed questionnaires were returned to the Regional Offices (ROs) and then submitted to WHO Headquarters (HQ) for analysis.

Topics covered in the questionnaire included the following:

Topics

- Establishment and set up of rotavirus and pediatric bacterial meningitis surveillance
- Uses of the surveillance data
- Partners involved in with the surveillance
- Other available data sources for rotavirus and pediatric bacterial meningitis disease burden
- Sharing of surveillance data in the country
- Strengths, weaknesses, challenges and lessons learned
- Future direction of surveillance
- Costs and funding of surveillance

Data analysis

Data were entered into CSPro and exported to SAS, version 9.3, for analysis. Analyses were stratified by region, if applicable. The number and proportion of respondents was calculated for each answer. Free response answers were summarized and categorized by question.

SUMMARY OF FINDINGS

Respondent countries and in-country positions

Respondents from 27 countries in AFR, 13 countries in EMR, and 7 countries in WPR (2 respondents in the Philippines) returned completed questionnaires (Table 32). The majority of respondents were EPI managers and or vaccine-preventable diseases (VPD) surveillance coordinators (Table 33).

Table 32. Survey respondents by region and country

Region	AFR (n=27)		EMR (n=13)	WPR (n=8)
Countries	• Benin • Burkina Faso • Cape	• Madagascar • Malawi Mali • Namibia • Niger	• Bahrain • Djibouti • Egypt • Iran	• Cambodia • China • Lao PDR • Mongolia

	• Verde • Comores • Côte d'Ivoire • Eritrea • Gambia • Ghana • Guinea • Guinea Bissau • Kenya • Lesotho • Liberia	• Nigeria • Rwanda • Senegal • Sierra Leone • South Africa • Togo • Uganda • Zimbawbwe	• Iraq • Kuwait • Morocco • Pakistan • Occupied Palestine Territories • Qatar • Somalia • United Arab Emirates • Yemen	• Papua New Guinea • Philippines (2) • Vietnam

Table 33. Survey respondents by positions in country

Position[1]	n (% of total)			
	AFR	EMR	WPR	All regions
EPI manager	16 (62%)	9 (69%)	4 (50%)	29 (62%)
NITAG member	0	2 (15%)	0	2 (4%)
VPD surveillance coordinator	3 (12%)	4 (31%)	4 (50%)	11 (23%)
Other[2]	7 (27%)	3 (23%)	0	11 (23%)
Total	**26**	**13**	**8**	**47**
Missing[3]	*1*	*0*	*0*	*1*

[1] Some respondents with >1 position; [2] 'Other' includes EPI deputy manager or WHO focal point, Head of CDC, Director of Central Prevention, logistician, rotavirus surveillance coordinator/focal point/officer, statistician; [3] 'Missing' includes non-responses

Surveillance and vaccine introduction status

Most respondents reported that they had sentinel surveillance for rotavirus and or pediatric bacterial meningitis in their country (Tables 34 and 35). Most countries included in the survey have introduced Hib vaccine, while a smaller proportion have introduced pneumococcal and/or rotavirus vaccines (Table 36).

Table 34. Number (%) of respondents reporting sentinel surveillance for rotavirus, by region

Rotavirus surveillance established	n (% of total)			
	AFR	EMR	WPR	All regions
Yes	18 (67%)	8 (67%)	8 (100%)	34 (72%)
No	9 (33%)	4 (33%)	0 (0)	13 (28%)

Total	**27**	**12**	**8**	**47**
Missing[1]	*0*	*1*	*0*	*1*

[1] 'Missing' includes both non-responses and skipped questions for countries without sentinel surveillance

Table 35. Number (%) of respondents reporting sentinel surveillance for pediatric bacterial meningitis, by region

Pediatric bacterial meningitis surveillance established	**n (% of total)**			
	AFR	**EMR**	**WPR**	**All regions**
Yes	19 (76%)	9 (75%)	7 (88%)	35 (79%)
No	6 (24%)	3 (25%)	1 (12%)	10 (22%)
Total	**25**	**12**	**8**	**45**
Missing[1]	*2*	*1*	*0*	*3*

[1] 'Missing' includes both non-responses and skipped questions for countries without sentinel surveillance

Table 36. Number (%) of countries that have introduced rotavirus, pneumococcal and/or Hib vaccine, by region

Vaccine introduced	**AFR (n=27)**	**EMR (n=13)**	**WPR (n=7)**
Rotavirus vaccine	5 (19%)	5 (38%)	1 (14%)
Pneumococcal vaccine	13 (48%)	7 (54%)	0
Hib vaccine	27 (100%)	10 (77%)	6 (86%)

[1]No. of countries that have introduced >1 vaccine - RV/PCV/Hib: AFR (5), EMR (3), WPR (0); RV/Hib: AFR (0), EMR (1), WPR (1); PCV/Hib: AFR (6), EMR (4), WPR (0);

Establishment and coordination of rotavirus and pediatric bacterial meningitis surveillance

The median years during which rotavirus surveillance was established were: 2009.5 (range: 2006-2013) for AFR, 2006.5 (range: 2005-2008) for EMR, and 2009 (range: 1998-2012) for WPR. The median years during which pediatric bacterial meningitis surveillance was established were: 2002 (range: 1998-2011) for AFR, 2005 (range: 1999-2007) for EMR, and 2009 (range: 2006-2012) for WPR. The majority of respondents reported that surveillance for rotavirus and/or pediatric bacterial meningitis was established and currently is coordinated by the Ministry of Health (MoH) (Tables 37 and 38).

Table 37. Establishing organization for rotavirus surveillance, by region

Establishing Organization[1]	**n (% of total)**			
	AFR	**EMR**	**WPR**	**All regions**
MOH	13 (68%)	8 (100%)	5 (63%)	26 (74%)

Ministry of Education	0 (0)	0 (0)	0 (0)	0 (0)
Other Ministry[2]	0 (0)	0 (0)	0 (0)	0 (0)
University	4 (21%)	0 (0)	0 (0)	4 (11%)
Hospital	3 (16%)	0 (0)	3 (38%)	6 (17%)
Other[2]	5 (26%)	1 (13%)	2 (25%)	8 (23%)
Total	**19**	**8**	**8**	**35**
Missing[3]	*8*	*5*	*0*	*13*

[1] >1 response possible; [2] 'Other' includes WHO, UNICEF, NAMRUs, country in collaboration with Wellcome Trust, PATH, National Institute for Communicable Diseases, WHO Country Office, Institute of Medical Research, Polyvac; [3] 'Missing' includes both non-responses and skipped questions for countries without sentinel surveillance

Table 38. Central coordination of rotavirus and pediatric bacterial meningitis surveillance, by region

Coordinating Entity[1]	n (% of total)			
	AFR	**EMR**	**WPR**	**All regions**
MOH-EPI Programme	13 (65%)	2 (22%)	3 (8%)	18 (49%)
MOH-Health Systems Info	1 (5%)	1 (11%)	1 (13%)	3 (8%)
MOH-VPD Surveillance	9 (45%)	6 (67%)	3 (38%)	18 (49%)
Ministry of Education	0 (0)	0 (0)	0 (0)	0 (0)
Other Ministry[2]	6 (30%)	1 (11%)	3 (38%)	10 (27%)
Total	**20**	**9**	**8**	**37**
Missing[3]	*7*	*4*	*0*	*11*

[1] >1 response possible; [2] 'Other' includes CDC surveillance section, country in collaboration with Wellcome Trust, National Primary Care Health Agency, National Institute for Communicable Diseases, WHO Country Office, MOH Lab Dept of NCCD, hospital, MOH; [3] 'Missing' includes both non-responses and skipped questions for countries without sentinel surveillance

Reasons for establishing and maintaining surveillance

Most respondents reported that the main reasons for establishing and maintaining support for rotavirus and/or pediatric bacterial meningitis surveillance were/are to assess disease burden, prepare for vaccine introduction, and/or to monitor vaccine impact. Strengthening laboratory capacity also was mentioned for pediatric bacterial meningitis surveillance.

Staffing for surveillance

The number of MoH professional staff involved in rotavirus and/or pediatric bacterial meningitis surveillance at the central level varied from <10 to >20 people by region and within each region. Respondents from AFR countries reported greater numbers of staff working on surveillance while

respondents in WPR reported smaller numbers of staff. There was greater variability in the staff numbers reported by respondents from EMR countries. All respondents reported that all MoH professional staff involved in rotavirus and/or pediatric bacterial meningitis surveillance are also responsible for other activities not related to the surveillance systems and that most of these staff spend <50% of their working hours on surveillance.

Regarding laboratory support for surveillance, the majority of respondents reported that there is dedicated staff for both rotavirus and pediatric bacterial meningitis surveillance systems, mostly based in the MoH or in a hospital. Only a small proportion of these staff work under the supervision of an EPI manager.

Factors in decisions for vaccine introduction and maintain vaccination programmes

When assessing the importance of different factors considered in the decision to introduce a vaccine or to maintain funding for vaccine, the majority of respondents rated national surveillance data gathered in country, other national data (e.g., special studies, passive national health information, mortality data systems), disease burden estimates from WHO or the literature, and WHO guidance documents as being of high importance (Tables 39 and 40). Still important, although less so, were data from other countries and vaccine introduction in neighboring countries.

Table 39. Importance[1] of factors in decision for vaccine introduction, by region

Factor	Median (range)			
	AFR	EMR	WPR	All regions
• **National surveillance data gathered in country**	9 (5-10)	10 (7-10)	10 (1-10)	10 (1-10)
• **Other national data, such as special studies, passive national health info, mortality data systems**	7 (3-10)	8 (4-10)	8 (1-10)	8 (1-10)
• **Disease burden estimates from WHO or in literature**	8 (4-10)	9 (6-10)	6 (6-10)	8 (4-10)
• **WHO guidance documents**	9 (5-10)	9 (6-10)	6 (6-10)	8 (5-10)
• **Data from other countries**	6.5 (3-10)	5.5 (2-8)	5 (1-10)	6 (1-10)
• **Vaccine introduction in neighboring coutnries**	7 (3-10)	6.5 (1-9)	6 (4-10)	7 (1-10)

[1] Importance rated on a scale of 1-10, with 10 being of highest importance

Table 40. Importance[1] of factors in maintaining funding for a new vaccine, by region

Factor	Median (range)			
	AFR	EMR	WPR	All regions

• **National surveillance data gathered in country**	9 (6-10)	10 (8-10)	10 (9-10)	10 (6-10)
• **Other national data, such as special studies, passive national health info, mortality data systems**	8 (3-10)	8 (4-10)	8 (8-10)	8 (3-10)
• **Disease burden estimates from WHO or in literature**	8 (5-10)	9 (4-10)	6 (6-10)	8 (4-10)
• **WHO guidance documents**	8.5 (5-10)	8.5 (6-10)	7 (5-10)	8 (5-10)
• **Data from other countries**	7 (2-10)	5 (3-8)	6 (4-10)	7 (2-10)
• **Vaccine introduction in neighboring coutnries**	7 (2-10)	5.5 (1-9)	7 (4-9)	7 (1-10)

[1] Importance rated on a scale of 1-10, with 10 being of highest importance

Use and sharing of surveillance data

Uses of surveillance data

When asked about the uses of rotavirus and pediatric bacterial meningitis surveillance data in country, the majority of respondents reported that data from both surveillance systems are used for advocacy to or within the government on the importance and burden of rotavirus diarrhea and pediatric bacterial meningitis (Tables 41 and 42). Many also reported that data are used for vaccine impact assessments, hospital clinical practice guidance, development of national clinical guidelines, and adverse events following immunization assessments.

Table 41. Uses of rotavirus surveillance data in country, by region

Factor	n (% of total) [1]			
	AFR	EMR	WPR	All regions
Advocacy to or within the government on the importance/ burden of rotavirus diarrhea	13 (81%)	8 (89%)	8 (100%)	29 (89%)
Decision making on vaccine introduction	15 (93%)	8 (89%)	4 (67%)	27 (87%)
Assessment of vaccine impact	6 (43%)	2 (40%)	5 (71%)	13 (50%)
Guidance for clinical practice locally (hospital based)	11 (73%)	4 (67%)	2 (40%)	17 (65%)
Development of National Clinical Guidelines	9 (60%)	4 (57%)	2 (40%)	12 (44%)
Assessing adverse events following vaccination	7 (50%)	3 (60%)	3 (43%)	13 (50%)

[1] Number (%) of countries that selected an answer and reported 'yes'

Table 42. Uses of pediatric bacterial meningitis surveillance data in country, by region

Factor	n (% of total) [1]			
	AFR	EMR	WPR	All regions
Advocacy to or within the government on the importance/ burden of pediatric bacterial meningitis	16 (89%)	7 (78%)	8 (100%)	31 (89%)
Decision making on vaccine introduction	15 (83%)	7 (78%)	8 (100%)	30 (86%)
Assessment of vaccine impact	14 (78%)	4 (57%)	7 (100%)	25 (78%)
Guidance for clinical practice locally (hospital based)	13 (76%)	4 (57%)	5 (100%)	22 (76%)
Development of National Clinical Guidelines	8 (50%)	4 (57%)	4 (80%)	16 (57%)
Assessing adverse events following vaccination	10 (56%)	3 (60%)	4 (57%)	17 (57%)

[1] Number (%) of countries that selected an answer and reported 'yes'

Sharing of surveillance data

Regarding sharing of surveillance data, the majority of respondents reported that data are reported and shared regularly within the MoH and with sentinel surveillance sites. Surveillance data from other non-governmental sources and other governmental sources also are used for advocacy and decision making.

Funding sources for surveillance

Regarding funding and funding sources for surveillance, the majority reported that current funding is insufficient to maintain surveillance activities. Main funding sources reported were WHO, government and MoH funds, and other partners or external funding. When asked whether it would be possible for the MoH/government to fund surveillance without donor support, answers differed by region. Most respondents from AFR reported that it would not be possible; most respondents from EMR reported that it would be possible; and respondents from WPR were divided 50/50 in their answers (Table 43).

Table 43. Number (%) of respondents reporting whether their MoH/government would be able to fund surveillance without donor support

Is it possible for MOH/Govt to fund without donor support?	n (% of total)			
	AFR	EMR	WPR	All regions
Yes	7 (37%)	7 (78%)	3 (50%)	17 (50%)
No	12 (63%)	2 (22%)	3 (50%)	17 (50%)
Total	**19**	**9**	**6**	**34**
***Missing*[1]**	*8*	*4*	*2*	*14*

[1] Missing' includes both non-responses and skipped questions for countries without sentinel surveillance

Almost 40% of respondents reported that there are additional sources of surveillance funding, although this varied by region – 32% of respondents from AFR, 22% of respondents from EMR, and 71% of respondents from WPR reported additional sources. Of those that reported additional sources of funding, the majority answered that <50% of the total cost of surveillance is funded by other sources and that most of this funding is used for specimen collection kits and laboratory supplies.

Partner support for surveillance

The majority of respondents reported that they receive partner support for rotavirus and/or pediatric bacterial meningitis surveillance. Of those that reported receiving partner support, all answered that WHO is a supporting partner, while other agencies and organizations, such as the US Centers for Disease Control and Prevention, universities, the GAVI Alliance, the Bill and Melinda Gates Foundation, some non-governmental organizations, and international cooperation agencies provided some support. All partners provided different types of support, including technical support, advocacy, financial support, and data sharing support.

When asked whether additional support could be sought from partners for rotavirus and pediatric bacterial meningitis surveillance, answers differed by region – 70% of respondents from AFR, 45% of respondents from EMR, and 29% of respondents from WPR reported that additional support could be sought. The main types of support sought were financial, technical (e.g., training, evaluation, help for network expansion), that related to laboratory supplies and equipment.

Respondent opinions about the surveillance systems

Future of rotavirus and pediatric bacterial meningitis surveillance

When asked whether the objectives of each surveillance system had been fulfilled, most answered 'yes,' and that rotavirus and/or pediatric bacterial meningitis surveillance would continue to be a priority for many years (Tables 44 and 45).

Desire to expand sites

The MoH expressed a desire to increase the number of sites in countries to increase the representativeness of the surveillance system.

Table 44. Opinions about rotavirus surveillance, by region

Opinion	n (% of total)			
	AFR	EMR	WPR	All regions
Objecitves have been fulfilled ('yes')	10 (59%)	7 (88%)	4 (80%)	21 (70%)
Rotavirus surveillance will continue to be a priority ('yes')	18 (100%)	8 (89%)	8 (100%)	34 (97%)
Priority for how long	At least 3y=0	At least 3y=0	At least	At least

	At least 5y=5(28%) >5y=13(72%)	At least 5y=0 >5y=8(100%)	3y=2(25%) At least 5y=2(25%) >5y=4(50%)	3y=2(6%) At least 5y=7(21%) >5y=25(74%)

Table 45. Opinions about pediatric bacterial meningitis surveillance, by region

Opinion	n (% of total)			
	AFR	EMR	WPR	All regions
Objecitves have been fulfilled ('yes')	13 (72%)	6 (75%)	4 (100%)	23 (77%)
Bacterial meningitis surveillance will continue to be a priority ('yes')	18 (100%)	8 (89%)	8 (100%)	34 (97%)
Priority for how long	At least 3y=2(11%) At least 5y=2(11%) >5y=14(78%)	At least 3y=0 At least 5y=0 >5y=8(100%)	At least 3y=2(25%) At least 5y=1(13%) >5y=5(63%)	At least 3y=4(12%) At least 5y=3(9%) >5y=27(79%)

In addition to the surveillance systems continuing as a priority, most respondents reported that the current surveillance networks can be used as platforms to support surveillance for other disease with new vaccines, that these networks will be used to provide data for rotavirus and/or pneumococcal vaccine introduction, and that VPD surveillance is a priority for the MoH (Table 46).

