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Article Doi : 10.1093/infdis/jix077

Article Title : Expansion of Surveillance for Vaccine-preventable Diseases: Building on the Global Polio Laboratory Network and the Global Measles and Rubella Laboratory Network Platforms

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Expansion of Surveillance for Vaccine-preventable Diseases: Building on the Global Polio Laboratory Network and the Global Measles and Rubella Laboratory Network Platforms

Mick N. Mulders,1 Fatima Serhan,1 James L. Goodson,2 Joseph Icenogle,2 Barbara W. Johnson,2 and Paul A. Rota2

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Laboratory networks were established to provide accurate and timely laboratory confirmation of infections, an essential component of disease surveillance systems. The World Health Organization (WHO) coordinates global laboratory surveillance of vaccine-preventable diseases (VPDs), including polio, measles and rubella, yellow fever, Japanese encephalitis, rotavirus, and invasive bacterial diseases. In addition to providing high-quality laboratory surveillance data to help guide disease control, elimination, and eradication programs, these global networks provide capacity-building and an infrastructure for public health laboratories. There are major challenges with sustaining and expanding the global laboratory surveillance capacity: limited resources and the need for expansion to meet programmatic goals. Here, we describe the WHO-coordinated laboratory networks supporting VPD surveillance and present a plan for the further development of these networks.

Keywords. xxx.
The GPNL has served as a model for the development of other global laboratory networks making contributions that will continue long after the polio eradication goal is achieved.

### Measles and Rubella

In 2012, the WHA endorsed the Global Vaccine Action Plan and its objective to eliminate measles and rubella in 5 of the 6 WHO regions by 2020. As of September 2013, countries in all 6 WHO regions had adopted measles elimination goals, and in 3 regions, additional goals for the elimination of rubella and congenital rubella syndrome (CRS) had been adopted [4]. Case-based surveillance is a key strategy for monitoring transmission, informing vaccination activities, and verifying elimination. The Global Measles and Rubella Laboratory Network (GMRLN) was established to provide high-quality, standardized testing to support case-based surveillance [5–7]. Development of the GMRLN started in 2000 using a multi-tiered structure similar to the design of the GPLN. As of January 2016, the GMRLN has 703 laboratories in 165 countries serving 191 countries, including 506 subnational, 180 NLs, 14 RRLs, and 3 GSLs, compared to the 146 laboratories comprising GPLN. Similarly, the GMRLN has a Global Laboratory Coordinator based at the WHO headquarters in Geneva, and each WHO region has a Regional Laboratory Coordinator. NLs and subnational laboratories are closely linked with the national immunization program and perform laboratory testing for case confirmation. The national laboratories are supported by the RRLs that serve as the global laboratory networks making contributions that will continue long after the polio eradication goal is achieved.

#### Table 1. Summary of Serologic and Molecular Testing by the Global Measles and Rubella Laboratory Network (GMRLN), 2010–2015

<table>
<thead>
<tr>
<th>Year</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>JRF</td>
<td>171,170</td>
<td>152,810</td>
<td>148,177</td>
<td>197,469</td>
<td>258,339</td>
<td>226,004</td>
</tr>
<tr>
<td>Monthly</td>
<td>64,864</td>
<td>85,953</td>
<td>122,719</td>
<td>160,611</td>
<td>161,115</td>
<td>131,513</td>
</tr>
<tr>
<td>Percent serum samples testing positive for measles or rubella IgM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>NA</td>
<td>NA</td>
<td>32</td>
<td>31</td>
<td>37</td>
<td>26</td>
</tr>
<tr>
<td>Rubella</td>
<td>NA</td>
<td>NA</td>
<td>17</td>
<td>10</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Number of sequences submitted to the GMRLN databases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>4329</td>
<td>5817</td>
<td>2911</td>
<td>2521</td>
<td>7368</td>
<td>8691</td>
</tr>
<tr>
<td>Rubella</td>
<td>67</td>
<td>143</td>
<td>112</td>
<td>39</td>
<td>148</td>
<td>346</td>
</tr>
</tbody>
</table>

Abbreviations: IgM, immunoglobulin M; JRF, joint reporting form; MeaNS, Measles Nucleotide Surveillance database; NA, data not available; RubeNS, Rubella Nucleotide Surveillance database.

