SUPPLEMENT ARTICLE

Surveillance for Respiratory Infections in Low- and Middle-Income Countries: Experience From the Centers for Disease Control and Prevention's Global Disease Detection International Emerging Infections Program

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HISTORY AND MISSION OF THE GLOBAL DISEASE DETECTION (GDD) INTERNATIONAL EMERGING INFECTIONS PROGRAM (IEIP)

In 2001 with its first International Emerging Infections Program (IEIP) established in Bangkok, Thailand, the Centers for Disease Control and Prevention (CDC) began building capacity in strategically located countries for infectious disease surveillance, diagnostics, epidemic detection and response, and collection of epidemiologic data to drive policy on prevention and control of priority infectious diseases. The vision of establishing programs that focus on emerging infectious disease detection and response evolved into what are now called Global Disease Detection (GDD) Regional Centers. The GDD program was established in 2004 to provide support for the CDC's international programs and was expanded to include the IEIP and other programs as part of the GDD Regional Centers when CDC's Center for Global Health was established in 2010 [1]. The GDD Program builds global capacity to identify and respond to emerging diseases, and to conduct applied public health research on disease prevention and control [2]. The GDD Centers include 6 programs that support their host countries in building capacity to comply with the Revised International Health Regulations (IHR 2005). The 3 core programs are the International Emerging Infections Program, the cornerstone of the GDD Centers that serves as a platform to study emerging diseases and their prevention and control; the Field Epidemiology Training Program, which trains scientists in applied epidemiology and public health laboratory science; and the Influenza Program, which supports detection and response for seasonal and pandemic influenza. The remaining 3 GDD programs include the One Health Program, integrating animal and human health investigations of zoonotic diseases; the Strengthening Laboratory Capacity Program; and the Risk Communication and Emergency Response Program, supporting health communication and helping countries establish infrastructure for Emergency Operations Centers and systems. Some GDD Centers additionally have a Refugee Health Program that works closely with IEIP and other GDD programs.

GDD Centers work in partnership with Ministries of Health and the World Health Organization in their host countries, and often also work in nearby or

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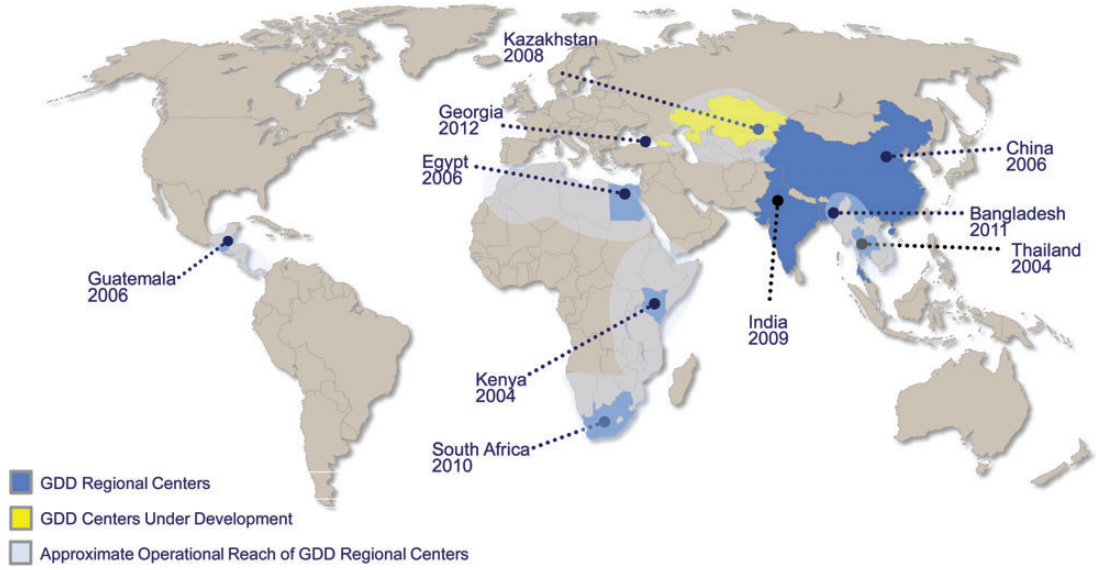