Table 46. Future directions for rotavirus and pediatric bacterial meningitis surveillance networks

Opinion	n (% of total)			
	AFR	EMR	WPR	All regions
These surveillance networks can be used as platforms to support surveillance for other diseases with new vaccines ('yes')	20 (100%)	9 (100%)	8 (100%)	37 (100%)
These networks wil be used to provide data for vaccine rotavirus/PCV introduction ('yes')	21 (100%)	5 (56%)	7 (100%)	33 (89%)
VPD surveillance is a priority for the MOH ('yes')	20 (95%)	9 (100%)	7 (100%)	36 (97%)

Main strengths and weaknesses of rotavirus and bacterial meningitis surveillance

The main strengths and weaknesses of rotavirus and bacterial meningitis surveillance, as cited by the respondents, are the following (Table 47):

Table 47. Main strengths and weaknesses of rotavirus and pediatric bacterial meningitis, as cited by survey respondents

Main strengths of both surveillance systems
• A strong commitment to surveillance • Dedicated and trained staff • An existing surveillance system infrastructure • Strong laboratories • Timely reporting • Generation of data to understand disease patterns
Main weaknesses of rotavirus surveillance
• Insufficient funding and human resources • Increase in workload • Need for more technical support • Limited number of sentinel sites (e.g., sites may be located only in the capital city)
Main weaknesses of pediatric bacterial meningitis surveillance
• Insufficient funding and human resources • Inadequate training or refresher trainings for staff • Diagnostic issues (e.g., low detection rate, shortages of reagents or shipping delays)

Lessons learned and areas for improvement

Some lessons learned and areas for improvement, as cited by respondents, are provided in Table 48:

Table 48. Lessons learned

Some lessons learned
• Sentinel site location may be important (e.g., should all sentinel sites be located in the capital city) • Training is important • Communication among surveillance staff is important • Supportive supervision is important • Terms of reference for staff should be clear • Data collection and management tools should be tested before starting surveillance
Some areas for improvement
• Financing • Site selection (e.g., so that not all sites are located in one area) • Training and supervision

- Laboratory capacity
- Availability of laboratory reagents
- Performance quality rather than quantity

8. WHO ROLES AND RESPONSIBILITIES

The original roles and responsibilities of WHO defined in 2008 were the following:

- "Provide technical guidance, training, coordination and standardization of the surveillance network
- Set up and coordinate global laboratory networks for invasive bacterial diseases and rotavirus diarrhoea
- Promote linkages and information exchange between regions and partners
- Support communication of surveillance data and its use for decision making in the country and regional level"

Activities of staff from WHO ROs and HQ were reviewed for their relevance to the original stated roles and responsibilities. Overall, staff at WHO ROs and HQ are providing support and conducting activities that fulfill the 2008 roles and responsibilities.

Examples of WHO HQ activities to support IB-VPD and RV surveillance are provided in Table 49:

Table 49. WHO headquarters activities to support IB-VPD and RV surveillance

Capacity building activities	Laboratory-specific activities
• IB-VPD: agreement on case definitions in 2010, standardized sentinel sites assessment tools, laboratory manual, laboratory poster, clinical poster, data management pamphlet, laboratory EQA programme • RV: agreement on case definitions in 201, standardized sentinel sites assessment tools, laboratory EQA programme • Global RV and IB-VPD surveillance bulletins, twice annually • Annual global surveillance meeting, including laboratory network • Attending RO surveillance meetings • Travel for sentinel sites assessments • Identification of lessons learned in one region to share with other regions (e.g., WPRO experience on transition to MoH was shared with SEARO; EMRO Access database was share with EURO)	• Set up and coordinate global laboratory networks for IB-VPD and RV • Formalized a tiered structure such as the polio/measles lab net • Developed roles and responsibilities for each tier • Ongoing coordination calls with ROs and RRLs to agree on priorities • Annual global network and TWG meetings • GRL trainings of RRLs supported via HQ's TSA with the GRLs

Examples of WHO RO activities are provided in Table 50:

Table 50. WHO regional office activities to support IB-VPD and RV surveillance

Regional Office	Capacity building activities	Laboratory-specific activities
AFRO	• Technical regional guidelines and SOPs • Surveillance data analysis and feedback to surveillance sites • National/regional workshops/meetings • GAVI peer review workshops on data use • Attendance at international meetings	• Virology and bacteriology lab strengthening to improve rotavirus and bacterial meningitis diagnosis • Regional reference laboratory capacity strengthening • Support of annual lab workshops for public health labs in collaboration with RRLs
AMRO	• Guidelines for rotavirus and bacterial pneumonia and meningitis surveillance • National evaluations for countries with rotavirus and/or pneumococcal disease surveillance • Financial and technical support for special studies • Regional and sub-regional meetings on IB-VPD and rotavirus surveillance • Participation in international meetings to share lessons learned	• Support to strengthen the rotavirus regional lab network • Integration of the IB-VPD regional lab network with online database – SIREVA-II • Participation of all rotavirus labs in the WHO EQAP • Development of EQAP by the SIREVA-II network
EMRO	• Development of regional guideline and SOPs for IB-VPD and rotavirus surveillance • Pre-engagement training of all sentinel site staff on SOPs and data management support • Regional training workshops • Country visits for follow up and on site capacity building • Support to countries for presenting data to NITAGs for vaccine introduction decisions	• RRL support of sentinel sites (QC, sites assessments, training) • Regional training workshops on rotavirus EIA and genotyping • National training workshops on enrollment, periodic review, and capacity building of IB-VPD and rotavirus surveillance
EURO	• Development of national protocols for IB-VPD and rotavirus surveillance • Development of standardized case report form and data management software • National trainings for epidemiologists and lab staff	• National IB-VPD and rotavirus training workshops • Training of staff at RRL • IB-VPD and rotavirus surveillance network meetings

	• Support for vaccine impact evaluations • Regional network meetings	
SEARO	• Technical guidance to IB-VPD and rotavirus sentinel sites • Coordination of regional SOPs implementation for receipt, storage, and transport for rotavirus specimens • Surveillance coordinators meetings • Inter-country workshop on IB-VPD and rotavirus sentinel surveillance • Use of surveillance data for PCV introduction decisions in Bangladesh and Nepal	• Training workshops on IB-VPD detection and pneumococcal serotyping • Rotavirus genotyping capacity strengthening in Myanmar and Indonesia • Coordination of other capacity building activities and EQA
WPRO	• Technical guidance to countries on all aspects of surveillance • Coordination and standardization by guiding countries to follow WHO standards, definitions, and other guidance • Data management training • Provision of standardized data feedback to each country • Inclusion of surveillance data in summaries of disease burden data for countries considering GAVI applications or other new vaccine introductions	• Establishment of the regional network including RRLs for rotavirus and IB-VPD, national labs, and sentinel site labs • Training for laboratory components of surveillance • Lab network meetings

9. SURVEILLANCE NETWORKS FUNDING

Sources and amount of funding

Funding of the global IB-VPD and rotavirus surveillance networks has been provided by the GAVI Alliance since the inception of these two networks. Although the two surveillance networks tend to function separately, with the exception of common sentinel surveillance sites, it is difficult to specify how funds have been allocated to support each network. Table 51 provides an overall picture of GAVI Alliance funding during 2009-2013:

Table 51. GAVI Alliance funding for WHO IB-VPD and RV surveillance, 2009-2013

Year	WHO Activity Millions, USD		WHO Staffing Millions, USD		WHO Total Millions, USD
	Total	%	Total	%	Total
2009	7.1	89%	0.9	11%	8.0
2010	7.8	86%	1.3	14%	9.1
2011	8.0	81%	1.9	19%	9.9
2012	7.5	78%	2.1	22%	9.6
2013	6.3	71%	2.6	29%	8.9
Total	**36.7**	**81%**	**8.8**	**19%**	**45.5**

Additional funding for surveillance-related activities has been provided by the participating countries themselves, especially in regional networks such as AMR and EMR, where are large proportion of countries are not GAVI eligible. The US Centers for Disease Control and Prevention (CDC) also provides support for site assessments, surveillance in middle income countries, data quality assessments, staff, and technical assistance.

Funding challenges

Feedback from the sentinels sites, laboratories and ROs repeatedly identified year-to-year funding as one of the main challenges with maintaining and strengthening the surveillance networks. Almost all have encountered difficulty in maintaining consistent reporting and staff given the uncertainty of additional funding each year. One example provided by WHO HQ was the loss of a RRL due to lack of longer term funding. Other examples provided have mentioned gaps in reporting and loss of staff. Additionally, some ROs reported that funding is not sufficient to sustain surveillance at their sentinel sites.

10. SUMMARY AND RECOMMENDATIONS

With the main tasks of reviewing information generated by the strategic review regarding IB-VPD and RV surveillance and laboratory networks performance, data flow, country-level expert opinions about the surveillance networks, WHO roles and responsibilities, and funding, WHO HQ staff, WHO RO staff, and iTAG members convened in September 2013 to: 1) discuss to what extent the original 2008 objectives for the surveillance networks have been met and 2) provide conclusions and recommendations for the future vision for the networks. During this meeting, the IB-VPD and RV surveillance networks were discussed jointly in some sessions and separately in others. The following sections provide summaries of discussions and recommendations set forth by the participants of the meeting.

Review of the IB-VPD surveillance network

Over the past 5 years, the IB-VPD surveillance network has had some notable accomplishments that include the following:

- Achievement of the 2008 surveillance objectives for presence of disease and use of data for decision making
- Use of the IB-VPD surveillance platform
    - Surveillance sites used for special studies in Brazil and Mongolia
    - Capacity to detect other VPDs (e.g., typhoid)
    - Capacity building and increasing laboratory presence in many countries
- Use of data from the IB-VPD surveillance network
    - Use of surveillance data in GAVI applications for Hib vaccine and PCV
    - Outbreak detection: meningitis outbreaks
    - Baseline surveillance data to be used for PCV impact evaluations

However, this network is still developing and much can be done to further strengthen and improve the system in order to fully achieve the objectives of the surveillance network. Based on review of all relevant information and findings from the independent consultants, specific recommendations for the IB-VPD surveillance network were made (Table 52).

Looking ahead, it was noted that countries are beginning to or already recognize the importance of PCV introductions and monitoring changes in aetiologic agents of invasive bacterial disease and of the contributions that the IB-VPD surveillance network makes in providing disease burden data and potential vaccine impact data. Countries also are interested using in tools and processes to provide evidence-based decision making for the introduction of new vaccines, such as the ProVac Initiative that was developed by Pan American Health Organization/AMRO. Country-level surveillance data (e.g., IBD and pneumonia morbidity and mortality) are important inputs for these tools, which include cost-effectiveness models and costing models.

Table 52. Recommendations for the future direction of the IB-VPD surveillance network

Recommendations for the IB-VPD surveillance network

Overall surveillance system recommendations

- Encourage all (GAVI and non-GAVI eligible countries) to participate in the network
  - Participation to require meeting minimum data quality standard
  - Participation subject to financial and human resource constraints
- Standardize data across sties/regions
- Work toward a system with real-time verification and analysis
- Modify future Global Bulletins to show all reporting countries on map, but limit analyses to subset of reporting sites
- Encourage network (e.g., laboratory collaboration with measles, polio, RV networks; sharing of resources)

Laboratory-specific recommendations

- Continue and further strengthen laboratory network at sites and reference laboratories
  - On-site assessment
  - EQA
  - QC: 10% of specimens should be submitted for reference testing
  - Data analysis to validate to validate test and laboratory performance
- Standardize sample selection for serotyping/serogrouping
  - Will provide more geographically representative data
- Link case-based data to serotype/serogroup data

Sentinel-site specific recommendations

- Review standard definition of a sentinel site to ensure that sites meet surveillance objectives
- Initiate zero reporting (i.e., site to report zero if no cases/results rather than leave a blank field)
  - Ensures that a site is functioning even when there are no cases
- Update eligibility criteria for inclusion in data analyses
  - 12 months reporting and >100 meningitis cases or ≥500 pneumonia/sepsis/meningitis cases at a single site
- Develop strategies to improve performances at all sites (GAVI and non-GAVI)
  - Capacity building is a key component
  - Strategies may be based on findings from monitoring and evaluation of the surveillance system
  - Prioritize site assessments (external, MoH, local institutions, etc.)

Review of the rotavirus surveillance network

Over the past 5 years since surveillance was transitioned to WHO coordination, a large amount of data has been generated, which has made this surveillance review very timely. Essentially, the global RV surveillance network has grown over time in number and, with this growth, improvements in the quality of reporting have been noted. Great efforts have been made to standardize data, and accessibility of EQA has allowed the evaluation of laboratory

network performance. Data generated by the RV surveillance network are being used by countries for disease burden estimates, vaccine introduction decisions, vaccine impact evaluations, and advocacy.

The analyses performed and information provided by the strategic review have demonstrated that the RV surveillance network has met largely the 2008 objectives. However, as noted with the IB-VPD surveillance network, the RV surveillance network can be improved to generate better quality data that can be used to achieve the surveillance objectives. Based on review of all relevant information and findings from the independent consultants, specific recommendations for the RV surveillance network were made (Table 53).

Table 53. Recommendations for the future direction of the RV surveillance network

Recommendations for the RV surveillance network
Overall surveillance system recommendations
• Standardize data across sties/regions • Report surveillance data, possibly including genotype data, twice yearly • Report case-based data to WHO Headquarters • Examine current performance indicators for usefulness • Improve data management and quality • Modify future Global Bulletins to show all reporting countries on map, but limit analyses to subset of reporting sites • Encourage all (GAVI and non-GAVI eligible countries) to participate in the network • Network across regions for lessons learned and opportunities for collaboration
Laboratory-specific recommendations

• Standardize sample selection for genotyping
  ○ Will provide more geographically representative data
  ○ Will allow for closer examination of time trends and seasonality
• Consider linking case-based data to genotype data
• Examine country-level genotype distribution
• In addition to distribution at regional and global levels
• Build additional technical capacity at the national laboratory (NL) level, if possible
  ○ e.g., involvement of NL staff in building capacity at national level
  ○ Could reduce workload for Regional Reference Laboratories
• Network with other laboratories (e.g., measles, polio, IB-VPD networks) to look for opportunities for efficiencies

Sentinel-site specific recommendations
• Review standard definition of a sentinel site to ensure that sites meet surveillance objectives • Initiate zero reporting (i.e., site to report zero if no cases/results rather than leave a blank field)   ○ Ensures that a site is functioning even when there are no cases • Update eligibility criteria for inclusion in data analyses

    - 12 months reporting and >100 specimens at a single site (no enrollment through satellite sites)
- Develop strategies to improve performances at all sites (GAVI and non-GAVI)
    - Capacity building is a key component
    - Strategies may be based on findings from monitoring and evaluation of the surveillance system
    - e.g., allow all sites to participate in EQAs

In summary, the global IB-VPD and RV surveillance networks have been able to document the presence of disease and are using data from the networks. There is also evidence to show that countries, Ministries of Health, WHO RO and HQ staff, and global immunization partners are dedicated to maintaining and strengthening each surveillance network and that these networks are building country-level capacity for disease surveillance and generating data that have been used to estimate disease burden, inform vaccine introduction decisions, monitor vaccine impact, and provide information for advocacy. While the RV surveillance network appears to be further developed and closer to reaching its objectives, there is still room to improve both surveillance networks, and future plans should look to strengthen the quality of data reported and laboratory capacities. In addition to the recommendations listed, longer-term funding can provide countries and their surveillance sites and laboratories with greater stability that would result in more consistent reporting and higher quality surveillance data.

APPENDIX A. iTAG REVIEW TEAM

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APPENDIX B. NUVI DATA ANALYSIS PLAN

NUVI Surveillance Strategic Review: Data Analysis Plan

Table of Contents:

Background and objective of this document:

As part of the strategic review of the WHO-coordinated invasive bacterial vaccine preventable diseases (IB-VPD) and rotavirus (RV) surveillance networks, WHO with the technical guidance of the iTAG for NUVI Surveillance will undertake targeted, supplementary data analysis to better understand the quantity, quality, and uses of data produced by both surveillance networks. The data analysis plan needs to consider the following critical elements:

1. As part of the strategic review, WHO is making available data from all WHO reporting levels including from over 50 WHO Member States, 150 sentinel sites and 20 reference laboratories. Due to the volume of data available, a targeted data analysis plan is required, so that key questions raised during the review can be efficiently answered with data analysis conducted

during June and July, and synthesis of findings in August. In depth discussion of findings will take place during the strategic review meeting the week of 16 September 2013.

2. Because the review is being conducted in a focused timeframe, data analysis needs to be limited to information already available.
3. For IB-VPD surveillance, a 'proof of concept' is required to demonstrate that the WHO coordinated network is capable of meeting the original network objectives set in 2008, and the currently important objective of detecting vaccine impact. For RV, such a proof of concept is less required. Hence, the data analysis plan for the two networks will differ.

The objective of this document is to outline the plan for data analysis and to provide background information that is useful to determine the data analysis plan.

Original 2008 NUVI surveillance objectives with outcomes and deliverables by surveillance Tier WHO's roles and responsibilities, and activities for the laboratory networks:

In 2008, WHO outlined the key objectives of NUVI surveillance with specific outcomes / deliverables, WHO's roles and responsibilities and activities for the laboratory networks[2]. These are copied below:

Original 2008 objectives of NUVI surveillance with specific outcomes / deliverables[1]

"Surveillance objectives during the pre-vaccine introduction period include the following:

- Document presence of disease, describe the disease epidemiology and provide data for estimating disease burden
- Establish system to measure impact after vaccine introduction
- Identify circulating serotypes and measure serotype distribution
- Monitor antibiotic sensitivity

Long term surveillance following vaccine introduction will also be required. In the post-vaccine introduction period, additional objectives will include:

- Assess disease trends over time
- Monitor vaccination program impact
- Monitor changes in circulating strains/serotypes
- Platform for effectiveness and safety evaluation"

The 2008 document further developed specific outcomes/deliverables for each objective and Tier of surveillance. The below table is copied from the 2008 document[1]:

Types of surveillance	Type of Site	Outcome /deliverable
Sentinel hospital based for meningitis and rotavirus diarrhea	Tier 1 (called 'core' sites in 2008)	- Document the vaccine preventable causes of bacterial meningitis and rotavirus diarrhea - Increase awareness of bacterial causes of meningitis and rotavirus diarrhea - Provide local data for decision making - Isolate and store specimens to allow for identification of serotypes (serotyping conducted at a reference laboratory) - Monitor antibiotic susceptibility in meningitis-causing organisms (pre and post-vaccine intro) - Measure impact after vaccine introduction - Assess disease trends over time (as % of meningitis cases and rotavirus diarrhea) - Platform for case-control studies for vaccine effectiveness

[2] Working paper on WHO's strategy for new vaccine surveillance in 2009 and onwards, August 18th 2008.