Data reported to MeaNS (www.who-measlesmeasles.org) and RubeNS (www.who-rubella.org) as of 15 June 2016.
yellow fever virus is an arthropod-borne virus with both human and nonhuman primate transmission cycles, which causes sporadic outbreaks in Africa and the Americas. The recognition of YF cases in the early stages of an outbreak is difficult because the differential diagnosis considers several diseases, including malaria, viral hepatitis, dengue, leptospirosis, or other hemorrhagic fevers. However, 1 laboratory-confirmed YF case may initiate an outbreak investigation, necessitating a response, which may include mass vaccination campaigns. A definitive diagnosis of YF infection cannot be made based solely on clinical impressions, and laboratory confirmation is necessary for final case classification [18, 19]. The WHO has established a global tiered YF laboratory network (GYFLN) comprising more than 40 laboratories in the AMR and the African Region (AFR), predominantly within existing GPLN and GMRLN laboratories, which capitalize on investments by global partners to develop those networks. The terms of reference of the GSLs, RRLs, and NLs are similar to the other networks. High-quality commercial diagnostic kits for IgM detection are not available, and laboratories must rely on IgM capture assays produced by GSLs at the CDC and Pasteur Institute of Dakar for case confirmation. IgM detection remains the primary diagnostic test in the NLs with limited technical capacity. Confirmation of positive results by the RRL is an essential component of the GYFLN because of the cross-reactivity of YF virus–specific IgM antibodies with IgM antibodies elicited against cocirculating flaviviruses. Following capacity-building by partner organizations for other VPDs, some laboratories in the GYFLN are now using molecular techniques for case confirmation. Improved diagnostic assays for YF in resource-limited settings is a critical need for the GYFLN.

Japanese Encephalitis

A similar approach has been taken to establish and coordinate the laboratory network for Japanese encephalitis (JELN), which is a major cause of childhood mortality and morbidity in countries of South-East Asia Region (SEAR) and Western Pacific Region (WPR). It is the most important cause of arboviral encephalitis globally. JE is a zoonotic disease, transmitted...
between mosquito vectors and nonhuman vertebrate hosts (primarily birds and pigs). Vaccination is the only effective protection for humans living in areas where the JE virus is circulating. Approximately 3 billion people live in JE-endemic regions, and JE causes at least 50 000 acute encephalitis syndrome (AES) cases with an estimated 10 000 deaths annually [20]. The JE vaccine was WHO-prequalified in 2013. Introduction of the JE vaccine will reduce the number of JE cases, but it will also increase the need for enhanced surveillance to determine the disease burden and trends, substantiate the need for vaccination, monitor the impact of vaccination programs, and detect outbreaks [21]. Laboratory confirmation of JE infection is essential for accurate surveillance, to determine the disease burden and trends, substantiate the need for vaccination, monitor impact of vaccination programs, and to detect outbreaks. The JELN, a tiered laboratory network comprising 25 laboratories, has been established in the SEAR (n = 15) and WPR (n = 10), with an additional 10 subnational JE laboratories added to the Chinese network in 2013, building on the existing GPLN and GMRLN. JE testing is based on the detection of IgM antibodies in clinical specimens, particularly in cerebrospinal fluid. As the proportion of subclinical infections during a JE outbreak is very high (>90%), testing for IgM in serum samples needs to be interpreted carefully, as other pathogens may be the cause of AES. Like the YF virus, the JE virus is a flavivirus, and cross-reactivity of JE virus–specific IgM with cocirculating flaviviruses (e.g., dengue) can confound a diagnosis. Therefore, standardized differential diagnostic testing has been an essential component for the JELN. Furthermore, in contrast to IgM for measles or rubella, JE virus–specific IgM antibodies may not be detectable if acute serum samples are collected within 7 days of disease onset; a second serum sample may be required. Coordination, quality assurance, and accreditation for both the GYFLN and JELN have been implemented following the models established by the GPLN and GMRLN [22]. Annual proficiency testing was established in 2010. Many NLs participated for the first time in 2015 and 86% of them passed.