Figure 1. Global Disease Detection (GDD) Regional Center locations and year established.

adjacent countries. Some GDD centers are embedded in Ministries of Health (eg, China) or their institutes (eg, Kenya); others in universities (eg, Guatemala), public–private research institutes (eg, Bangladesh), or United States Department of Defense research units (eg, Egypt). GDD Centers have been established in countries where CDC had established IEIP sites (Thailand, Kenya, Guatemala, Egypt, China, Bangladesh), and new GDD Centers and their embedded IEIP programs have been subsequently established in Kazakhstan and India, South Africa, and Georgia (Figure 1). Six of the IEIP programs in the Regional Centers (Thailand, Kenya, Guatemala, Egypt, China, and Bangladesh) operate population-based infectious disease surveillance for pneumonia and acute respiratory infections. Pneumonia and acute respiratory illness are well established as leading causes of child mortality worldwide, and the emergence of severe acute respiratory syndrome (SARS) in 2003 and avian influenza A(H5N1) highlighted the need for continued detection and response for emerging respiratory pathogens.

Population-based surveillance provides the opportunity to define burden, risk factors, and transmission characteristics of new or emerging infectious diseases, as well as to assess effectiveness of strategies to reduce disease burden or prevent spread of pathogens causing diseases of significant public health importance. Many IEIPs have also undertaken surveillance for additional syndromes, including acute febrile illness, acute diarrhea, acute jaundice, and acute infectious neurologic disease (meningitis, encephalitis, and acute flaccid paralysis), with testing for multiple etiologies.

The methodologies and catchment population of the respiratory disease surveillance systems vary depending upon key local characteristics (Table 1). In Thailand, where healthcare utilization rates are high even in rural settings (Sa Kaeo and Nahkhon Phanom) [3, 4], hospital-based surveillance was established to identify cases of moderate to severe illness. In contrast, in Kenya, where healthcare utilization—even for cases of severe illness—is low both in urban [5] and rural [6] areas, a community-based system was established. This system consists of biweekly household visits during which information about illness is collected for all household members, and patients with serious illness are referred to the study clinic where more detailed clinical information and specimens are collected. Because hospital-based systems are relatively inexpensive to operate [7], they can cover large populations. In a community-based system with household visits, large population sizes would require resources beyond those available for conducting population-based surveillance. Large hospital-based systems provide more capacity to detect emerging pathogens and provide larger sample sizes for evaluating the effectiveness of interventions. Rigorous community-based systems provide greater opportunities to evaluate transmission rates, determinants, and risk factors for common diseases, and sometimes yield incidence rates inclusive of more disease episodes; however, the smaller surveillance area limits the ability to fully define the spectrum of illness caused by particular pathogens.

OVERVIEW OF IEIP SURVEILLANCE FOR RESPIRATORY INFECTIONS

Although subtle differences in the acute respiratory illnesses tracked in the IEIP population-based surveillance exist, sites generally start by capturing acute respiratory infections (ARIs) as defined by evidence of acute infection (typically fever or abnormal white blood cell count) plus 1 or more signs or symptoms of

Table 1. Characteristics of Respiratory Disease Surveillance by Global Disease Detection International Emerging Infections Program Site