Sentinel hospital based for meningitis + pneumonia and sepsis (invasive bacterial disease surveillance using standardized criteria)	Tier 2 (called 'added' sites in 2008)	The above PLUS +Demonstrate sepsis and pneumonia disease and its etiology +Identify circulating serotypes isolated from pneumonia and sepsis cases +Monitor antibiotic sensitivity in pneumonia and sepsis causing organisms +Assess disease trends over time (as % of IBD cases) +Indirect estimate of IBD serotype distribution
Population based surveillance for meningitis and IBD (may also consider other syndromes of interest)	Tier 3 (called 'enhanced' sites in 2008)	The above PLUS +Provide incidence data which can be used to estimate disease burden +Monitor vaccination program impact with population based denominators +Establish platform for effectiveness and safety evaluations +Evaluate serotype ~~replacement~~ 'epidemiology'[3] Assess disease incidence trends over time

WHO's roles and responsibilities[1]

- "Provide technical guidance, training, coordination and standardization of the surveillance network
- Set up and coordinate global laboratory networks for invasive bacterial diseases and rotavirus diarrhoea
- Promote linkages and information exchange between Regions and partners
- Support communication of surveillance data and its use for decision making in the country and Regional level"

Activities for the laboratory networks[1]

- "Establish laboratory technical advisory group for rotavirus and bacterial diseases
- Formalize global new vaccines laboratory network (considering a tiered-structure such as measles and polio and lab networks)
- Establish global laboratory standards for quality assurance, proficiency testing, accreditation
- Develop and distribute laboratory manuals for the diagnosis and characterization of specific diseases as needed
- Establish new national/sub-national/Regional laboratories where needed
- Standardize data collection, sharing and feedback among the Regions
- Conduct laboratory training workshops in the various Regions
- Organize laboratory meetings in conjunction with Regional technical advisory group (TAG) meetings
- Ensure Regional-level staffing needs are met for Rota and Bacterial Laboratory Network implementation"

This 2008 document was shared with key partners including GAVI, the main funding organization for these activities. Currently, WHO and GAVI agree that the above is an accurate representation of the original objectives for the NUVI surveillance networks.

NUVI surveillance strategic review: Overview of data analysis objectives and plan:

The review will use an approach most likely determine whether the original 2008 objectives listed above were attained. Additionally, because PCV and RV vaccine introductions are planned or on-

[3] Wording revised at request of iTAG (25 May conference call)

going in GAVI-eligible countries, the review will also assess what is/could be the contribution (if any) of data generated by the NUVI surveillance networks to document impact (short- and long-term) of new vaccines introduction (e.g. PCV, rota).

Data analysis will include:

(i) Use of data from sentinel hospital sites most likely to have accomplished the original surveillance tasks (at least 1 per region) to illustrate how data generated by the network can/is being used to contribute to impact evaluation efforts ;
NB: this is in contrast to an effort to collect and synthetize all data available from sites and laboratories that will probably have varied sensitivity, quality etc.

(ii) An assessment of attainment of WHO surveillance performance indicators used by the networks to monitor performance; and

(iii) An evaluation of the laboratory networks and the available serotype/genotype data.

Data analysis plan:
Due to the inherent differences in IB-VPD and RV surveillance, data analysis for the two networks will differ. Please refer to Annex 1 for the details of the data analysis plan.
Action 1: Assessment of data completeness with data cleaning

- For each sentinel site, assess the completeness of reporting of the minimum data set, identify duplicates and run exploratory data analysis with the intent of identification of inconsistencies (e.g. date of birth is later than date of hospitalization)

Action 2a: In each WHO Region and sub-Region, identify one to three sentinel sites most likely to have accomplished the original 2008 surveillance tasks most completely, based on some of the following criteria:

For IB-VPD:
- Tier 3 sites, mostly dependent on WHO support
- Consistent reporting throughout the period
- Data available on the individual case level
- Age data available on most cases
- Information available on laboratory diagnostic tests used and results, by test
- Reported the largest number of laboratory-confirmed invasive VPD cases for Tier 1 and/or Tier 2
- Reported the largest number of probable IBD cases for Tier 1 and/or Tier 2
- Enrolled the largest number of suspect IBD cases
- Met all/the majority of surveillance performance indicators over time

For RV:
- Reported data to WHO for at least the most recent years or the most number of years from 2008 to 2012;
- Reported data for at least 10 months of each year (to account for disease seasonality);[4] and
- Tested at least 100 stool specimens annually among children <5 years of age hospitalized with acute gastroenteritis.

Action 2b: Assess the laboratory networks

[4] Data reported must include at least one stool specimen tested each month; hence,' zero reporting' of stool specimen testing is excluded.

- Describe whether the original 2008 activities were accomplished
- For IB-VPD surveillance, assess the utility of September 2010 (to check date) decisions to implement rapid diagnostic testing at all sentinel hospital sites as well as polymerase chain reaction testing at reference laboratories
    - Generate 2x2 table displaying testing results for cases with specimens obtained with the following information available: culture result, and rapid diagnostic testing at the sentinel site (or in country)
    - Generate 2x2 table testing results for cases with specimens obtained with the following information available: organism identified based on culture results at the sentinel site (or in-country) plus rapid diagnostic testing at the sentinel site (or in-country) versus PCR at a reference laboratory
    - For selected sentinel sites (using the above criteria as a guide), generate Stacked bar chart illustrating by year the number of laboratory-confirmed cases identified by culture plus additional cases identified by LA, Binax, and PCR

Action 2c: Assess activities undertaken by WHO to fulfil the original roles and responsibilities

Action 3: Assess attainment of surveillance performance indicators

- For the identified sentinel sites, assess annual attainment of WHO-established surveillance performance indicators
- Compare surveillance performance indicators for the identified sites with those of the other sites

Action 4: Assess attainment of original 2008 objectives

- For the identified sentinel sites, assess whether the original objectives with outcomes/deliverables have been achieved (refer to Annex 1, detailed data analysis plan, and Annexes providing the status of PCV and RV vaccine introductions)

Action 5: Assess surveillance sensitivity[5]

- For the sub-set of sentinel sites that were assessed using the WHO standard protocol, assess sensitivity of surveillance to determine whether potential suspect cases were missed (i.e. not enrolled.)

Action 6: Assess complementary data sources as outlined in last Annex

[5] The proportion of cases enrolled into surveillance. Note: introduction of new laboratory diagnostic tests such as the rapid diagnostic tests introduced for IB-VPD surveillance will increase the sensitivity of surveillance to identify laboratory-confirmed VPDs.

Annex 1: NUVI Surveillance Strategic Review: Targeted Analysis Related to the Original 2008 Objectives for RV and IB-VPD Surveillance Networks

NOTE: Columns shaded in gray are copied from the original 2008 document.

Time Period for Objectives	Original Objectives	Original Outcome/Deliverable	Analysis Targeted to	Analysis for Each Year of Data

Pre-Vaccine Introduction	Document presence of disease, describe disease epidemiology, and provide data for estimating disease burden	**Tier 1:** Document the vaccine preventable causes of bacterial meningitis & rotavirus diarrhoea	Sentinel sites most likely to permit assessment of objectives	**IB-VPD**
				• # hospitalized children <5 years of age enrolled into surveillance with suspect/probable meningitis, and laboratory-confirmed Hib, Spn, Nm
				  ○ Age distribution of above children, (consider: <12 months, 12-<24 months, 24-60 months)
				• % Hib, Spn, and Nm detected among children <5 years of age hospitalized with suspect / probable meningitis
				  ○ Age distribution of above children (consider: <12 months, 12-<24 months, 24-60 months)
				• Describe the clinical picture of IBD hospitalizations
				• Case-fatality ratio
				RV
				• % of diarrhoea hospitalizations due to RV among children <5 years of age
				  ○ Age distribution of the above cases (<1 year and 1-4 years; or by year or month of age) of RV cases
				• Describe the seasonality of RV hospitalizations
				• Case-fatality ratio

		Tier 2: The above plus sepsis & pneumonia disease & its etiology	Tier 2 sentinel sites most likely to permit assessment of objectives	**IB-VPD** • # Hib, Spn sepsis/pneumonia cases detected among children <5 years of age enrolled into surveillance ○ Age distribution (consider: <12 months, 12-<24 months, 24-60 months) of Hib, Spn sepsis/pneumonia cases • % of pneumonia/sepsis cases positive by culture among children <5 years of age enrolled into surveillance • % of culture positive (laboratory-confirmed?) cases with detection of Hi and Spn • Case-fatality ratio **RV: Not applicable; no Tier 2 sites/strategy**

		Tier 3: Provide incidence data which can be used to estimate disease burden	Tier 3 site/s	**IB-VPD** • incidence rates by time, by age strata (consider: <12 months, 12-<24 months, 24-60 months) for suspect/probable meningitis, pneumonia, and sepsis • incidence rates by time, age strata (consider: <12 months, 12-<24 months, 24-60 months) for laboratory-confirmed cases of Hib, Spn, Nm, stratified by disease syndrome • Refer to methodology to establish a denominator for an IB-VPD Tier 1 / meningitis sentinel site • refer to studies from participating sites for additional incidence data? **RV** • incidence rates by time, by age strata (<1 year and 1-4 years; or by year or month of age) for enrolled cases and RV positive cases • refer to existing studies from participating sites for additional incidence data
		Tier 1: Increase awareness of bacterial causes of meningitis & rotavirus diarrhoea	WHO Member States with sentinel sites most likely to permit assessment of objectives	**IB-VPD** • Input from RO plus review of country surveys, WHO standardized sentinel site assessments, and PAHO NUVI assessments **RV** • Input from RO plus review of country surveys, WHO standardized sentinel site assessments, and PAHO NUVI assessments
		Tier 1: Provide local data for decision making	WHO Member States with sentinel sites most likely to permit assessment of objectives	**IB-VPD** • Review of country surveys, GAVI country applications and APRs, to identify use of NUVI surveillance data • Input from RO on NITAG, ICC etc. use of NUVI surveillance data **RV** • Review of country surveys, GAVI country applications and APRs, to identify use of NUVI surveillance data • Input from RO on NITAG, ICC etc. use of NUVI surveillance data • Review of literature and input from ROs for published studies of RV disease burden from participating sentinel sites

	Establish system to measure impact after vaccine introduction	**All Tiers**	All participating WHO Member States in IB-VPD and RV networks	**IB-VPD** • # of sentinel sites with consistent/sufficient baseline data to monitor trends for changes pre- and post-vaccine introduction, and have capacity to identify sufficient confirmed cases to conduct a case-control study. • # VE studies planned that include surveillance data/use surveillance as a platform **RV** • # of sentinel sites that reported data for the most recent years, reported at least 10 months of data annually for each considered, enrolled at least 100 children <5 years of age into surveillance annually, and reported at least 1 stool specimen tested monthly (the latter to exclude 'zero' reporting) • # VE studies planned that include surveillance data/use the surveillance as a platform
	Identify circulating serotypes and measure serotype distribution	**Tier 1:** Isolate and store specimens to allow for identification of serotype (serotyping conducted at reference laboratory)	All participating WHO Member States in IB-VPD and RV networks	**IB-VPD: stratification by pre-, post-vaccine introduction** • Describe annual distribution of Spn/Hib/Nm serotypes by country and Region • Describe serotype epidemiology by age (consider: <12 months, 12-<24 months, 24-60 months) and disease syndrome, by country and Region • Input from RO, country surveys, sentinel site assessments **RV: stratification by pre-, post-vaccine introduction** • Describe annual distribution of RV genotypes by country and Region • Input from RO, country surveys, sentinel site assessments
		Tier 2: Identify circulating serotypes isolated from pneumonia and sepsis cases	All IB-VPD Tier 2 WHO Member States	**IB-VPD: stratification by pre-, post-vaccine introduction** • Describe serotypes isolated from sepsis/pneumonia cases by country and WHO region/sub-region • Describe serotype epidemiology by age (consider: <12 months, 12-<24 months, 24-60 months) and disease syndrome, by country and Region **RV: Not applicable; no Tier 2 sites/strategy**
	Monitor antibiotic sensitivity	**Tier 1:** Monitor antibiotic susceptibility in meningitis-causing organisms	All participating WHO Member States in IB-VPD network	**IB-VPD** • Input from RO, country surveys, sentinel site assessments, IB-VPD EQA programme **RV: Not applicable**

Post-Vaccine Introduction	Assess disease trends over time			
		All Tiers: assessment of annual surveillance performance	Sentinel sites most likely to permit assessment of objectives in vaccine introducing WHO Member States	**IB-VPD: countries that have introduced PCV for >1 year (Annex 2)** • In countries with standardized sentinel site assessment, determine (quantify?) whether suspect cases are not enrolled into surveillance, as assessment of surveillance sensitivity • Describe laboratory diagnostic testing options over time • Assess surveillance performance indicators over time • Assess surveillance performance indicators in other sentinel sites **RV: countries that have introduced RV vaccine for >1 year (Annex 3)** • In countries with standardized sentinel site assessment, determine whether suspect cases are not enrolled into surveillance, as assessment of surveillance sensitivity • Describe laboratory diagnostic testing options • Assess surveillance performance indicators over time • Assess surveillance performance indicators in other sentinel sites

		Tier 1: Assess disease trends over time as % of meningitis cases and rotavirus diarrhoea
		
		Note: also refer to below point on monitor vaccination programme impact
			Sentinel sites most likely to permit assessment of objectives in vaccine introducing WHO Member States	**IB-VPD: countries that have introduced PCV for >1 year (Annex 2)**
				• Annual #s and %ages of lab-confirmed Hib, Spn, Nm among suspect meningitis cases with a culture result recorded in children (consider: <12 months, 12-<24 months, 24-60 months), pre- and post- vaccine introduction
				  ○ Including change in % before and after vaccine introduction
				• Annual #s and %ages of lab-confirmed Hib, Spn, Nm among probable meningitis cases in children (consider: <12 months, 12-<24 months, 24-60 months), pre- and post- vaccine introduction
				  ○ Including change in % before and after vaccine introduction
				RV: countries that have introduced RV vaccine for >1 year (Annex 3)
				• % hospitalizations due to RV among children hospitalized with acute gastroenteritis by age (<1 year of age and <5 years of age), pre- and post-vaccine introduction
				  ○ Including change in % before and after vaccine introduction
				• Refer to existing studies from participating sites for additional incidence data

		Tier 2: Assess disease trends over time as % of IBD cases	Tier 2 sentinel sites most likely to permit assessment of objectives in vaccine introducing WHO Member States	**IB-VPD: countries that have introduced PCV for >1 year (Annex 2)** • Annual #s of suspect pneumonia and sepsis cases in children <5 years of age, pre- and post-vaccine introduction • Annual #s and %ages of lab-confirmed Hib and Spn cases among suspect sepsis and pneumonia cases in children <5 years of age with a BC performed over time, pre- and post-vaccine introduction **RV: not applicable**
		Tier 1: Monitor antibiotic susceptibility in meningitis-causing organisms	Sentinel sites most likely to permit assessment of objectives in vaccine introducing WHO Member States	**IB-VPD: countries that have introduced PCV for >1 year (Annex 2)** • Input from RO, country surveys, sentinel site assessments pre- and post-vaccine introduction **RV: not applicable**
		Tier 2: Monitor antibiotic sensitivity in pneumonia and sepsis causing organisms	Tier 2 sentinel sites most likely to permit assessment of objectives in vaccine introducing WHO Member States	**IB-VPD: countries that have introduced PCV for >1 year (Annex 2)** • Input from RO, country surveys, sentinel site assessments **RV: not applicable**
		Tier 3: Assess disease incidence trends over time	Tier 3 site/s	**IB-VPD: countries that have introduced PCV for >1 year (Annex 2)** • Annual incidence of suspect/probable meningitis, pneumonia & sepsis, pre- and post-vaccine introduction • Annual incidence of lab-confirmed Hib, Spn, Nm by time & age strata (consider: <12 months, 12-<24 months, 24-60 months), pre- and post-vaccine introduction **RV: countries that have introduced RV vaccine for >1 year (Annex 3)**

				• RV incidence by time and age strata (<1 year and 2-4 years), pre- and post-vaccine introduction • Refer to existing studies from participating sites for additional incidence data
	Monitor vaccination programme impact	**Tier 1:** Measure impact after vaccine introduction ***Note: also refer to above point on monitor disease trends over time***	Sentinel sites most likely to permit assessment of objectives in vaccine introducing WHO Member States	**In addition to analysis outlined above ("**Assess disease trends over time as % of meningitis cases and rotavirus diarrhoea"): **IB-VPD: countries that have introduced PCV for >1 year (Annex 2)** • #s of suspect/probable meningitis cases among children <5 years of age, pre- and post-vaccine introduction • #s of lab-confirmed Hib, Spn, Nm by age strata (consider: <12 months, 12-<24 months, 24-60 months) pre- and post-vaccine introduction **RV: countries that have introduced RV vaccine for >1 year (Annex 3)** • Describe the seasonality of RV hospitalizations pre- and post-introduction (aggregate data) • Describe the age distribution and clinical picture of RV positive cases hospitalized pre- and post-vaccine introduction (individual level data)
		Tier 3: Monitor vaccination programme impact with population based denominators	Tier 3 site/s	**IB-VPD: countries that have introduced PCV for >1 year (Annex 2)** • As above using incidence rates **RV: countries that have introduced RV vaccine for >1 year (Annex 3)** • Review literature for published studies of RV disease burden from participating sentinel sites
	Monitor changes in circulating strains/serotypes	**Tier 2:** Indirect estimate of IBD serotype distribution	IB-VPD laboratory network (all WHO Member States) All Tiers	**IB-VPD: countries that have introduced PCV for >1 year (Annex 2)** • changes in epidemiology of % VT over time by age strata (consider: <12 months, 12-<24 months, 24-60 months), by country, Region and/or globally • VT cases by time ***?? no rates available*** **RV: countries that have introduced RV vaccine for >1 year (Annex 3)** • Annual distribution of RV genotypes by country and region pre-and post-vaccine introduction

		Tier 3: Evaluate serotype ~~replacement~~ *'epidemiology'*[6]	Tier 3 site/s	**IB-VPD: countries that have introduced PCV for >1 year (Annex 2)** • By site, % VT over time by age strata (consider: <12 months, 12-<24 months, 24-60 months) • By site, VT case series by time • ***Or, pooled data?***
	Platform for effectiveness and safety evaluation	**Tier 1:** Platform for case-control studies for vaccine effectiveness	All sentinel sites in vaccine introducing WHO Member States	**IB-VPD: countries that have introduced PCV for >1 year (Annex 2)** • # VE/ vaccine safety studies or evaluations planned, in process, or completed that include surveillance data/use the surveillance as a platform • Input from PAHO NUVI assessments **RV: countries that have introduced RV vaccine for >1 year (Annex 3)** • # VE/ vaccine safety studies or evaluations planned, in process, or completed that include surveillance data/use the surveillance as a platform • Input from PAHO NUVI assessments
		Tier 3: Establish platform for effectiveness and safety evaluations	Tier 3 site/s	**IB-VPD: countries that have introduced PCV for >1 year (Annex 2)** • Tier 3 site conducting vaccine effectiveness and safety evaluation **RV: countries that have introduced RV vaccine for >1 year (Annex 3)** • Tier 3 site conducting vaccine effectiveness and safety evaluation

[6] Wording modified per request from iTAG (25 May 2013 conference call)

Annex 2: NUVI Surveillance Strategic Review: Planned assessment of WHO's roles and responsibilities, and activities for the laboratory networks, as outlined in 2008

NOTE: Columns shaded in gray are copied from the original 2008 document.