**Rotavirus**

Rotavirus is the most common cause of severe diarrhea among children under 5 years of age [23, 24]. In 2009, the WHO recommended that countries (particularly those with high childhood mortality from diarrhea) introduce rotavirus vaccines into their national immunization system [25]. Surveillance data on laboratory-confirmed rotavirus cases were important in order to allow countries to make informed decisions on vaccine introduction. By the end of 2014, more than 70 countries had introduced rotavirus vaccine into their routine childhood immunization program. Following the introduction of rotavirus vaccines, it is important to monitor the impact of vaccination in reducing rotavirus morbidity and mortality, evaluate vaccine effectiveness, detect the emergence of rotaviruses that are not prevented by vaccine-induced antibodies, and monitor the safety of rotavirus vaccines [26]. To monitor trends of severe rotavirus disease, sentinel surveillance (including laboratory testing) was established at health-care facilities. Genotype surveillance is important to monitor possible shifts in rotavirus genotypes [27]. In 2008, WHO established the Global Rotavirus Laboratory Network (GRLN) based on previously existing regional networks [28]. The GRLN supports laboratory testing for stool samples collected from hospitalized children with severe diarrhea (Figure 2). The function and structure are similar to those of the GPLN and GMRLN, with GSLs and RRLs providing technical support to NLs and hospital laboratories. The initial testing is performed at the sentinel hospital level with WHO-recommended, commercial enzyme immunoassay (EIA) kits [29]. Genotyping of rotavirus-positive samples is performed at the NL or RRL. In 2015, the laboratory network tested 45 240 of 49 078 (92.18%) stool samples collected from diarrheal cases. Of those samples, 12 429 (27.47%) were tested by EIA and were positive for rotavirus, and 3 238 genotypes from 25 countries were obtained.

The GRLN has adopted approaches similar to those of the GPLN and GMRLN to confirm and improve the accuracy of collected data. The GRLN monitors the laboratory performance through site visits, data review and analysis, external quality control program for confirmatory testing, and annual external quality assurance (EQA) using proficiency test panels. In 2015, 113 (97%) of 116 laboratories that participated in EQA passed the EIA testing, and 49 (91%) of 54 labs that had genotyping capacities passed the molecular quality control. Since 2013, the GRLN has been used as a platform for surveillance for other diarrheal pathogens (including the use of molecular diagnostic technologies) for the simultaneous detection of more than 20 enteric pathogens, including bacteria, viruses, and protozoa.

### Invasive Bacterial Disease

The WHO and partners coordinate a global sentinel surveillance network in selected hospitals for vaccine-preventable IBD that was brought together from preexisting regional IBD networks in 2008. In 2015, the global IBD laboratory network included 117 sentinel hospitals, 20 NLs, 9 RRLs, and the CDC Global Reference Laboratory. The objectives of this network are to gather standardized data on children under 5 years of age suspected to have contracted invasive, severe infection caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*. These data are used by policy-makers to inform evidence-based decisions on vaccine introduction and to assess the effectiveness of vaccine introduction by monitoring disease trends and serotype/serogroup distribution before and after vaccine introduction [30]. The IBD laboratory network has followed similar approaches of the aforementioned laboratory networks. The complexity of bacteriologic testing and the limited laboratory capacities for diagnosis of bacterial meningitis...
in countries were significant challenges in expanding the IBD network. However, the IBD network has made great progress in enhancing the capacity to test for bacteriologic pathogens, and it is the first established global laboratory network for bacteriology, providing high-quality data for IBD surveillance [31]. Cerebrospinal fluid specimens are collected from suspected meningitis cases and tested in a laboratory (e.g., gram stain, bacterial culture, and, where available, a rapid diagnostic test based on immunochromatography or latex agglutination). Culture is performed on clinical specimens collected from suspected pneumonia and sepsis cases. A system of specimen referral between the sentinel hospital laboratories and the NL or RRL has been established to identify the pathogens from clinical samples. The IBD network has established quality-assurance and quality-control systems for laboratory testing. In 2015, 90 of the 98 IBD network laboratories that participated in the EQA program passed.

LESSONS LEARNED FROM VPD LABORATORY NETWORKS

A continuing and significant challenge to all of the WHO-coordinated laboratory networks is the long-standing shortage of human and financial resources. Global donors, as well as national governments, often earmark funds for interventions such as vaccines or injection devices, but fail to recognize the critical role of surveillance to detect diseases and monitor vaccine impacts. Surveillance laboratory networks require sustained investments to support operations that are often in resource-limited and in logistically challenging settings. To some extent, integration of efforts across laboratory networks is possible; therefore, resources that support one network may also have a beneficial effect on other networks. For example, the GMRLN was largely built on (and is still partially supported by) the existing GPLN, and, in turn, the YF and JE surveillance networks were built onto the GMRLN. Of serious concern and a major risk to global VPD surveillance is the imminent diminishing of resources currently supporting polio eradication. There is an urgent need to communicate to donors the important role that disease surveillance plays, and to mitigate the threat of resources flattening or decreasing, particularly once polio eradication is achieved.