Characteristic	Country and Year IEIP Established					
	Thailand 2001	Kenya 2004	Guatemala 2006	China 2006	Egypt 2006	Bangladesh 2008[a]
Surveillance characteristic	General surveillance methods					
Respiratory syndromes under surveillance	ARI, including: • ALRI (including pneumonia) • ILI (until 2007)	ARI, including: • SARI • ILI	ARI, including: • Pneumonia • ILI	ARI, including: • SARI • ILI	ARI, including: • SARI • ILI	ARI, including: • Pneumonia[b]: severe, very severe, chest X-ray confirmed
Geographic setting	Two rural provinces: 1. Sa Kaeo (eastern) 2. Nakhon Phanom (northeast)	1. Kibera (urban slum) 2. Lwak (rural, western)	1. Department of Santa Rosa 2. Department of Quetzaltenango	Jingzhou, Hubei Province	Beheira governorate, Damanhour district	Kamalapur (urban slum)
Estimated catchment population, total	1.2 million	58 000	1.7 million	1.1 million	763 804	200 000
Participating health facilities, sources of cases	• 18 public hospitals • 2 military hospitals • 2 outpatient clinics (ILI)	• Household surveillance: 5500–6000 households per site • 1 private hospital, 1 clinic	• 2 hospitals • 4 health centers • 6 health posts	• 4 hospitals • 1 municipal Center for Disease Control	• 3 MOH hospitals, and their outpatient clinics • 2 private hospitals	• All households • 1 project clinic • 2 principal hospitals
	Routine specimen collection and testing					
Specimens collected (and pathogens routinely tested for) by syndrome or outcome of interest	• ARI/ALRI: NP swab (PCR for viral panel[c]); urine (>18 y: Sp, Lp); BCx; paired sera • ILI: nasal swab, NP swab (viral panel)	• ARI/SARI: NP/OP swabs (PCR for viral panel[c]), all ages; urine (≥5 y: Sp); BCx; paired sera and clot (Lwak only, since 2007) • ILI: NP/OP swabs • Healthy controls: NP/OP swabs	• ARI/pneumonia: NP/OP swabs (PCR for viral panel[c], Mp, Cp, Leg); urine [Sp antigen/ Binax (>10 y)]; BCx; paired sera (2009–2011) • ILI: NP swab (PCR for viral panel[b])	• ARI/SARI:NP/OP swabs (viral panel[c]); BCx; urine (>18 y: Sp)	• ARI/SARI: • NP/OP swab (PCR for viral panel[c], Cp, MP, until 2010); BCx (<5 y); paired sera • ILI: NP/OP swabs (influenza A/B[d])	• ARI/pneumonia: NP wash on all ages (influenza; other pathogens as per special studies); BCx; paired sera

Routine laboratory testing has changed over time in multiple sites; shown are the predominant and most current tests performed unless otherwise indicated.

Abbreviations: ALRI, acute lower respiratory infection; ARI, acute respiratory infection; BCx, blood culture; Cp, *Chlamydia pneumoniae*; IEIP, International Emerging Infections Program; ILI, influenza-like illness; Leg, *Legionella* species; Lp, *Legionella pneumophila*; MOH, Ministry of Health; Mp, *Mycoplasma pneumoniae*; NP, nasopharyngeal; OP, oropharyngeal; PCR, polymerase chain reaction; SARI, severe acute respiratory infection; Sp, *Streptococcus pneumoniae*; WBC, white blood cell count.

[a] Respiratory disease surveillance in Kamalapur, Bangladesh, began in 1998, established by the International Centre for Diarrhoeal Disease Research, Bangladesh and other public health partners.

[b] Adapted from the World Health Organization severe/very severe pneumonia criteria.

[c] IEIP viral panel: influenza A/B viruses, adenovirus, respiratory syncytial virus, human metapneumovirus, human parainfluenza viruses 1–3.

[d] Influenza A also tested for H5N1, pandemic A(H1N1)2009, seasonal H1N1, and H3N2 when indicated.