Category of Tasks Outline in 2008	Original Tasks	Planned Assessment
WHO's roles & responsibilities	Provide technical guidance, training, coordination & standardization of the surveillance network	• Number of global and regional technical guidance documents, technical consultations to network countries, network meetings coordinated by WHO • Country-level opinions on value of these activities and the complementary role of other partners at the country-level • Data sources: RO & HQ input, review of country surveys and sentinel site assessments
	Set up and coordinate global laboratory networks for IBD and rotavirus diarrhoea	• Number of participating sentinel hospital laboratories, RRLs, and GRLs • Number of technical guidance documents, technical consultations to network laboratories, laboratories network meetings coordinated by WHO • Data sources: RO & HQ input, review of country surveys and sentinel site assessments
	Promote linkages and information exchange between Regions and partners	• Number of global and regional surveillance reports and network meetings coordinated by WHO • Data sources: RO & HQ input, review of country surveys and sentinel site assessments
	Support communication of surveillance data and its use for decision making in the country and Regional level	• Number of global and regional surveillance reports and network meetings coordinated by WHO • Number of country and regional level surveillance meetings coordinated by WHO • Data sources: RO & HQ input, review of country surveys and sentinel site assessments
Laboratory Network	Establish laboratory technical advisory group for RV & IBD	• Document existence of IB-VPD and RV laboratory technical advisory group • Describe frequency of meetings and key policy decisions made to improve the IB-VPD and RV surveillance networks • Data sources: RO & HQ input
	Formalize global new vaccines laboratory network (considering a tiered-structure such as measles and polio lab networks	• Document structure of existing IB-VPD and RV laboratory networks • Documentation describing the roles and responsibilities of each level of reference laboratory • Describe strengths and weaknesses of the current IB-VPD and RV laboratory networks, particularly of the reference laboratories in supporting the surveillance networks • Data sources: RO & HQ input, review of country surveys and sentinel site assessments

	Establish global laboratory standards for quality assurance, proficiency testing, accreditation	• Document existence of global IB-VPD and RV laboratory standards for quality assurance, proficiency testing, accreditation • Summarize results of IB-VPD and RV EQA programmes • Summarize results of IB-VPD and RV QC programmes • Data sources: RO & HQ input, laboratory QA/QC processes
	Develop and distribute laboratory manuals for the diagnosis & characterization of specific diseases as needed	• Document existence and distribution of laboratory manuals for the diagnosis and characterization of IB-VPD and RV disease • Data sources: RO & HQ input and websites
	Establish new national/sub-national/Regional laboratories where needed	• Document expansion of IB-VPD and RV laboratory networks over time • Data sources: RO & HQ input
	Standardize data collection, sharing and feedback among the Regions	• Document existing standardized IB-VPD and RV data collection forms, and process of sharing and feedback among the Regions • Data sources: RO & HQ input and websites
	Conduct laboratory training workshops in the various Regions	• Document number of IB-VPD and RV laboratory training workshops conducted in each Region • Data sources: RO & HQ input
	Organize laboratory meetings in conjunction with Regional technical advisory group (TAG) meetings	• Document number of WHO coordinated laboratory and regional TAG meetings • Data sources: RO & HQ input
	Ensure Regional-level staffing needs are met for rota and bacterial laboratory network implementation	• Document number of technical consultations requested and fulfilled by WHO • Document WHO Regional level staffing numbers • Data sources: RO & HQ input

Annex 3: PCV introduction among WHO Member States that reported IB-VPD surveillance data in 2008-2012 to the WHO-coordinated Global IB-VPD Surveillance Network[7]

Year of Introduction or Year of Planned Introduction	WHO Member State (WHO Region)
2009	The Gambia (AFR), Peru (AMR), Rwanda (AFR)
2010	Brazil (AMR), El Salvador (AMR), Morocco (EMR), Nicaragua (AMR)
2011	Benin (AFR), Burundi (AFR), Cameroon (AFR), Central African Republic (AFR), Congo (AFR), DR Congo (partial, AFR), Ethiopia (AFR), Honduras (AMR), Kenya (AFR), Malawi (AFR), Mali (AFR), Panama (AMR), Sierra Leone (AFR), Yemen (EMR)
2012	Ghana (AFR), Guatemala (AMR), Pakistan (phased, EMR), Madagascar (AFR) Paraguay (AMR), Zimbabwe (AFR)
2013	Angola (AFR), Mozambique (AFR), Uganda (partial, AFR), Tanzania (AFR), Zambia (AFR)
Planned introduction	
2013	Afghanistan (EMR), Azerbaijan (EUR), Bangladesh (SEAR)
	Bolivia (AMR), Burkina Faso (AFR), Cote d'Ivoire (AFR), Lesotho (AFR), Mongolia (partial, WPR), Namibia (AFR), Niger (AFR), Nigeria (AFR), PNG (WPR), Senegal (AFR), Sudan (EMR), Swaziland (AFR)
2014	Nepal (SEAR)

[7] WHO tracks vaccine introduction in countries closely, and updates information regularly. This information thus will quickly become out of date.

Annex 4: Hib vaccine introduction among WHO Member States that reported IB-VPD surveillance data in 2008-2012 to the WHO-coordinated Global Rotavirus Surveillance Network[8]

Year of Introduction or Year of Planned Introduction	WHO Member State (WHO Region)
1997	The Gambia (AFR)
1998	
1999	Brazil (AMR), Honduras (AMR), Nicaragua (AMR)
2000	Bolivia (AMR), Panama (AMR), Venezuala (AMR)
2001	Kenya (AFR), Syria (EMR)
2002	El Salvador (AMR), Ghana (AFR), Malawi (AFR), Paraguay (AMR), Rwanda (AFR), Uganda (AFR)
2003	Ecuador (AMR)
2004	Burundi (AFR), Zambia (AFR)
2005	Benin (AFR), Guatemala (AMR), Mongolia (WPR), Senegal (AFR), Yemen (EMR)
2006	Angola (AFR), Burkina Faso (AFR), Ukraine (EUR)
2007	Ethiopia (AFR), Libyia (EMR), Mali (AFR), Morocco (EMR), Sierra Leone (AFR)
2008	Central African Republic (AFR), Eritrea (AFR), Lesotho (AFR), Madagascar (2008), Niger (AFR), Pakistan (EMR), Papua New Guinea (WPR), Sri Lanka (SEAR), the Sudan (EMR), Togo (AFR), Zimbabwe (AFR)
2009	Afghanistan (EMR), Bangladesh (SEAR), Cameroon (AFR), Cote d'Ivoire (AFR), Democratic Republic of Congo (AFR), Mozambique (AFR), Namibia (AFR), Nepal (SEAR), Swaziland (AFR), Tanzania (AFR), Uzebekistan (EUR)
2010	Cambodia (WPR), Georgia (EUR), Viet Nam (WPR)
2011	Azerbaijan (EUR), India (SEAR, partial), Iran (EMR)
2012	Iraq (EMR), Nigeria (AFR)

[8] WHO tracks vaccine introduction in countries closely, and updates information regularly. This information thus will quickly become out of date.

2013

Planned introduction

2013

2014

Annex 5: Men A conjugate vaccine introduction among WHO Member States that reported IB-VPD surveillance data in 2011 to the WHO-coordinated Global Rotavirus Surveillance Network[9]

Year of Introduction or Year of Planned Introduction	WHO Member State (WHO Region)
2010	Burkina Faso (AFR)
2011	Cameroon (AFR), Nigeria (AFR)
2012	Ghana (AFR), Senegal (AFR), the Sudan (EMR)
2013	
Approval	

[9] WHO tracks vaccine introduction in countries closely, and updates information regularly. This information thus will quickly become out of date.

Annex 6: RV vaccine introduction among WHO Member States that reported RV surveillance data in 2011 to the WHO-coordinated Global Rotavirus Surveillance Network[10]

Year of Introduction or Year of Planned Introduction	WHO Member State (WHO Region)
2006	Brazil (AMR), Colombia (AMR), El Salvador (AMR), Panama (AMR), Venezuela (AMR)
2007	Ecuador (AMR)
2008	Bolivia (AMR)
2009	Colombia (AMR), Honduras (AMR)
2010	Guatemala (AMR), Guyana (AMR), Morocco (EMR), Paraguay (AMR)
2011	Sudan (EMR)
2012	Armenia (EUR), Fiji (WPR), Ghana (AFR), Iraq (EMR), Moldova (EUR), Rwanda (AFR), Yemen (EMR), Zambia (AFR)
2013	Georgia (EUR), Tanzania (AFR)
Planned introduction	
2013	Ethiopia (AFR), Kenya (AFR)
2014	Cameroon (AFR), Guinea-Bissau (AFR), Nepal (SEAR), Senegal (AFR), Tajikistan (EUR), Uganda (AFR), Uzbekistan (EUR), Zimbabwe (AFR)

[10] WHO tracks vaccine introduction in countries closely, and updates information regularly. This information thus will quickly become out of date.

Annex 7: Data sources available for the strategic review

- **Data routinely reported to WHO** by WHO Member States and sentinel sites participating in the RV and IB-VPD surveillance networks. These data variables and reporting time frames were agreed during a data standardization meeting in 2008[11];
- **Surveys of country-level decision makers** (primarily of EPI Managers and surveillance coordinators) of WHO Member States both conducting and not conducting NUVI surveillance activities. These surveys include assessment of NUVI surveillance in the context of new vaccine introduction, including its value for decision making, estimated costs, programme sustainability, and its uses post-vaccine introduction. WHO developed these standardized surveys with input from CDC and JHSPH, piloted the drafts in selected countries and subsequently revised and adapted the self-administered survey questionnaire. These surveys are facilitated by WHO Regional Offices during key meetings with WHO Member States, and are currently available for the following countries:
    - AFR: Benin, Burkina Faso, Cape Verde, Comoros, Cote d'Ivoire, Eritrea, Ethiopia, Ghana, The Gambia, Guinea, Guinea Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Namibia, Niger, Nigeria, Rwanda, Senegal, Sierra Leone, South Africa, Togo, Zimbabwe;
    - EMR: Bahrain, Djibouti, Egypt, Iran, Iraq, Kuwait, Morocco, Pakistan, Palestine, Qatar, Somalia, United Arab Emirates, Yemen;
    - WPR: Cambodia, China, Laos, Mongolia, Papua New Guinea, Philippines, Viet Nam;

- **WHO standardized hospital sentinel assessments of IB-VPD and RV surveillance.** WHO has developed standardized guidelines for the evaluation and monitoring of IB-VPD and RV sentinel hospital sites. The standardized assessment process and tools were developed by WHO in partnership with CDC and other selected global technical experts, and assessment tools were piloted in several WHO regions. Findings and recommendations have been provided for the following countries (***to be completed and revised by WHO RO colleagues)***:

Region and WHO Member State	IB-VPD Assessment	RV Assessment
AFR		
• The Gambia		
• Kenya		
• Senegal		
• Uganda		
AMR		
• Bolivia		
EMR		
• Afghanistan		
EUR		
• Georgia		
• Ukraine		
SEAR		

[11] Summary report on meeting to standardize new vaccines surveillance data to be collected, shared and reported (focus on rotavirus and invasive bacterial diseases surveillance), October 6-7th 2008, Geneva Switzerland.

- Nepal
- Sri Lanka

WPR

- Lao

- **Ad-hoc in-depth assessments of NUVI surveillance** conducted in the following countries:
    - **Costing the integrated all-VPD surveillance pilot in Costa Rica:** included an assessment of external and country-supported costs of surveillance. Costa Rica became the first country to implement integrated VPD surveillance in 2009, with support from PAHO and CDC. An assessment was made of costs associated with establishing and subsequently operating integrated surveillance. Costs were retrospectively collected for the institutions supporting surveillance including personnel, meetings, infrastructure, office equipment and supplies, transportation, and laboratory facilities. Results of this cost-estimation are described in detail in a paper being published in Vaccine (de Toscano et al, 2013, Vaccine);
    - **AMR/PAHO assessment of new vaccine introduction process:** From March 2010 to April 2011, PAHO evaluated a subset of countries that had introduced rotavirus and/or PCV in the previous five years through interviews with key informants at the country level and a systematic review of published data, grey literature, official technical documents, and country-specific health indicators (paper in press, de Oliveria et al, 2013, Vaccine). Countries evaluated were:
        - Bolivia, Brazil, Nicaragua, Peru, and Venezuela.
- **WHO Regional Office** knowledge of the strengths, limitations and uses of the NUVI surveillance network and generated data at the Regional and country levels ***NOTE: WHO HQ-RO videoconferences planned for July will be an important venue to collect this information***;
- **GAVI applications and Annual Progress Reports**; and
- **Laboratory EQA:** For IB-VPD, globally available for two years. For RV, reference laboratories for two years (global RV EQA is currently in progress)
- **Laboratory line-lists** of specimens with test results

APPENDIX C. NUVI STRATEGIC REVIEW MEETING AGENDA

DRAFT Agenda

NUVI Strategic Review Meeting, 16-20 September 2013

Monday, 16 September 2013: IB-VPD Strategic Review

09:00 – 10:00: Opening and review of meeting objectives

Topics **Person**

- Introductions

Thomas

- Impact evaluation: objectives of the meeting and expected outcomes — Claire

- Review of 2008 objectives for both NUVI surveillance networks — Mary

COFFEE

10:30 - 12:30: Global Overview

Topics	**Person**

• Global overview of the IB VPD network, including the laboratory
  ○ Formation of the network, current network status
  ○ Global data related to the 2008 objectives set for the network
• Global overview of the laboratory network
  ○ Findings from an independent review of the laboratory network
	Mary
	
	Fatima
	
	Ray

• Discussion	Claire

LUNCH

13:30 - 15:00: Regional Perspectives of the IB-VPD Network

Topics	**Person**
• Regional perspectives on the successes of the network (5 minutes presentation from each Region)	RO Colleagues
• Panel discussion with ROs	

Claire

COFFEE

15:30 - 18:00: Country Data and Experiences

Topics	**Person**
• WPRO: Mongolia o 15 minutes presentation/15 minutes discussion	Kim
• SEARO: Bangladesh o 15 minutes presentation/15 minutes discussion	Samir (Ranjan unable to attend)
• EURO: Azerbaijan o 15 minutes presentation/15 minutes discussion	Annemarie
• Regional Presentation: TBD o 15 minutes presentation/15 minutes discussion	Jason

<u>Tuesday, 17 September 2013: IB-VPD Strategic Review Continued</u>

08:00 – 15:00 Joint sessions with measuring PCV impact meeting

15:00 – 18:00: Discussion Regarding 2008 Objectives and Future Directions

Topics	**Person**
• Discussion • Are the 2008 objectives relevant now? • What is the future role of the network? • What are the objectives for the network in this era of vaccine introductions? • Conclusions (potentially to be continued Thursday)	Claire

<u>Wednesday, 18 September 2013: Rotavirus Strategic Review and NUVI Surveillance Data Landscape Analysis</u>

09:30 – 10:00: Opening and review of meeting objectives

Topics	Person
• Introductions and meeting objectives	Gagandeep
• Review of 2008 objectives for both NUVI surveillance networks	Mary

COFFEE

10:30 - 12:30: Global Overview of RV Surveillance Network Infrastructure and Development, and Data Generated from the Network

Topics	Person

• Global overview of the IB VPD network, including the laboratory
  o Formation of the network, current network status
  o Global data related to the 2008 objectives set for the network
	Mary

• Global overview of the laboratory network o Findings from an independent review of the laboratory network	Fatima
	Ray
• Discussion	Gagandeep

LUNCH

13:30 - 15:00: RV Network: Global Overview Conclusions & Regional Implementation Issues

Topics	Person
• Discussion	Gagandeep

- AMRO: Regional experience in Bolivia and vaccine introducing countries — Lucia
    - 15 minutes presentation/15 minutes discussion

- EMRO: Regional experience in Sudan — Eltayeb
    - 15 minutes presentation/15 minutes discussion

- Discussion

COFFEE

15:30 - 18:00: (1) RV Network: Strategy Issues

(2) NUVI Surveillance Data Landscape Analysis

Topics	Person

• Rotavirus Discussion
  o Monitoring differences in case enrolment practices
  o The role of the surveillance network in monitoring vaccine impact
• Conclusions
	Gagandeep

• Data Landscape Analysis	Dave Jackson
• Discussion	
• iTAG discussion on conclusions	

Cocktail

Thursday, 19 September 2013: NUVI Strategic Review:

08:00 – 10:30 Joint sessions with measuring PCV impact

10:30 – 12:30: NUVI Surveillance Strategic Review: Conclusions and Recommendations

Topics	Person
• Main conclusions and recommendations for IB-VPD and rotavirus surveillance networks	Claire Gagandeep
• Discussion	

12:30 – 15:00 Joint sessions with measuring PCV impact

15:30 – 18:00: WHO Closed Session

Topics	Person

- Review of conclusions, recommendations — Thomas

  All

- Discussion on next steps

Friday, 20 September 2013: NUVI Strategic Review:

Venue: WHO Building, Room M205

09:00 – 12:30: WHO Closed Session

(10:30 – 11:00: Coffee)

Topics	**Person**
• Implications of data landscape analysis	Mary, Fatima, Simar
	Dave
• Discussion on next steps	

Lunch

13:30 – 17:00: WHO Closed Session

(15:30 – 16:00: Coffee)

Topics	**Person**
• Strengthening the laboratory network	Fatima
• Discussion on next steps	

APPENDIX D. IB-VPD and RV Laboratory Network Independent Review

NUVI Surveillance Strategic Review: critical review of the WHO Rotavirus and Invasive Bacterial Vaccine Preventable Diseases laboratory networks.

Draft 13/9/2013

Dr Ray Sanders, Independent Consultant.

