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.