Table 2. Principal Case Definitions Used for Respiratory Surveillance, Global Disease Detection International Emerging Infections Program Sites[a]

Respiratory Syndrome	Case Definition
Influenza-like illness (ILI)	• Fever >38°C AND • Cough and/or sore throat among a person who is not hospitalized
Acute respiratory infection (ARI)	Fever[b] AND One or more of the following respiratory signs or symptoms: cough, tachypnea, sore throat, shortness of breath, hemoptysis, chest pain, abnormal auscultation findings, chest radiographic abnormality
Severe acute respiratory illness (SARI)	Persons ≥5 y of age: • Sudden onset of fever >38°C, AND • Cough or sore throat, AND • Shortness of breath or difficulty breathing, AND • Requiring hospital admission Children <5 y of age: • Any child <5 y old clinically suspected of having pneumonia and requiring hospital admission.
Pneumonia[c]	Pneumonia • Age-specific tachypnea AND • Crepitation on auscultation Severe pneumonia: • Children <5 y of age: pneumonia plus chest indrawing • Persons ≥5 y of age: pneumonia plus 1 danger sign[d] OR moderate/severe hypoxemia Very severe pneumonia: • Children <5 y of age: pneumonia PLUS ≥1 danger sign[d] • Persons ≥5 y of age: pneumonia PLUS ≥2 danger signs OR 1 danger sign and severe hypoxemia Chest radiograph–confirmed pneumonia: • Clinical pneumonia PLUS • Radiographic findings of alveolar or interstitial infiltrate or consolidation

[a] Subtle differences exist among sites (eg, temperature cutoff = 38°C vs 37.5°C).

[b] Subtle differences exist among sites (eg, in Guatemala, ARI patients may be afebrile if the white blood cell count is elevated).

[c] Thailand conducts surveillance for acute lower respiratory infection, the definition of which is (1) evidence of an acute infection and (2) signs and symptoms of lower respiratory tract infection. (Complete definition can be found in reference [30]).

[d] Danger signs: children <5 years of age: head nodding, nasal flaring, grunting, inability to drink, lethargy, vomiting; persons ≥5 years of age: central cyanosis, severe respiratory distress, convulsions, altered mental status.

respiratory illness (Table 2). Most sites also track subsets of ARI cases: influenza-like illness among outpatients; severe acute respiratory infection (SARI) among hospitalized patients, and pneumonia, which may apply to outpatients or inpatients (Table 2). Respiratory specimens from enrolled patients are collected for molecular diagnostic testing principally using nasopharyngeal and oropharyngeal swabs. Sites test respiratory secretions by polymerase chain reaction (PCR) for a core IEIP respiratory diagnostic panel of viral pathogens: respiratory syncytial virus (RSV), influenza A and B viruses, adenovirus, parainfluenza viruses 1–3, and human metapneumovirus. A detailed description of the GDD laboratory program, including methods used to identity RSV and other respiratory pathogens, is included in this journal supplement [8]. Testing is performed by GDD laboratories (Thailand, Kenya, Guatemala) or laboratories run by the GDD partner institution (China, Bangladesh), or through a combination of GDD and partner laboratories (Egypt) [8].

Several sites use urine to routinely test for the presence of *Streptococcus pneumoniae* (among older children/adults) and *Legionella pneumophila*. More extensive testing has often been done for special studies of limited duration, such as testing of nasopharyngeal/oropharyngeal specimens for the presence of *Mycoplasma pneumoniae* and *Chlamydia (Chlamydophila) pneumoniae*.

Blood cultures are collected from patients with pneumonia in several IEIP sites (Table 2) in an attempt to identify bacteremic pneumonia. Some sites also collect and store sera from febrile patients as part of acute febrile illness surveillance for emerging zoonotic diseases, and occasionally use sera from the subset of febrile patients meeting respiratory surveillance criteria for serologic studies of respiratory pathogens. In Kenya, acute and convalescent sera have been tested by serology for influenza viruses, RSV, human metapneumovirus, adenovirus, and parainfluenza viruses in a special study to evaluate the additional diagnostic yield of serology for respiratory pathogens in addition to PCR [9]. In the event of an apparently newly introduced pathogen, such as the Middle East Respiratory Syndrome coronavirus (MERS-CoV), these banked sera could be used to assess the extent of disease by evaluating the seroprevalence of antibodies or seroincidence of infection, as well as evaluating whether the pathogen was circulating previously without detection. In Thailand, paired sera have been tested for *M. pneumoniae*, *C. pneumoniae*, *Legionella longbeachae*, and *Coxiella burnetii*; in Bangladesh, paired sera have been tested for respiratory pathogens from patients with fever and/or ARI and acute lower respiratory infection. Respiratory specimens from matched healthy controls have been useful to determine usual rates of asymptomatic infection with respiratory viruses (especially adenoviruses and rhinoviruses) and colonization with *S. pneumoniae* and other bacteria for estimation of pathogen-attributable fractions of lower respiratory tract disease [10–12].