Contents

Introduction

Under the WHO New and Under-utilized Vaccines Implementation (NUVI) programme the WHO-coordinated global Invasive Bacterial Vaccine Preventable Diseases (IB-VPD) and Rotavirus (RV) surveillance networks have been in existence for 5 years. According to the original programme objectives the laboratory networks were established to support the following:

> "Surveillance objectives during the pre-vaccine introduction period include the following:
> - Document presence of disease, describe the disease epidemiology and provide data for estimating disease burden
> - Establish system to measure impact after vaccine introduction
> - Identify circulating serotypes and measure serotype distribution
> - Monitor antibiotic sensitivity
>
> Long term surveillance following vaccine introduction will also be required. In the post-vaccine introduction period, additional objectives will include:
> - Assess disease trends over time
> - Monitor vaccination program impact
> - Monitor changes in circulating strains/serotypes
> - Platform for effectiveness and safety evaluation"[12]

The laboratory networks are now at a stage of development that warrants review to determine if they are achieving the original programme objectives. The review should also identify strengths and weaknesses of the networks and propose strategies and required actions to ensure both laboratory networks meet agreed current and planned programme objectives.

An analysis was made of the major components and outputs of the Global IB-VPD and RV Laboratory Networks according to a series of questions posed by the Global Programme. Questions were framed with reference to the original programme objectives and the 2008 proposals for data collection, analysis and sharing (1). These questions were:

7. Are the IB-VPD and RV laboratory networks supporting the surveillance systems in the most effective/efficient manner?
8. Are the Regional Reference Laboratories performing effectively and appropriately?

[12] Working Paper on WHO's Strategy for New Vaccine Surveillance in 2009 and Onwards (Aug 18th, 2008)

9. Are participating sites meeting global standards for quality assurance, proficiency testing, and SOPs?
10. Do the IB-VPD and RV networks link with other existing laboratory networks for viral and bacterial diseases?
11. Did the genotype and serotype data generated by the IB-VPD and RV networks address the 2008 objectives, as outlined in the data analysis plan including the list of activities for the laboratory?
12. Are laboratory data components complete and of high-quality?

Information for the review was gathered through access to documents available at WHO HQ and on the WHO HQ website, interview with WHO HQ programme staff, and documentation provided by WHO Regional Offices and available on WHO Regional Office websites. In June 2013 the WHO Global Programme sent structured requests to each WHO Regional Office to provide detailed information on the nature and performance of the Regional surveillance systems in place. The requests included structured questions on laboratory training, activities and monitoring together with questions on laboratory data collection analysis and dissemination. Information provided in the responses from the Regional Offices was used for the review. Given the severe time limitations Regional Laboratory Coordinators were not contacted further during the review process.

Due to the time restriction and the limited opportunity for Regional Office comment there is a strong bias towards viewing the networks from the perspective of WHO HQ, since that was the source of the majority of information used for the review. Where possible and appropriate attempts have been made to reflect information provided directly and indirectly from the WHO Regional Offices and the GRLs and RRL, but the perspective remains predominantly that of the programme and the laboratory networks viewed from the global position.

Executive summary

Both laboratory networks have made huge advances in strengthening national and regional laboratory capacities, standardization of laboratory testing, improving laboratory quality and performance, and establishing functional international networks. Both, however, remain in a state of development. Of the 2 laboratory networks, the RV network is significantly closer to achieving effective support of the programme. The RV laboratory network has inherent advantages over the IB-VPD laboratory network in that not only is laboratory testing significantly less complex, but laboratory requirements are more compatible with those of existing global networks, including polio and measles/rubella. Evidence has been presented that data generated by the RV laboratory network is now capable of demonstrating declines in rotavirus detection rates post introduction of vaccine, and data collected during 2012 and 2013 may well provide evidence of shifting patterns of predominant rotavirus genotypes in response to vaccine introduction.

Shortcomings in performance of the 2 laboratory networks are not due to lack of technical support. The quality and quantity of technical support provided through the TWGs and WHO are outstanding. As technical issues have arisen they have been addressed rapidly and appropriately and any changes to practices or procedures have been presented for implementation with minimal delay. While WHO has been very effective in providing and contributing to technical guidance of the laboratory networks, provision of overall management and oversight has been less impressive. The Regional Offices have clearly been under staffing constraints and Regional Office policies may not place a high priority on network development and supervision. At Global level, while the quality of technical support has been excellent, provision of participatory oversight of the Regional networks has been lacking. There are many valid reasons why this aspect of the Global Programme has remained under-developed, but it needs to be recognised that this is a key function of the Global laboratory coordinator. The 2 Global laboratory networks are each effectively a super-network of the 6 regional networks and each regional network has characteristics and attributes that are region-specific. For WHO HQ to manage the global network effectively there must be a detailed understanding of the characteristics of each Regional network and the conditions under which the network operates. Time permitted for this review has not allowed a detailed assessment of Regional network performance, but one of the outcomes from the current activity should be a detailed assessment of Regional network development, activities and outputs since 2008.

In general, available evidence suggests that all network Regional Reference Laboratories RRLs are performing appropriately, but a more detailed review of the regional networks may reveal issues that have not be detected in this overview. In addition to providing laboratory testing services the

RRLs are expected to monitor and participate in implementation of Quality Assurance/Quality control (QA/QC) programmes; provide technical support to improve capacities of the NLs and sentinel hospital laboratories; provide technical advice to the WHO surveillance programme, and; conduct research aimed at improving or developing methods of diagnosis and pathogen characterization. In many cases, however, even if they agree to undertake these activities, they lack the staffing levels and financial resources necessary. Unless these RRLs are adequately supported with technical and financial resources, either from national or international sources, experience gained through the polio and measles/rubella networks strongly suggests they will struggle to meet expectations and, not infrequently, fail.

With 131 participating laboratories in the IB-VPD network and 153 laboratories in the RV network it is unlikely that all meet required standards, and evidence from analysis of reported data, Regional reports and discussions at technical meetings suggest that failure to meet standards is an on-going problem. Development and roll-out of the global EQA programmes, development of regional and global QC guidelines and development and distribution of generic SOPs are all appropriate technical responses to improving laboratory quality.

Detailed genotype and serotype data generated from 2009 to 2011 failed to address the original 2008 objective of monitoring disease trends and genotype/serotype distribution over time. However, a detailed analysis of the 2012 data may go some way towards meeting those objectives. It is possible that the 2012 RV genotype data will provide evidence for a shift in predominant RV genotypes in response to introduction of RV vaccine under specific conditions.

Incompatibilities exist between the data-generating laboratory networks envisaged in 2008 and the networks evident in 2013. The 2008 objectives appear to assume that the sentinel surveillance conducted will depend on a small number of sites producing high quality data. Although the term 'sentinel surveillance' is used to describe the activities of both the IB-VPD and RV surveillance networks, for several participating countries the surveillance activities have characteristics that are intermediate between true sentinel surveillance and population-based surveillance. This indeterminacy places stress on the laboratory networks as they are attempting to provide the level of quality of performance associated with sentinel surveillance while also providing the flexibility and scope of population-based surveillance. It would be very helpful to the laboratories if the Programme were to review its surveillance strategy and expectations of the laboratory networks so that appropriate laboratory resource requirements can be determined.

It is almost certain that the laboratory data components are not universally complete and of high quality. While it is highly likely that the serotype/serogroup and genotype data received by WHO HQ is of itself high quality, as there is no indication of the source of the isolate, the site of initial testing, or any history of processing of the specimens/isolates, the quality of the data with reference to the programme objectives must be in doubt. The fidelity with which laboratory data is entered into the reporting system and the completeness of reporting is clearly inadequate. This problem can be addressed to some extent by ensuring strict linkage between laboratory data and clinical and epidemiology data through the more effective use of unique case ID numbers. This is not a technical problem; it is one of network management and oversight.

Key Recommendations

Based on the results of external analysis and assessment the following recommendations have been made:

4. **Networks size and surveillance function:** Incompatibilities exist between the current networks size, in terms of number of participating laboratories, and availability of resources to support, monitor and maintain those laboratories. A rationalization process is required to more closely match networks size with expected surveillance outputs and the level of resources available.
    a. In-depth Regional reviews of laboratory networks function and output are required in each of the WHO Regions to identify region-specific issues and provide region-appropriate evaluations. The reviews should document laboratory performance, output and resource requirements for each laboratory in the Regional network together with Regional network coordination and management, performance and network resource requirements. These reviews should be under the direction of the Global Laboratory Coordinator with support from the Regional Laboratory Coordinators, Global Reference Laboratory and selected Regional Reference Laboratory staff.
    b. Following Regional review, here appropriate and possible the number of participating network laboratories should be reduced to more closely match programme capacity to fully support and supervise these laboratories to an extent that guarantees confidence in reported laboratory results.
    c. For participating laboratories in Member States that have established ***de facto*** population-based surveillance using multiple 'sentinel' sites, the programme should determine if this form of surveillance is appropriate to achieving programmatic objectives. If this form of surveillance is not considered technically appropriate within resource limitations, steps should be taken to reallocate programme resources more effectively. Great care must be taken, however, to maintain the laboratory networks within existing Regional programme and initiative structures rather than establishing separate, vertical programmes.

5. **Networks coordination and management:** Coordination and performance management of the laboratory networks by WHO at Global and Regional levels have not matched the level of provision of technical support and guidance, and urgently need to be strengthened.
    a. The roles and responsibilities of WHO Regional and Global laboratory coordinators should be reviewed and revised, within the bounds of existing job descriptions, to place

more emphasis on active management of network performance. The roles and responsibilities of the Global laboratory coordinator must be clearly distinguished from those of Regional laboratory coordinators to reflect the additional functions associated with coordinating and monitoring the distinctive Regional networks.

b. Support and encouragement should be provided to the WHO Global and Regional laboratory coordinators to play more active participatory roles in the routine management of the networks. Every opportunity should be taken for the coordinators and key Regional and Global Reference Laboratory staff to meet to discuss and resolve laboratory network issues.

c. Appropriate tools exist for the on-site assessment of participating laboratories from sentinel site hospital to Regional Reference Laboratory levels. Greater use should be made of these assessment tools and every effort should be made to assess every participating laboratory at least once each year. These assessments should be regarded as a component of an external quality assurance programme and conducted in addition to any external quality assessment (proficiency testing).

6. **Reporting and data management:** A primary programmatic objective is to provide detailed and accurate information on the aetiologic agents associated with specific disease presentations, including detailed characterization according to serotype/serogroup or genotype. While the technical capacity to achieve this objective exists in both Global networks, the information management systems are failing to provide accurate and complete data for full analysis and monitoring of progress towards achieving programme objectives.

    a. To encourage more accurate systematic reporting from WHO Regions to WHO Headquarters the frequency of reporting serotype/serogroup and genotype data should be increased from the current annual reporting of aggregate data to at least 6-monthly reporting of aggregate data. This should be complemented by more frequent feedback of global analysis results to the Regional Offices and to participating laboratories.

    b. To more accurately monitor progress towards achieving programme objectives Regional Offices should provide case-based data on all pathogen-positives to WHO Headquarters on a quarterly or 6-monthly basis, whichever is appropriate to their Regional reporting schedules. This should be conducted in addition to routine reporting of aggregate data. If WHO Regional Offices are constrained in their capacity to fully analyse laboratory-based data from their Regional networks case-based data on all reported cases

(including pathogen negatives) could be forwarded to WHO Headquarters following consultation.

c. Greater emphasis should be placed on the global requirement for all reported laboratory results to be unequivocally linked to case and epidemiological information. If necessary additional support should be provided to the Regions to establish routine information management systems capable of meeting this requirement.

List of Abbreviations

AFR	African Region of the World Health Organization
AMR	Americas Region of the World Health Organization
BMGF	Bill and Melinda Gates Foundation
CDC	US Centers for Disease Control and Prevention
CSF	cerebrospinal fluid
EMR	Eastern Mediterranean Region of the World Health Organization
EQA	external quality assessment
EUR	European Region of the World Health Organization
GRL	Global Reference Laboratory
IB-VPD	invasive bacterial vaccine preventable diseases
NL	National Laboratory
NUVI	New and Under-utilized Vaccines Implementation
PAGE	polyacrylamide gel electrophoresis
PCR	polymerase chain reaction
QA	quality assurance
QC	quality control
RRL	Regional Reference Laboratory
RT-PCR	reverse transcription polymerase chain reaction
RV	rotavirus
SEAR	South-East Asian Region of the World Health Organization
SOP	standard operating procedures

TWG	laboratory technical working group
WPR	Western Pacific Region of the World Health Organization

Analysis

1. The IB-VPD and RV laboratory technical advisory groups

i. Beginning in 2008 various laboratory-supported networks for surveillance of rotavirus (RV) and invasive bacterial disease (IB-VDP) came under the co-ordination of WHO and the process of consolidating, standardizing and strengthening these networks was initiated (1). Technical advice was provided by an *ad hoc* group of recognised laboratory experts, representatives from designated global and regional reference Laboratories, WHO technical staff and representatives from partner institutions including the US Centers for Disease Control and Prevention (CDC), the GAVI Alliance and the Bill & Melinda Gates Foundation (BMGF).

ii. The Global Surveillance meeting in 2010 (2) provided the first opportunity for technical advisors to the RV and IB-VDP laboratory networks to meet and develop an action plan for strengthening laboratory activities. At this meeting agreed roles and responsibilities for the global reference laboratories (GRL), regional reference laboratories (RRLs), national laboratories (NL), and sentinel hospital laboratories were formalized. Training of laboratory staff was prioritized, as was providing access to essential laboratory supplies. Laboratory assessment and performance standards were agreed and priority was placed on developing and distributing standard operating procedures (SOPs) for use by network laboratories.

iii. Further strengthening and development of the RV and IB-VPD laboratory networks were also a focus of attention during the Global Surveillance meeting in 2011 (3). At this meeting it was agreed that regional external quality assurance (EQA) programmes for both RV and IB-VPD networks should be supported to best target laboratories still requiring further support. For IB-VDP, rapid diagnostic testing for bacterial pathogens in cerebrospinal fluids (CSF) should be available at sentinel hospitals to ensure decreased diagnostic variability. A decision was made to develop a standard algorithm for CSF testing at sentinel sites. This decision resulted in the development of a laboratory poster on CSF specimen processing published by WHO (4). It was also agreed that NL and RRL expertise should be used to provide molecular testing support for sentinel hospital sites through a specimen referrals system. For the RV laboratory network it was agreed that regional laboratory quality control programmes should be standardized and that further standardization of genotyping methods was required. SOPs on specimen collection, transport, storage and referral from sentinel site to NLs to RRLs should be developed under the direction of a small working

group of laboratory experts from within the network. It was also agreed that the higher priority was in consolidating the existing laboratory network rather than in expanding it further at this stage.

iv. Following recommendations made at the Global Surveillance in 2011 WHO established a laboratory technical working group (TWG) to assist with technical guidance needed to strengthen laboratory capacities within the Global IB-VPD Surveillance Network. The mandate of this group was to improve the quality of diagnostic and serotyping data, standardize lab methods and training modules, and improve the laboratory quality assurance (QA) and quality control (QC) systems. Members of the TWG include WHO Global and Regional Laboratory coordinators together with selected technical experts in the field of IBD surveillance from the WHO IB-VPD Surveillance Network. The current intention is for the IB-VPD TWG to meet on a quarterly basis via conference calls and on an annual basis through participation in physical meetings held in conjunction with the Global Surveillance Meeting or other appropriate technical meetings. In 2012, the group met via conference calls in February and May and reviewed the EQA programme, the use of Rapid Diagnosis testing at sentinel sites laboratory and the harmonization of the PCR methods used within the IBVPD network. A formal meeting of the IB-VPD laboratory TWG took place immediately following the Global Invasive Bacterial Vaccine Preventable Diseases Surveillance Meeting held in Washington DC, USA in October 2012. Key recommendations from this meeting included continued development and support for the global EQA programme, promotion of BinaxNow as the rapid assay of choice for sentinel site laboratory use, and the need to continue promoting culture over PCR detection for these laboratories. The need to develop standardized reporting of PCR results, including methods used, denominators, PCR cut offs, and specifying serotype and serogroup results obtained by RRLs was noted. It was also recommended that WHO should work with the GRLs to develop indicators and variables for a standard data laboratory management system for the RRLs (5). The most recent teleconference meeting of the TWG occurred in July 2013 and included a review of the development of the QC guidelines and discussions on the further standardization of laboratory procedures. The next physical meeting of the TWG is planned for October 2013.

v. The laboratory technical working group (TWG) of the WHO Rotavirus Surveillance Network was established in 2012, and comprised WHO Global and Regional Laboratory coordinators together with selected technical experts in the field of RV surveillance from the WHO RV Surveillance Network. The current intention is for the RV TWG to meet on a quarterly basis

via conference calls and on an annual basis through participation in physical meetings held in conjunction with the Global Surveillance Meeting or other appropriate technical meetings. The group met through teleconference in February 2012 to reviewed RV genotype classification and reporting of genotyping results. It was recommended that the original WHO data collection form be revised to more accurately reflect the strain prevalence differences observed from region to region by allowing reporting of a greater range of genotypes in a matrix format. At a subsequent teleconference meeting in May 2012 it was recommended that the genotyping protocols should be updated and that use of the Qiagen One-step kit for the first round of RT-PCR should be promoted in order to decrease the number of untypeable isolates. Given the relatively high cost and restricted availability of these commercial kits in some settings the group also recommended more studies on cost effectiveness and comparison of different protocols/kits should be conducted. The RV TWG met physically for the first time in Bangkok in September 2012 (6). This was a technically focussed meeting with discussions covering options to improve genotyping data quality and increase standardization of methods, and improving the quality of laboratory performance. It was recommended that existing SOPs for sample receipt, storage and shipping developed by the WHO Eastern Mediterranean Regional Office should be distributed to the other Regional Offices for adaption to regional conditions and requirements. It was also recommended that Regional coordinators share Regional guidelines used for referral of samples from sentinel sites and NLs to RRLs for confirmation and/or QC purposes, so that a draft global recommendation can be developed. The most recent teleconference meeting of the TWG occurred in June 2013 and included discussions on the further standardization of laboratory procedures and a review of development of the QC programme for genotyping. The next physical meeting of the TWG is planned for November 2013.