Another significant challenge is the needed expansion of the networks to meet increasing programmatic demands for high-quality surveillance data. Within the GMRLN network (particularly in SEAR), there is an immediate challenge to expand as new laboratories are designated in India, Thailand,
A major logistic challenge is maintaining an uninterrupted availability of supplies and reagents needed to perform the transportation and testing of specimens. As laboratory networks expand, the number of specimens collected and shipped, laboratory tests performed, and associated logistic issues increase. Local specimen transport requires maintenance of a reliable infrastructure for the reverse cold chain. International shipment of reagents, supplies, and clinical samples is becoming more expensive and time consuming because of more stringent regulations. Logistical issues are especially challenging during outbreaks (where there is a need for surge capacity stringently, and the testing will require a range of coordination at the global, regional, and national levels. Coordination is essential and allows for the maintenance of standard performance indicators, quality assurance and accreditation programs, standardized testing methods and data collection, and effective interfacing with the epidemiological units of national programs. Close collaboration to strengthen the networks creates esprit de corps for building long-lasting partnerships to achieve public health goals. However, maintaining the financial support for global and regional coordination is an ongoing challenge.

FUTURE OF VPD SURVEILLANCE NETWORKS IN A POSTPOLIO ERADICATION WORLD

The development of the GPLN demonstrated the great value of having globally coordinated laboratory surveillance, and provided infrastructure for public health laboratories that facilitated the development of the GMRLN and other disease surveillance laboratory networks. Laboratories in the GMRLN have benefited by the infrastructure provided by the GPLN, including the establishment of dedicated cell culture and polymerase chain reaction (PCR) facilities, including the availability of key equipment such as thermocyclers and automated sequencers, which are readily available for other disease surveillance activities. Because IgM detection is still the method of choice for the confirmation of measles and rubella cases, the GMRLN has helped to establish serologic testing for other viral diseases in many laboratories. This capacity for serologic testing is now being used by laboratories in the AMR, AFR, SEAR, and WPR to offer serologic testing for YF and JE. Also, many GMRLN laboratories have established molecular testing, including genotyping—techniques that will prove useful for detection of other pathogens.

The GPLN laboratories developed a work culture that valued timely and accurate testing with a strong foundation of capacity-building, quality control, data management, and biosafety and biosecurity, and this culture is shared by the other WHO-coordinated laboratory networks. The laboratory accreditation program initiated by the GPLN was adapted for use by the GMRLN and provides a basis for other assessment programs. In addition, these networks have built capacity through continuous training efforts. The GPLN and GMRLN networks have developed strong programs for referral of samples for confirmation, and both have developed external quality assurance programs through mandatory proficiency panels to assess the performance of serologic and molecular testing.

To enhance laboratory-based surveillance, the global laboratory networks are exploring new technologies to replace virus isolation for the identification of pathogens and serologic methods (such as the detection of pathogen-specific IgM) for case confirmation. These technologies are often based on common platforms such as real-time reverse transcriptase-PCR, next-generation sequencing, and high-throughput serologic testing. For example, there is an increasing use of PCR for laboratory confirmation. The network laboratories can take advantage of these common platforms and develop assays that are amenable to supporting surveillance for many viral and bacterial diseases.

To secure the investments made by the GPLN, we now have the opportunity to transition the resources targeted for the GPLN to further expand the laboratory networks and to develop an integrated approach that can support global surveillance for VPDs, including polio. The key objective of the transition is to...
maintain laboratory support for high-quality, case-based, and syndromic surveillance systems that meet performance indicators and can provide high-quality surveillance data needed to verify disease control and progress toward elimination. Efforts are underway to develop next-generation information systems to optimize the use of data for immunization program monitoring and VPD surveillance. Utilization of GPLN assets and experience to help achieve existing goals for other programs is a cost-effective way to transition the Global Polio Eradication Initiative, while developing integrated VPD surveillance to maintain needed polio surveillance capacity.

Notes

Acknowledgments. The authors thank Jon Gentsch, David A. Featherstone, and Adam Cohen for helpful comments on this manuscript. The authors also acknowledge the tremendous contributions of the Regional Laboratory Coordinators for the GPLN, GMRLN, GRLN, GYFLN, and JELN and IRD Laboratory network.

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