2. Structure of existing IB-VPD and RV laboratory networks

i. Both laboratory networks have adopted the pyramidal network structure of sentinel site and NLs, RRLs and GRLs. In the IB-VPD laboratory network, as of June 2013, there were 131 participating laboratories including 94 hospital sentinel site laboratories, 26 NLs, 9 RRLs and 2 GRLs (7). In June 2013 the RV laboratory network consisted of 153 laboratories including 107 hospital sentinel site laboratories, 36 NLs, 9 RRLs and 1 GRL (8). Development, structure and achievements of the RV laboratory network have been well documented in a recent edition of the WHO Weekly Epidemiological Record (9).

ii. As of the end of 2012 the Global IB-VPD Laboratory Network included the following RRL and GRL laboratories:

Region	Name of Laboratory	Location	Member States Served
African Region (AFR)	Medical Research Council Laboratories, WHO Regional Reference Laboratory for IB-VPD	Banjul, The Gambia	Benin, Burkina Faso, Cameroon, Côte d'Ivoire, DR Congo, Gambia, Ethiopia, Ghana, Guinea, Mali, Niger, Nigeria, Senegal, Sierra Leone, Togo
	KEMRI-Wellcome Trust Research Programme, WHO Regional Reference Laboratory for IB-VPD	Nairobi, Kenya	Burundi, Eritrea, Ethiopia, Kenya, Rwanda, Tanzania, Uganda
	National Institute for Communicable Diseases, WHO Regional Reference Laboratory for IB-VPD	Johannesburg, South Africa	Lesotho, Madagascar, Namibia, Swaziland, Tanzania, Zambia, Zimbabwe
Region of the Americas (AMR)	Instituto Adolfo Lutz, WHO Regional Reference Laboratory for IB-VPD	Sao Paolo, Brazil	Argentina, Brazil, Chile, Cuba, Dominican Republic, Paraguay, Uruguay, Venezuela
	Instituto Nacional de Salud,, WHO Regional Reference Laboratory for IB-VPD	Bogota, Columbia	Bolivia, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru, Trinidad & Tobago
Eastern Mediterranean Region (EMR)	Central Public Health Laboratory, WHO Regional Reference Laboratory for IB-VPD	Cairo, Egypt	Afghanistan, Iran, Iraq, Egypt, Libya, Morocco, Pakistan, Sudan, Syria, Yemen
European Region (EUR)	Gabrichevsky Research Institute for Epidemiology and Microbiology, WHO Regional Reference Laboratory for IB-VPD	Moscow, Russia	Armenia, Azerbaijan, Belarus, Georgia, Ukraine, Uzbekistan
South-East Asia Region (SEAR)	Christian Medical College, WHO Regional Reference Laboratory for IB-VPD	Vellore, India	Nepal, Sri Lanka
Western Pacific Region (WPR)	Microbiological Diagnostic Unit-Public Health Laboratory, WHO Regional Reference Laboratory for IB-VPD	Melbourne, Australia	Papua New Guinea, Philippines, Vietnam
	Korea Centers for Disease Control and Prevention (KCDC), WHO Regional Reference Laboratory for IB-VPD	Chungcheongbuk-do, Republic of Korea	Cambodia, Mongolia
Global Reference Laboratory	U.S. Centers for Disease Control and Prevention (CDC)	Atlanta, USA	Worldwide
	Health protection Agency (HPA)	Colindale, UK	Worldwide
	National Institute for Communicable Diseases (NICD)	Johannesburg, South Africa	Worldwide

iii. As of 2012 the Global RV Laboratory Network included the following RRL and GRL laboratories:

Region	Name of Laboratory	Location	Member States Served
African Region (AFR)	Noguchi Institute for Medical Research, WHO Regional Reference Laboratory for Rotavirus	Ghana	Benin, Ghana, Liberia, Niger, Nigeria, Sierra Leone
	University of Limpopo Medunsa Campus, WHO Regional Reference Laboratory for Rotavirus	South Africa	Burkina Faso, Cameroon, Côte d'Ivoire, Democratic Republic of the Congo, Ethiopia, Gambia, Kenya, Mauritius, South Africa, United Republic of Tanzania, Togo, Uganda, Zambia, Zimbabwe
Region of the Americas (AMR)	US Centers for Disease Control and Prevention (CDC), WHO Regional Reference Laboratory for Rotavirus	Atlanta, USA	Guatemala, Honduras Nicaragua, Suriname
	National Public Health Institute of Rio de Janeiro, Acting WHO Regional Reference Laboratory for Rotavirus	Rio de Janeiro, Brazil	Brazil
Eastern Mediterranean Region (EMR)	Naval Medical Research Unit No. 3 (NAMRU), WHO Regional Reference Laboratory for Rotavirus	Cairo, Egypt	Sudan, Syrian Arab Republic
European Region (EUR)	Republican Research and Practical Centre for Epidemiology and Microbiology, WHO Regional Reference Laboratory for Rotavirus	Minsk, Belarus	Armenia, Azerbaijan, Belarus, Georgia, Kyrgyzstan, Republic of Moldova, Tajikistan, Ukraine
South-East Asia Region (SEAR)	Christian Medical College, WHO Regional Reference Laboratory for Rotavirus	Vellore, India	Myanmar, Nepal
Western Pacific Region (WPR)	Murdoch Children's Research Institute (MCRI), Royal Children's Hospital, WHO Regional Reference Laboratory for Rotavirus	Melbourne, Australia	Fiji, Mongolia, Papua New Guinea, Philippines
	Korea Centers for Disease Control and Prevention (KCDC), WHO Regional Reference Laboratory for Rotavirus	Chungcheongbuk-do, Republic of Korea	Cambodia, Lao People's Democratic Republic, Mongolia
	Institute for Viral Disease Control and Prevention, China Centers for Disease Control and Prevention, Nominated as WHO Regional Reference Laboratory for Rotavirus	Beijing, China	China
Global Reference Laboratory	US Centers for Disease Control and Prevention (CDC)	Atlanta, USA	Worldwide

iv. Formal roles and responsibilities for GRLs, RRLs, NRLs and sentinel sites laboratories for the IB-VPD and RV surveillance networks were developed and finalized in December 2010 (10)

and August 2011 (11) respectively. The roles and responsibilities described are broadly in line with those developed for the WHO Global Polio and Measles/rubella Laboratory Networks and reflect the pyramidal structure of the networks. Activities expected of the sentinel sites laboratories and NRLs are predominantly technical in nature; receiving specimens, testing, reporting results and forwarding specimens and/or isolates for confirmation and characterization. In addition to the technical tasks of specimen/isolate confirmation and characterization designated roles and responsibilities of the RRLs and GRLs include administrative, supervisory, quality management and training activities. These additional responsibilities frequently place a significant burden on the laboratories, particularly the RRLs.

3. Laboratory standards for quality assurance, proficiency testing, accreditation

i. IB-VPD: In 2010, WHO partnered with the National Institute for Communicable Diseases in South Africa to expand the existing Microbiology External Quality Assessment EQA programme that was established in the African Region in 2002. The global EQA was launched during 2011 in stages with Regional Reference Laboratories (RRLs) participating in the first round held in February 2011, and subsequently expanded to National Laboratories and hospital sentinel sites later in the year (12). The EQA panel consisted of simulated cerebrospinal fluid (CSF) smears for Gram stain and corresponding lyophilized specimens for bacterial culture. A total of 60 laboratories participated in the November 2011 EQA round, of which 34/56 (61%) achieved an acceptable score; 22/56 (39%) achieved a non-acceptable score, and 4 could not be evaluated because either the laboratory did not receive the shipments or could not perform the tests due to lack of reagents or equipment. Among the 22 non-acceptable laboratories were 20 that failed to respond to the survey providing no reason for non-response. Support and training were offered to laboratories that failed to achieved an acceptable score (13) (14)

ii. In 2012 the panel consisted of 6 samples, compared to 2 in 2011, and was provided to 73 participating laboratories and 3 referee laboratories. Of these 4 laboratories were not evaluated because they did not receive the panels or could not perform tests due to lack of reagents and/or equipment. Of the remaining 69 laboratories, 47/69 (68%) achieved an acceptable score, an increase of 7% over the 2011 results. Among the 22 non-acceptable

laboratories were 16 that failed to respond to the survey (14) (15). Laboratories were assessed for microscopy, final identification of the organism, serotyping/serogrouping (where applicable), and antimicrobial susceptibility testing (AMST) although the AMST results were not scored. In an attempt to improve communication with participants and for ease of submitting results electronically, a new website was created. In all 40% of participant results were successfully received via the website, and this will be further developed for future use.

iii. There is, as yet, no global quality control (QC) programme for the IB-VDPV network, as the WHO Regions have established their own programmes according to regional requirements and circumstances. In this instance QC refers to a system for confirmation of an agreed proportion of sentinel site laboratory or NL results by an RRL or GRL through the shipment of samples for retesting. RRLs have been requested to share information and QC protocols with WHO so they can be compiled and a draft global guideline for referral of samples for QC can be developed (5). Guidelines are also being developed for the confirmation of a proportion of RRL results by the GRL. It is expected the draft guidelines will be discussed at the next IB-VDPV meeting (5).

iv. Standard laboratory assessment tools have been developed for conducting onsite laboratory reviews of sentinel site hospital laboratories, NLS and RRLs (16) (17). These follow the format of similar assessment tools used successfully to conduct on-site laboratory reviews of laboratories belonging to a range of networks over the past 15 years. These reviews are designed to assess all aspects of laboratory activity including receipt of specimens, use of SOPs, specimen processing and results reporting, specimen/isolate storage, information exchange with other network laboratories, laboratory data processing and quality. They include a checklist of available laboratory equipment and supplies. Assessment of sentinel site and NLs is usually expected to be conducted by staff from the WHO Regional Offices and/or staff from the RRLs, while assessment of RRLs is usually conducted by staff from the WHO Regional Offices and/or staff from WHO HQ. Very few assessment results appear to be available as yet, but those that have been made available demonstrate that the assessment process is being taken seriously by both the laboratories concerned and the assessment teams.

v. RV: In 2011, WHO partnered with the GRL (U.S. Centers for Disease Control and Prevention) launched the global EQA programme. In 2011 the GRL provided standard proficiency testing panels of simulated stool specimens, shipped on dry ice, to 10 RRLs in order to validate the

proficiency panels. The panel was designed to test the ability of laboratories to correctly identify positive and negative specimens by enzyme immunoassay and determine the genotypes of positive specimens (18). Nine of the 10 participating RRLs correctly identified the presence of rotavirus, while 8 correctly determined the genotype (19). The EQA panel distribution was expanded in 2012, to include 10 RRLs, 16 NLs and 17 provincial laboratories in China. Laboratories are expected to achieve at least 80% on each test to pass (9) (20). For the 2012 distribution, all 10 RRLs and all 17 provincial laboratories passed. Only 6 of the NLs submitting results achieved a passing score. For the 2013 panel distribution that began in May the samples were lyophilized so they could be shipped without dry ice. A total of 136 laboratories are expected to participate in this round of EQA; 10 RRLs, 17 provincial laboratories, 107 NLs and 2 referee laboratories (8). Results of the 2013 EQA have not yet been made available.

vi. Although there is, as yet, no global QC for the RV surveillance network, an advanced draft of guidelines for confirmatory testing of genotyping results from RRLs has been developed. According to current proposals each RRL will send a maximum panel of 50 stool samples containing rotavirus that has been genotyped isolates to the GRL for confirmatory testing. The first panels are expected to be sent as soon as possible in 2013 and the process will be under review for possible amendment (21). The WHO Regional networks have already developed guidelines and are conducting QC programmes for their NLs. In general, 10-20% or approximately 150 samples from the NLs are sent to the RRLs for confirmation, but the number sent varies from region to region (6). In the European Region, for example, the RRL at Minsk provides external quality control for NL from Azerbaijan, Armenia, Georgia, Kyrgyzstan, Moldova, Tajikistan, and both laboratories in Ukraine. In 2011 a total of 1,161 confirmatory ELISA tests were performed by the RRL on specimens forwarded from the 8 laboratories with a reported concordance rate of 97%.

vii. Standard assessment tools for review of RRLs and NLs have been developed (22) (23). These checklists follow the format successfully used by the WHO Global Polio Laboratory Network for self-assessment of NLs and RRLs. No details of use of the checklists have been made available, but the assessment tools themselves are comprehensive and, if used, would complement the EQA programme.

viii. There is, as yet, no information available on a formal accreditation process for network laboratories. However, the basis for such a process, namely an EQA programme, QC guidelines and on-site laboratory review assessment tools, are all in place and a formal

accreditation process could be initiated. This would place an additional burden on network administrative and management resources, however, and a thorough review of the additional resource requirements should be undertaken before such a process is started.

4. Laboratory manuals for the diagnosis and characterization of IB-VPD and RV disease.

i. The second edition of the WHO Manual, "Laboratory Methods for the Diagnosis of Meningitis caused by *Neisseria meningitides, Streptococcus pneumonia*, and *Haemophilus influenzae*" (WHO/IVB.11.09) produced in conjunction with the US Centers for Disease Control and Prevention, was published in 2011. This detailed and comprehensive laboratory manual is freely available for download from the WHO website (http://www.who.int/nuvi/surveillance/resources/en/index.html) and from the CDC website (http://www.cdc.gov/meningitis/lab-manual/index.html).

ii. The WHO "Manual of rotavirus detection and characterization methods" (WHO/IVB/08.17) was published in 2009 and is freely available for download from the WHO website (http://www.who.int/nuvi/surveillance/resources/en/index.html). This is a comprehensive manual of laboratory techniques ranging from simple detection through antigen assays to genotyping through RT-RCR. However, it has been recognised that the manual does not describe in sufficient detail specimen collection, aliquoting, storage, extract preparation, shipping and data management. SOPs covering these aspects have been developed, largely at WHO Regional level, and have been shared among the Regions. Every WHO Regional network has been encouraged to develop their own SOPs based on the shared material (2).

5. Expansion of the IB-VPD and RV laboratory networks over time.

i. Prior to 2008, rotavirus surveillance networks in the WHO regions of the Americas, Europe, Africa and Eastern Mediterranean were coordinated by the respective WHO Regional Offices with funding through the rotaADIP and technical support from the Centers for Disease Control and Prevention, Atlanta (CDC). Surveillance in Asia was conducted by the Asian Rotavirus Surveillance Network (ARSN) supported by CDC. In 2008, the coordination of the ARSN was transitioned to the WHO regional offices in the South-East Asia and Western Pacific Regions marking the initiation of the Global RV laboratory Network (24).

ii. In the years leading up to 2008 a number of IBD surveillance sites and networks were established to gather data to assess disease burden, estimate vaccine effectiveness, and

determine which specific serotypes of *Streptococcus pneumoniae* , *Neisseria meningitides* and *Haemophilus influenzae* were associated with the majority of disease in each WHO region. Attempts were also made to monitor changes in strain prevalence over time and in response to vaccine introduction (25). Some of these existing networks were funded under PneumoADIP and the Hib Initiative. During 2008 global coordination of some of these networks was taken over by WHO and the Global IB-VPD Laboratory Network was formed (26).

iii. Since 2009 the number of RRLs and GRLs participating in each network has remained broadly the same, although roles and responsibilities of individual laboratories have evolved with time (see Section 2 "Structure of existing IB-VPD and RV laboratory networks"). Over the same period there has been a trend to increase the number of participating countries and the number of sentinel site hospital laboratories in both networks. There are significant inconsistencies in the available data on the precise number of sentinel site laboratories at any one time, but it is possible to provide indicative summaries of the expansion in both laboratory numbers and workload since 2009. Table 1 provides an indication of the comparative size of the RV surveillance networks since 2009, and Table 2 provides a similar indication for the IB-VPD network. All data for these tables were taken from editions of the '*Global Rotavirus Information and Surveillance Bulletin'* and the '*Global Invasive Bacterial Vaccine Preventable Diseases (IB-VPD) Information and Surveillance Bulletin'* published by WHO Headquarters and available from their website (http://www.who.int/nuvi/surveillance/resources/en/index.html).

iv. The information in **Tables 1** and **2** must be considered indicative only as there appears to be no comprehensive listing of sentinel site laboratories held by WHO Headquarters. This information, presumably, is held in the WHO Regional Offices. Data published at global level does not include sentinel site laboratories that do not report regularly or that fail to meet programmatic reporting criteria. From published data it is clear that the number of reporting sentinel site laboratories fluctuates from year to year, but little evidence is available to document the details of these fluctuations. According to available evidence the original intention was to establish a single well-selected sentinel surveillance site in each participating country supported by a high-quality laboratory. Although this intention has been followed in some participating countries, it has been ignored in others, with multiple sentinel sites being established. Although there may be epidemiological, demographic or geographical grounds for establishing more than a single site per country, the establishment

of several tens of sites in some countries is difficult to justify if the intention is to establish high-quality sentinel surveillance. Countries that establish many 'sentinel' sites are establishing *de facto* population surveillance, which requires much broader based, and potentially more expensive, laboratory support.

Table 1. Indication of the comparative size and workload of the WHO Global RV Laboratory Network 2009 to 2012 (all data from the *Global Rotavirus Information and Surveillance Bulletin*).

Year	WHO Region	No. countries reporting	No. sentinel sites	Reported no. stools tested	No. countries reporting genotype data	No. of genotyping results
2009	AFR	12	18	5,071	12	451
	AMR	14	59	13,085	11	1,240
	EMR	13	68	10,910	1	294
	EUR	6	9	6,330	7	729
	SEAR	4	4	2,596	4	588
	WPR	6	13	4,977	2	747
	Global Total	**55**	**171**	**42,969**	**37**	**4,049**
2010	AFR	19	22	9,109	16	933
	AMR	13	55	10,078	11	1,607
	EMR	12	64	10,710	2	702
	EUR	6	9	6,207	7	730
	SEAR	4	7	2,678	2	271
	WPR	7	18	5,456	5	1,274
	Global Total	**61**	**175**	**44,238**	**43**	**5,517**
2011	AFR	19	33	8,841	16	898
	AMR	18	81	11,763	11	1,371
	EMR	8	38	9,836	0	0
	EUR	8	9	8,217	8	784
	SEAR	4	6	**Not available**	1	184
	WPR	7	18	5,512	7	1,686
	Global Total	**64**	**185**	**44,169**	**43**	**4,923**
2012	AFR	19	36	15,587	18	1,734
	AMR	8	43	15,848	10	1,554
	EMR	8	39	13,306	1	213
	EUR	6	10	11,671	7	681
	SEAR	4	6	3,664	3	513
	WPR	6	16	7,880	5	1,022
	Global Total	**51***	**150***	**67,956***	**44****	**5,717****

* Data from January to June 2012 only

** Probably represents incomplete data for 2012.

Table 2. Indication of the comparative size and workload of the WHO Global IB-VPD Laboratory Network 2009 to 2012 (all data from the *Global Invasive Bacterial Vaccine Preventable Diseases (IB-VPD) Information and Surveillance Bulletin*).

Year	WHO Region	No. countries reporting	No. sentinel sites	No. countries reporting serotype / serogroup data	No. of serotyping / serogrouping results
2009	AFR	21	28	Not available	973
	AMR	9	28	Not available	Not available
	EMR	7	101	Not available	Not available
	EUR	1	3	Not available	16
	SEAR	4	8	Not available	88
	WPR	5	24	Not available	13
	Global Total	**47**	**192**	**0**	**1090**
2010	AFR	23	30	11	204
	AMR	8	25	8	727
	EMR	6	32	3	20
	EUR	4	5	2	24
	SEAR	4	8	4	72
	WPR	4	21	2	23
	Global Total	**49**	**121**	**30**	**1070**
2011	AFR	27	31	16	143
	AMR	11	46	10	732
	EMR	7	92	3	39
	EUR	4	**4**	5	24
	SEAR	4	7	4	92
	WPR	4	15	3	14
	Global Total	**57**	**195**	**41**	**1044**
2012	AFR	26	30	13	211
	AMR	8	28	4	71
	EMR	6	27	0	0
	EUR	4	7	4	88
	SEAR	2	4	3	57
	WPR	4	19	2	14
	Global Total	**50***	**115***	**26****	**441****

* Data from January to June 2012 only

** Probably represents incomplete data for 2012.

6. Standardized IB-VPD and RV data collection forms, and the process of sharing and feedback among the Regions

i. A great deal of time and effort has been invested by the programme and its technical advisors in developing standardized data collection forms. The forms have progressively evolved since 2008, and become more tailored to the needs of the programme and to the requirements of the reporting process. Laboratory data reported from Regional to Global level is aggregated by country, and/or by RRL. From information available it appears that WHO HQ does not routinely have access to case-based data, although WHO Regional Offices do and some use the data for analysis.

ii. IB-VDP: For the 'sentinel' surveillance system there are 3 reporting forms for aggregated data associated with the 3 tiers of laboratory-based surveillance. The standardized reporting form for the first tier (meningitis surveillance) laboratory data, including that from sentinel site hospital laboratories, is provided in **Figure 1** (part form only). If this form is accurately and comprehensively completed at Regional level it should provide the data required to fulfil programme objectives for this level of laboratory.

The standardized reporting form for the second tier (pneumonia and sepsis) laboratory data is provided in **Figure 2** (part form only). Again, if this form is accurately and comprehensively completed at Regional level it should provide the data required to fulfil programme objectives for this level of laboratory, including routine laboratory performance monitoring.

For reporting of aggregate serotyping/serogroup data by RRL and country from the WHO Regional Office to WHO HQ the reporting form provided in **Figure 3** has been developed. This iteration of the form permits reporting of not only the 27 most 'common' pneumococcal serotypes as defined by the TWG but also allows reporting of identification of other less common serotypes. When accurately completed by the Regional Offices it provides a useful and comprehensive summary of aggregated results by RRL and/or by country. However, not all WHO Regional Offices use this format for reporting. Compliance has improved noticeably over the years, but even the most recent submissions from SEAR failed to use this form for results reporting, although compatible results have been reported. Although the form has been modified very slightly on two occasions, the first iteration was introduced globally in 2010. No information has been provided as to why SEARO is not using the form to report serotyping data to WHO HQ as requested. One problem encountered in use of this form is that WHO Regional Offices have a tendency to modify the form prior to sending. These modifications include re-sorting the order of pneumococcal serotypes and inserting additional serotypes within the order of the 27 'common' serotypes'. These forms have been prepared and distributed as Microsoft Excel worksheets for the convenience of

both the Regional Offices and WHO HQ. Modifications to the format of the worksheet prohibit the automated uptake of data for analysis and require HQ staff to manually enter the data into analysis packages, a process that is time-consuming, potentially error-prone, and unnecessary. Another common problem encountered with receipt of this form is the failure to complete all essential information, such as the country name, the RRL name, and the year to which the data refers. At the time of receipt in WHO HQ this information may be inferred or provided in accompanying documents or e-mails, but when the data file is archived it is often separated from accompanying information, making the process of identifying the data for review purposes extremely laborious.

With regard to completion of the form, it is unclear if the year for which the data is being reported refers to the year of case investigation, the year of receipt of isolates/specimens in the RRL or the year in which final serotyping results are available. It appears that for the 2012 data this uncertainty has been resolved through negotiation between WHO HQ and the Regional Offices/RRLs, but for previous years it remains uncertain.

Figure 1. Standardized reporting form for the first tier (meningitis surveillance) laboratory data (part for only)

Country	Total No. of sites reporting	No. (%) of sites that report data according to agreed timeline (at least quarterly) (Target 80%)		Age group (months)	No. (%) of suspected meningitis cases with HI identified by culture, latex or PCR		No. (%) of probable bacterial meningitis cases with HI identified by culture, latex or PCR		No. (%) of suspected meningitis cases with pneumococcus identified by culture, latex or PCR		No. (%) of probable bacterial meningitis cases with pneumococcus identified by culture, latex or PCR		No. (%) of suspected meningitis cases with meningococcus identified by culture, latex or PCR		No. (%) of probable bacterial meningitis cases with meningococcus identified by culture, latex or PCR		No. (%) of CSF samples logged into the lab within 1 hr of the LP (Target: 75%)		No. (%) of CSF samples contaminated (Target ≤5)		No. of CSF isolates forwarded to regional ref lab for typing
	No.	No.	%		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
				All <59m																	
				0 to 5																	
				6 to 11																	
				12 to 23																	
				24 to 59																	
				Unknown																	

Figure 2. Standardized reporting form for the second tier (pneumonia and sepsis) laboratory data (part for only)

Country	Total No. of sites reporting	No. (%) of sites that report data according to agreed timeline (at least quarterly) (Target 80%)		Age group (months)	No. (%) of pneumonia cases that have a blood culture performed (Target 75%)		No. (%) of pneumonia cases with a blood culture performed that have a culture result recorded (Target 90%)		No. of pneumonia cases with a blood culture performed with a bacterial pathogen identified by culture, latex or PCR	No. (%) of pneumonia cases with a blood culture performed with HI identified by culture, latex or PCR		No. (%) of pneumonia cases with a blood culture performed with pneumococcus identified by culture, latex or PCR		No. (%) of sepsis cases that have a blood culture performed (Target 75%)		No. (%) of sepsis cases with a blood culture performed that have a culture result recorded (Target 90%)		No. of sepsis cases with a blood culture performed with a bacterial pathogen identified by culture, latex or PCR	No. (%) of sepsis cases with a blood culture performed with HI identified by culture, latex or PCR		No. (%) of sepsis cases with a blood culture performed with pneumococcus identified by culture, latex or PCR		Total No. (%) of blood cultures contaminated (Target < 5%)		Total No. of blood isolates forwarded to regional ref lab for typing
	No.	No.	%		No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.	
				All <59m																						
				0 to 5																						
				6 to 11																						
				12 to 23																						
				24 to 59																						
				Unknown																						

Figure 3. Standardized reporting form for IB-VPD serotyping/serogroup data.

Date of report:					*Haemophilus influenzae*							Pneumococcus					Neisseria Meningitidis		
Reporting period:		Did the country use the following vaccines in its national immunization programme during this reporting period?																	
Country	Name of RLL	Hib (yes/no)	Strep pneum (yes/no)	N. menin (yes/no)	Serotype	Meningitis		Other invasive disease				Serotype*	Meningitis		Other invasive disease		Serogroup	Meningitis	
						No.	%	No.	%	No.	%		No.	%	No.	%		No.	%
					Type b							1					Type A		
					Non type b							2					Type C		
					non-typeable							3					Type W135		
					Not done							4					Type Y		
												5					Other serogroup		
												6A					Non-type-able		
												6B							
												7F							
												8							
												9A							
												9N							
												9V							
												10A							
												11A							
												12A							
												12F							
												14							
												15B							
												17F							
												18C							
												19A							
												19F							
												20							
												22F							
												23F							
												33F							
												45							
												<Enter other>							
												<Enter other>							
												<Enter other>							

Date of report:
Reporting period:

<Country Name>

Did the country use rotavirus vaccine in its national immunization programme during this reporting period?	Name of RRL	No. of rotavirus positive specimens sent to RRL for typing this reporting period	No. (%) of rotavirus positive (ELISA confirmed) specimens sent to RRL that are confirmed to be positive by the RRL		Strain characterization technique used in RRL	No. (%) of genotype results reported back to the country/site within 6 months		**Genotyping Additional Results:**		**Sequencing Results:**		
			Target 80%			Target 90%		mixed*	untypeable	Total No. of rotavirus samples that were sequenced	No. and % of untypable samples that were identified by sequencing	
Yes / No			No.	%		No.	%			No.	No.	%

* Please specify mixed infection by entering data such as G1G2 or P[4]P[8]

GENOTYPE RESULTS
PLEASE ENTER THE TOTAL NUMBER OFGENOTYPE FOUND IN THE TABLE BELOW. FEEL FREE TO ADD AS MANY COLUMNS AND ROWS AS NECESSARY.

	P[1]	P[2]	P[3]	P[4]	P[5]	P[6]	P[7]	P[8]	P[9]	P[10]	P[11]	P[12]	P[14]	P[19]	P[25]	P[28]	other (specify)	other (specify)
G1																		
G2																		
G3																		
G4																		
G5																		
G6																		
G7																		
G8																		
G9																		
G10																		
G11																		
G12																		
G20																		
other (specify)																		
other (specify)																		

Figure 4. Standardized reporting form for RV genotyping data.

iii. RV: There are two reporting forms for the RV laboratory network. The first constitutes part of the 'Regional Office Rotavirus Data Form' used to report aggregated monthly data on the number of children hospitalized with acute diarrhoea, those meeting the case definition and enrolled into the study, and with specimens collected and tested. This form also requests aggregate data on the number of enrolled cases tested positive for rotavirus and the number of rotavirus positive fatalities. Included in the form are a number of performance monitors, such as the number of stool specimens collected within 2 days of hospital admission.

No data laboratory data submitted using form was provided for review, so it is not possible to comment on the level of compliance. However, the form is quite unwieldy and may be time-consuming for Regional Office staff to complete and it is not unlikely that compliance in completing the form is low.

The second form used by the RV laboratory network is the 'Regional Genotyping and Quality Assurance Form' which should be used by Regional Offices to provide the annual genotype data from each RRL (**Figure 4**). Original versions of this form maintained a linear format and permitted reporting of only the 5 genotypes considered to be most common together with aggregated 'uncommon' genotypes. Globally 15-20% of reported RV genotype results were falling into the 'uncommon' category so significant modifications were made to the form in 2010 to permit reporting of a larger range of genotypes. These modifications resulted in the current in the current matrix format. Although apparently complex this format is easy to use, and if the format is strictly adhered to, with no Regional Office modifications made to the formatting, should be amenable to automated uptake of data for analysis by WHO HQ. As with the IB-VPD serotyping report forms, any modification to the formatting prohibits automated uptake and requires manual data entry in WHO HQ. Although compliance from Regional Offices has improved significantly with time, there remains a tendency for Regional Office staff to omit key information and to make modifications to the report format. Again, for even the most recent submissions from SEAR the standard form for results reporting has not been used, although compatible results have been reported. No information has been provided as to why SEARO is not using the form to report serotyping data to WHO HQ as requested.

Figure 5. Surveillance data reporting calendar.

Reporting Frequency	Site to national /regional WHO			
At least Quarterly*	**January**	**April**	**July**	**October**
	Site sends data from previous **Oct-Dec** to MOH and WHO CO**	Site sends data from previous **Jan-Mar** to MOH and WHO CO**	Site sends data from previous **Apr-Jun** to MOH and WHO CO**	Site sends data from previous **Jul-Sept** to MOH and WHO CO**
	Regional Reference Laboratory (RRL) to WHO RO			
6-Monthly	**Apr-May**		**Oct-Nov**	
	Annual data Jan-Dec of previous year		Data from Jan-June of same year	
	Regions to countries (regional feedback bulletin)			
Quarterly	**Jan**	**Apr**	**July**	**Oct**
	RO prepares quarterly bulletin of country data from **Jul-Sept** of previous year	RO prepares quarterly bulletin of country data from **Oct-Dec** of previous year	RO prepares quarterly bulletin of country data from **Jan-Mar** of previous year	RO prepares quarterly bulletin of country data from **Apr-Jun** of previous year
	Regions to WHO HQ (regional feedback bulletin)			
6-Monthly	**July**		**Nov**	
	WHO RO sends aggregate regional data from **Jan-Dec** of the previous year to WHO HQ. These data include serotype results from RRLs***		WHO RO sends regional data from **Jan-Jun** of previous year to WHO HQ	
	HQ to regions (global bulletin)			
6-Monthly	**Oct**		**Feb**	
	WHO HQ drafts a global bulletin with data from **Jan-Dec** of the previous year to the regions which includes serotype information***		WHO HQ drafts bulletin with data from **Jan-June** of the previous year to the regions	

*Many sites are currently reporting to WHO monthly and this should be continued. Quarterly reporting is the minimum accepted and monthly reporting is preferred.
**MOH - Ministry of Health, CO - country office, RO - Regional office (in AFRO this may be sub-regional office)
***Although regional reference laboratories should report serotype data to the regional office on a 6-montly basis this will only be shared with WHO HQ and the countries in the region annually

iv. The surveillance data reporting calendar is provided in **Figure 5**. If complied with this reporting schedule should provide an adequate level of information exchange and process monitoring for sentinel surveillance programmatic needs. However, from information provided for this review it is not obvious that this calendar is being followed within the Regions or that all Regional Offices are providing quarterly feedback bulletins to the countries. The 6-monthly Global bulletins for both IB-VPD and RV have been consistently produced since 2009, provide comprehensive feedback on results and key features of the two networks and have shown consistent improvements in both presentation and content over this period. All bulletins are freely available for download from the WHO website (http://www.who.int/nuvi/surveillance/resources/en/index.html). One problem with the existing calendar is that serotyping and genotyping data received by WHO WQ is always at least 8 months out of date and results published in the bulletin are at least 10 months out of data. Some data is almost 2 years out of date by the time it is published. As a strictly reporting issue this does not present a problem, but for systems monitoring and data

validation it represents a significant problem. This is all aggregated data, and the time and effort required by WHO HQ to investigate and rectify data inconsistencies and anomalies is considerable. This problem may be mediated by more frequent reporting of serotype and genotype data to WHO HQ so that any inconsistencies and anomalies can be dealt with closer to the time the data were generated, rather than waiting for 10 to 22 months to elapse.

7. Document the level to which laboratory network-generated genotype and serotype data has achieved the 2008 objectives

i. The original objectives for the RV laboratory network-generated genotype data were to:

- Generate local data for decision making and informing policy regarding rotavirus vaccine introduction and sustained use;
- Assess and monitor disease trends and genotype distribution over time (nationally, regionally, globally);
- Develop a platform for vaccine effectiveness studies;
- Highlight the value of surveillance data and use for fundraising and advocacy (1).

The original objectives for the IB-VPD laboratory network generated data were to:

- Generate local data for decision making and informing policy regarding introduction and sustained use of vaccines for invasive bacterial diseases (i.e. Hib, pneumococcal and meningococcal vaccines);
- Assess and monitor disease trends and serotype distribution over time (nationally, regionally, globally);
- Develop a platform for vaccine effectiveness studies;
- Highlight the value of surveillance data and use for fundraising and advocacy (1).

ii. Summaries of annual RV genotype and IB-VPD serotype/serogroup results by country have been provided separately as MS Excel workbooks. The laboratory networks have generated a large volume of detailed data that can be analysed to generate summaries and reports used to meet the 2008 objectives. Clearly, the uses to which the data can be put are dependent on the stage of vaccine introduction and, where vaccines have been introduced, the extent of vaccine coverage and the time since reasonable coverage levels were established. Although the data provided at Global level is extensive, there are concerns over the quality and completeness. Because only aggregate data is received at WHO HQ there is no real

opportunity to provide a global summary of disease trends and serotype/genotype distribution over time. Case-based reporting of positive results would be required to achieve this. From information received from Regional Office staff it appears that case-based data is not consistently available in all Regions, as problems with linking epidemiological and laboratory data occur in discussion. The original 2008 objectives were founded on establishing consistent case-based surveillance and there are indications that this has not been achieved in all Regions.

iii. There are inherent problems with the IB-VPD laboratory data that are not apparent in reporting of the RV laboratory data, due to the complexities of bacteriology laboratory testing, the range of non-equivalent laboratory tests that can be used and the requirement to report on separate three pathogens. It is very difficult to see how, in a routine, systematic manner, the IB-VPD laboratory-generated data has yet fulfilled the original objectives. However, a great deal has been achieved in establishing the laboratory network, providing standard methodologies and performance indicators, developing standardized reporting systems and establishing a basis and structure for achieving the original objectives that did not exist in 2008. In terms of generating usable serotyping/serogrouping data on a global basis the IB-VPD laboratory network remains a work in progress.

iv. Although there remain uncertainties and restrictions on the extent to which the RV genotyping data can be interpreted, credible analyses of the impact of RV vaccine introduction on the detection of RV in enrolled cases has recently been presented for Bolivia, Columbia, Ecuador, Guatemala, Honduras and Sudan (27). Summarizing country-specific trends of rotavirus detection before and after rotavirus vaccine introduction is a useful way to share information generated by this sentinel surveillance network, but due to uncertainties in the data collection and reporting system these summaries need to be interpreted with caution. No information has been made available for this review on assessment of changes to the frequency of detection of RV genotypes in response to vaccine introduction. An annual summary of global RV genotype detections by country for 2011 was presented in 2012, including Regional summaries (20), but this summary did not attempt to assess changes in RV genotypes detected over previous years. Data for 2012 is available, summarised and an attempt to identify and changes that occurred since 2011 is ongoing.

8. IB-VPD and RV laboratory training workshops conducted in each Region

i. There is extensive evidence that numerous IB-VPD and RV laboratory training workshops have been conducted in all WHO Regions. The level and quality of documentation on these is, however, extremely variable. Extensive summary reports on some training workshops have been produced and distributed, while for others only the record of their title and date exists. Most of the training workshops have been conducted by staff from the RRLs with support from the GRLs and consultants provided through WHO. Some Regions have consistently maintained better records of training workshops than others.

ii. AFR: The 11th African Region Rotavirus Surveillance Network (AFR RSN) genotyping workshop was held from 6 to 17 June 2011 at the University of Limpopo, Pretoria, South Africa. A key objective of the workshop was to generate data on the circulating rotavirus strains in Africa using the WHO generic protocol and regional guidelines using a variety of molecular techniques which included PAGE, RT-PCR and genotyping assays. A total of 17 participants from 15 African countries (Cote d'Ivoire, Democratic Republic of the Congo, Ethiopia, Guinea Bissau, Kenya, Mauritius, Nigeria, Senegal, South Africa, Togo, Tanzania, Uganda, Zambia, Zanzibar and Zimbabwe) were trained and subsequently analysed samples from their countries.

A meeting was held in Nairobi on 17th August 2011 to officially hand over IB-VPD surveillance activities to WHO and the Ministries of Health in Tanzania, Uganda and Kenya. This meeting was combined with a data management and laboratory workshop for site participants from the three countries in Kilifi from 18th to 20th August.

The 3rd annual training workshop of Paediatric Bacterial Meningitis Surveillance in West Africa took place from the 23-27 April 2012 with the theme: "Improving Laboratory Diagnosis of Bacterial Meningitis." The overall objective of the training workshop was to refresh microbiologists from 18 African Countries on laboratory identification of pathogens causing meningitis, with particular emphasis on use of rapid test kits (BINAX NOW and Pastorex latex agglutination) to diagnose disease.

A Regional Integrated Laboratory and NUVI surveillance workshop was conducted in Harare, Zimbabwe, from 28 to29 May 2013.

iii. AMR: Both IB-VPD and RV laboratory networks are well established in this Region, and many laboratory training workshops have been held since 2008. Most of the documentation on these workshops is in Spanish, without English translation.

The Latin American workshop for phenotypic characterization of *Neisseria meningitides*, *Streptococcus pneumoniae* , and *Haemophilus influenzae* and MIC determination was conducted at the Adolfo Lutz Institute (IAL), São Paulo, Brazil, in 2011. A molecular characterization workshop for *Neisseria meningitides* (MLST) was conducted in Chile in 2011.

iv. Most recently a training workshop on rotavirus genotyping was held in Brazil in March 2013 with participants from 10 countries.

v. EMR: A Laboratory Training Workshop for diagnosis of invasive bacterial pathogens was held from 12 to 16 June 2012, in Cairo for staff from the three hospital laboratories Pakistan. Training included laboratory biosafety and management, quality control and quality assurance, specimen handling, processing and recording, identification of IBD, specimen/isolate storage and shipment and an overview on the use of PCR in the diagnosis and serotyping of IB-VPD.

vi. EUR: Evidence has been presented for extensive in-country training and provision of individual training for NL staff at the RRL, including training workshop for laboratory diagnosis of bacterial meningitis held in Baku, Azerbaijan, in October 2009, Tbilisi, Republic of Georgia in October 2010, and Baku, Azerbaijan, in July 2012.

vii. SEAR: An inter-country workshop on sentinel surveillance of invasive bacterial diseases and rotavirus gastroenteritis was held from 20 to 21 June 2013, in New Delhi, India.

viii. WPR: In 2009 a Regional workshop on PCR for bacterial meningitis pathogens was conducted in Manila, the Philippines. A Regional Training Workshop on the detection of invasive bacterial diseases pathogens was held from 15-19 November, 2010 in Manila, Philippines. Representatives from 9 laboratories around the Region participated in this training session.

A Regional Laboratory Training Course on Rotavirus Detection and Strain Characterization as held from 25-29th July, 2011 in Seoul, Korea. This was an inter-country hands-on training workshop on rotavirus detection and strain characterisation including use of PCR genotyping techniques and evaluation.

The Third Regional Workshop on surveillance and laboratory networks for New Vaccine-Preventable Diseases was held from 24 to 26 October, 2012 in Manila, Philippines. The objectives of this meeting included providing technical updates and introducing revised

standard operating procedures for RV and IB-VPD surveillance and laboratory testing, and review findings from the global and regional RV and IB-VPD surveillance and laboratory networks and programmatic use of the data.

ix. It appears that several regional laboratory training workshops remain undocumented at global level as there are references to training activities in the documentation. A more thorough review at Regional level may be necessary to fully document the extent of laboratory training that has been conducted.

9. WHO coordinated laboratory and regional TAG meetings

i. Very little evidence has been presented that regions have been organizing laboratory meetings in conjunction with Regional Technical Advisory Group (TAG) meetings, although there is ample evidence from AMR, EUR, and WPR that laboratory aspects of NUVI surveillance have been discussed and recommendations made at recent meetings. In EUR annual rotavirus surveillance network meeting were held in 2010, 2011 and 2012. Similar meeting for IBD networks were held in 2011 and 2012. Laboratory counterparts participated in these meetings as did staff from the RRLs and laboratory activities and performance were major component of meeting agendas.

10. Technical consultations requested and fulfilled by WHO

i. AFR: Staff from the IB-VPD RRL National Institute for Communicable Diseases (NICD), Centre for Respiratory Diseases and Meningitis - Bacteriology, Johannesburg, South Africa participated in three on-site assessments in 2012. These included Swaziland, (24–27 July), Zimbabwe, (15–17 August) and Namibia (28–31 August). All visits included sentinel site assessments and refresher hands-on laboratory training of standardized methodologies for the isolation, identification and long-term storage of pathogens. Strengths and weaknesses at both clinical and laboratory level were identified and feedback was provided with suggestions for improvement.

In 2011 staff from the IB-VPD RRL at the KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya participated in on site assessments of St. Mary's Hospital, Lacor; Mbale Regional Referral Hospital, Mbarara Regional Referral Hospital and Mulago National Referral Hospital in Uganda from 18th to 28th July, and on site visits to Bugando Medical Centre, Mwanza;

Mnazi Mmoja Hospital, Zanzibar; Bombo, Tanga; and Teule Hospital, Muheza in Tanzania from 29th May to 4th June.

Staff from the IB-VPD RRL at the Medical Research Council (MRC), Banjul, Gambia participated in technical support missions from 14 to 25 May, 2012 providing on-site assessments and training to 3 potential sentinel sites in Nigeria together with on-site assessments of Lagos University Teaching Hospital, Lagos and University of Nigeria Teaching Hospital, Enugu.

A follow-up technical visit to IB-VPD RRL at the Medical Research Council (MRC), Banjul, Gambia on 28 February to 1 March 2013 by the Global Laboratory Coordinator, the Regional Laboratory Coordinator for New Vaccines Surveillance in AFRO and a Global reference Laboratory representative from US CDC.

ii. EMR: Staff from the IB-VPD RRL, Central Public Health Laboratory (CPHL), Cairo, Egypt undertook field visits to assess three sentinel sites in three provinces in Pakistan during 21-24 December 2011.

A review of the RV RRL at the U.S. Navy Medical Research Unit-3 (NAMRU) Cairo, Egypt was conducted June 4, 2013 by the Global Laboratory Coordinator, The Regional Laboratory Coordinator for EMRO and a representative from the GRL. A follow-up technical visit to the IB-VPD RRL at CPHL, Cairo, Egypt was conducted on June 5, 2013.

iii. EUR: Numerous assessments and in-country missions have been conducted and documented These include missions to Armenia (2009), Azerbaijan (2009, 2012), Georgia (August 2013), Moldova 2009, 2013), Tajikistan (2010) and Ukraine (2012) for rotavirus, and Armenia (2011), Azerbaijan (2008, 2010, 2011), Georgia (2012), Ukraine (2007, 2009, 2012), Uzbekistan (2011, 2012, 2013) and Belarus (2012) for invasive bacterial meningitis surveillance. It is presumed that these missions have incorporated aspects of laboratory function and activity but no details have been provided. Reports on these missions are available in the Regional Office. No details on the assessment or review of network laboratories have been provided.

iv. WPR: A WHO mission was sent to Hanoi and Ho Chi Minh City, Vietnam, from 14 to 21 March 2012 for an evaluation of the performance and practices of the Enterovirus Laboratories at the National Institute of Hygiene and Epidemiology (NIHE) in Hanoi and the Pasteur Institute in Ho Chi Minh City. Laboratory practices and results from rotavirus antigen testing and genotyping were reviewed.

v. There are undoubtedly many other technical consultations that have taken place over the past 5 years, but documentation available at global level is lacking. A more detailed review at Regional level would no doubt provide a more comprehensive list of activities conducted.

vi. A minimal level of three WHO staff responsible for NUVI surveillance has been recommended at Regional level. These three positions comprise the surveillance coordinator, the laboratory coordinator and the data manager. Although available evidence suggests that each of these positions officially exists in the WHO Regional Offices, several regions currently have at least one position unfilled. All Regions have voiced the opinion that the level of staffing support is inadequate, particularly for laboratory coordination and data management.

Assessments

Based on results of the analysis answers have been provided to the following key questions posed by the Global Programme. These assessments have been provided on the basis of a fairly superficial review of all available data given the limited time available. There is a strong bias towards viewing the networks from the perspective of WHO HQ, since that was the source of the majority of the information used for the review. Where possible and appropriate attempts have been made to reflect information provided directly and indirectly from the WHO Regional Offices and the GRLs and RRL, but the perspective remains predominantly that of the global position.

Are the IB-VPD and RV laboratory networks supporting the system in the most effective/efficient manner?

i. Despite the enormous amount of work that has been achieved over the past 5 years, both laboratory networks remain in a state of development. Hugely important steps have been taken in strengthening national and regional laboratory capacities, standardization of laboratory testing, improving laboratory quality and performance, and establishing functional international networks. Although both networks are providing technical information that, in some instances, may be influential in developing vaccine policies at national and/or international level, neither network can presently be described as supporting the system in the most effective/efficient manner.

ii. Of the 2 laboratory networks, the RV network is significantly closer to achieving effective support of the programme. The RV laboratory network has inherent advantages over the IB-VPD laboratory network in that not only is laboratory testing significantly less complex, but laboratory requirements are more compatible with those of existing global networks, including polio and measles/rubella. Indeed some of the laboratories serving RV sentinel sites also participate in the global polio and/or measles/rubella networks. Even if the laboratories have not participated in WHO global networks before, the concepts of WHO laboratory standardization, quality control and standard reporting are familiar to the national health authorities through their exposure to the polio and measles/rubella programmes. The task of applying these concepts to the RV laboratories is relatively easy and intuitive. Evidence has been presented that data generated by the RV laboratory network is now capable of demonstrating declines in rotavirus detection rates post introduction of vaccine. Data collected during 2012 and 2013 may well provide evidence of shifting patterns of predominant rotavirus genotypes in response to vaccine introduction.

iii. Any shortcomings in performance of the 2 laboratory networks are not due to lack of technical support. The quality and quantity of technical support provided through the TWGs and WHO are outstanding, as evidenced through the outcomes of the various technical meetings since 2010. As technical issues have arisen they have been addressed rapidly and appropriately and any changes to practices or procedures have been presented for implementation with minimal delay. Support for developing EQAs and QC programmes and SOPs, improving laboratory testing sensitivity and specificity, and rationalising reporting processes has been exemplary.

iv. While WHO has been very effective in providing and contributing to technical guidance of the laboratory networks, provision of overall management and oversight has been less impressive. The Regional Offices have clearly been under staffing constraints and Regional Office policies may not place a high priority on network development and supervision. Nevertheless, some Regions have performed their management and oversight roles far more effectively than others. At Global level, while the quality of technical support in managing the TWG, gaining technical consensus and providing guidelines, generic SOPs and recommendations has been excellent, provision of participatory oversight of the Regional networks has been lacking. There are many valid reasons why this aspect of the Global Programme has remained under-developed, but it needs to be recognised that this is a key function of the Global laboratory coordinator. One of the outcomes of this review should be

the adoption of a more hands-on approach to supporting Regional laboratory coordinators in the development and management of the regional networks.

v. The 2 Global laboratory networks are each effectively a super-network of the 6 regional networks and each regional network has characteristics and attributes that are region-specific. For WHO HQ to manage the global network effectively there must be a detailed understanding of the characteristics of each Regional network and the conditions under which the network operates. Time permitted for this review has not allowed a detailed assessment of Regional network performance, but one of the outcomes from the current activity should be a detailed assessment of Regional network development, activities and outputs since 2008.

Are the Regional Reference Laboratories performing effectively and appropriately?

i. Given that there are 10 RRLs and 3 GRLs in the IB-VPD laboratory network and 9 RRLs and 1 GRL in the RV laboratory network, there is obviously variation in level of network involvement, activities undertaken and standard of performance of the RRLs. In general, however, available evidence suggests that all RRLs are performing **appropriately**, but a more detailed review of the regional networks may reveal issues that have not be detected in this overview. As to whether the RRLs are performing **effectively** is another matter and is probably determined by factors outside of their control.

ii. Experience with other WHO laboratory networks has shown that the pyramidal or hierarchical structure can work effectively. With time and provision of adequate resources, this network structure can be very effective in providing accurate and timely laboratory-based surveillance information to drive infectious disease prevention and control programmes. However, the additional administrative, supervisory, quality management and training responsibilities expected of the RRLs are often not appreciated by the laboratories when they agree to participate in the network. Specifically, the RRLs are expected to monitor and participate in implementation of Quality Assurance/Quality control (QA/QC) programmes; provide technical support to improve capacities of the NLs and sentinel hospital laboratories; provide technical advice to the WHO surveillance programme, and; conduct research aimed at improving or developing methods of diagnosis and pathogen characterization. In many cases, even if they agree to undertake these activities, they lack the staffing levels and financial resources necessary. This is a major weakness of networks built on this structure. Unless these RRLs are adequately supported with technical and financial resources, either from national or international sources, experience gained through the polio and measles/rubella networks strongly suggests they will struggle to meet

expectations and, not infrequently, fail. Much of the discussion from the technical advisory meetings of the IB-VDP and RV laboratory networks suggests that this weakness is either directly or indirectly recognised within these networks (5) (3) (6). Although the pyramidal network structure has worked well for population-based surveillance programmes, such as polio and measles, it may not be the most appropriate model for laboratory-based sentinel site surveillance.

Are participating sites meeting global standards for quality assurance, proficiency testing, and SOPs?

i. With 131 participating laboratories in the IB-VPD network and 153 laboratories in the RV network it is unlikely that all meet required standards, and evidence from analysis of reported data, Regional reports and discussions at technical meetings suggest that failure to meet standards is an on-going problem. However, both networks remain in a state of development and there has clearly been improvement in the past 3 years. Development and roll-out of the global EQA programmes, development of regional and global QC guidelines and development and distribution of generic SOPs are all appropriate technical responses to improving laboratory quality.

ii. On-site laboratory assessment tools have been developed and are being used, but limited evidence of their effectiveness was provided for this review. Experience gained from the development of other laboratory networks suggests that as the laboratory assessment tools are more systematically and frequently used, so laboratory performance quality improves. The only potential problem anticipated with the IB-VPD and RV networks is that responsibility for assessing sentinel/national laboratories usually falls on the RRLs. Given the large number of sentinel/national laboratories and the relatively small number of RRLs, it may stretch the available resources of the RRLs and Regional Office staff to comprehensively and frequently review all laboratories. Assessment of the RRLs usually falls jointly on the GRLs, Regional Offices and WHO HQ. Comprehensive on-site assessment of the RRLs is underway and should not overtax available resources.

Do the IB-VPD and RV networks link with other existing laboratory networks for viral and bacterial diseases?

i. Available evidence suggests that both networks link with other laboratory networks to a greater or lesser extent. In several Regions the IB-VPD network, in particular, evolved out of existing bacteriological surveillance networks and has maintained the links those networks established. This is particularly true in AMR. The RV laboratory has obvious similarities to the

WHO polio and measles/rubella laboratory networks and opportunity to make use potential synergies, particularly in terms of training, has been exploited and probably could be used more often.

ii. In AFR there is a long-standing and ambitious policy to establish integrated surveillance for communicable diseases. This policy has achieved a good level of success and both the IB-VPD and RV laboratory networks are integrated the Regional system.

iii. Due to restricted time and paucity of information held at Global level this review has not considered antimicrobial susceptibility (AMS) surveillance. However, evidence is available that several of the Regional IB-VPD laboratory networks participate in AMS surveillance networks and provide valuable information.

Did the genotype and serotype data generated by the IB-VPD and RV networks address the 2008 objectives, as outlined in the data analysis plan including the list of activities for the laboratory?

i. Genotype and serotype data generated from 2009 to 2011 failed to address the 2008 to any meaningful extent. A detailed analysis of the 2012 data is underway and the results of that analysis may go some way towards meeting the 2008 objectives. There is far greater likelihood that the 2012 RV genotype data will provide evidence for a shift in predominant RV genotypes in response to introduction of RV vaccine under specific conditions.

ii. Given the level of achievement in developing the networks over the past 5 years it is highly likely, if more effective participatory management and oversight is provided by WHO, that both networks will address the 2008 objectives in a the near future. However, there are some incompatibilities between the data-generating laboratory networks envisaged in 2008 and the fledgling networks evident in 2013. The 2008 objectives appear to assume that the surveillance conducted will be 'classic' sentinel surveillance, with a small number of sites producing high quality data. The type of laboratory support required for this type of surveillance relies on strict adherence to standards and a high priority is given to routine quality control, quality assessment and quality assurance. This provides the surveillance system with a high level of confidence in the laboratory results, so that the limited amount of data provided through sentinel surveillance can be fully used and interpreted. The laboratory support provided to population-based surveillance tends to be based more towards quantity rather than quality. Laboratory quality is obviously important, but so is rapid throughput of large volumes of specimens. Population surveillance is usually more forgiving of lower quality or inconsistent laboratory performance, since selected suspect laboratory data can often be excluded without loss of analytic power. Although the term

'sentinel surveillance' is used to describe the activities of both the IB-VPD and RV surveillance networks, both have characteristics that are intermediate between true sentinel surveillance and population-based surveillance. This indeterminacy places additional stress on the laboratory networks as they are attempting to provide the level of quality of performance associated with sentinel surveillance which also providing the flexibility and scope of population-based surveillance. It would be very helpful to the laboratories if the Programme were to review its surveillance strategy and expectations of the laboratory networks and determine appropriate laboratory resource requirements for the next few years.

Are laboratory data components complete and of high-quality?

i. It is almost certain that the laboratory data components are not universally complete and of high quality. While it is highly likely that the serotype/serogroup and genotype data received by WHO HQ is of high quality in itself, since there is no indication of the source of the isolate, the site of initial testing, or any history of processing of the specimens/isolates, the quality of the data with reference to the programme objectives must be held in doubt. Receipt of case-based data at Global level would overcome these doubts. Given the level of observed inconsistencies in reported data it is also doubtful that the information provided is complete, in that they do not accurately reflect results of all specimens tested.

ii. The other aspect of accuracy and completeness, the fidelity with which laboratory data is entered into the reporting system and the degree to which all required data is provided, is clearly inadequate. This is a recurrent comment from the Regional Offices, that laboratory data reporting is both inaccurate and incomplete. This problem can be overcome to some extent by ensuring strict linkage between laboratory data and clinical and epidemiology data. This is not a technical problem. Appropriate reporting forms, guidelines, instructions and SOPs have been provided. The problem is one of network management and oversight.

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