KEY FINDINGS AND ACCOMPLISHMENTS

Data on the incidence of the syndrome of pneumonia and SARI have provided valuable information for considering the relative importance of specific etiologies, and for considering what fraction of pneumonia and associated poor health outcomes might be preventable through vaccines or other interventions. The GDD IEIP sites have documented a high incidence of

pneumonia and influenza-associated acute respiratory illness, especially among children [13–15].

Among IEIP sites with published data, a high incidence of RSV disease has been consistently demonstrated. For example, in hospital-based surveillance within known catchment populations in rural areas in Thailand, rates of RSV-associated acute respiratory illness were highest among children aged <1 year (1067/100 000) and children aged 1–4 years (403/100 000), but were comparatively low but still substantial (42/100 000) among adults aged ≥65 years [16]. In community-based studies in rural Kenya, the rate of RSV-associated acute respiratory illness was high in children aged <5 years (7100/100 000) with SARI, and was 440/100 000 in persons aged >5 years with ARI (including both inpatients and outpatients) [17, 10].

The IEIP respiratory surveillance systems have also documented the incidence of acute respiratory illness due to other respiratory viruses and bacteria, including human metapneumovirus, parainfluenza viruses, and adenoviruses [13]. Surveillance specimens from several sites have also been tested for additional viruses such as bocaviruses, coronaviruses, enteroviruses, parechoviruses, and rhinoviruses [12, 13]. The sites have also played a critical role in detection of and response to novel pathogens such as SARS [18] and described one of the first known outbreaks of pandemic A(H1N1)2009 at a primary school in China [19].

CHALLENGES ENCOUNTERED AND FUTURE DIRECTIONS

Some differences in surveillance methodology exist among the 6 GDD IEIP sites that conduct respiratory surveillance. These differences are partially due to site-specific differences in local laboratory capacity, standards of clinical care, limitations in the use, quality, and interpretation of routine diagnostics (eg, blood cultures and chest radiographs), and healthcare-seeking behaviors of the population under surveillance. A universal challenge is the aseptic collection of blood for culture and adequate capacity for processing. Because of the challenges of implementing blood culture, estimates of invasive bacterial infections, particularly bacteremic pneumococcal pneumonia, are uncertain. However, some sites, such as Bangladesh and Kenya, have successfully incorporated blood culture into their surveillance, enabling measurement of the proportion of invasive pneumococcal disease that may be prevented with use of newly developed conjugate vaccines [20] and documenting that blood culture–confirmed typhoid fever can be associated with significant respiratory manifestations [21]. Investigators in the GDD Regional Center in Thailand found that prior use of antibiotics (measured by serum antimicrobial drug levels) reduced the incidence estimates for pneumococcal bacteremia by 32% overall and 39% in children <5 years of age [22].

Because specimens are archived from patients with acute respiratory illness in the GDD IEIP programs with established respiratory surveillance sites, it is possible to rapidly characterize the incidence and epidemiology of newly identified pathogens (eg, pandemic A[H1N1]2009) [23–25] and to reexamine disease burden estimates when new, more sensitive and highly specific tests become available. Thus, the novel MERS-CoV first identified in 2012 among patients in Saudi Arabia, Qatar, and Jordan [26–28] can be examined as a cause of respiratory illness by testing prospective as well as archived samples from IEIP surveillance sites run by the GDD Regional Center in Egypt and other GDD Centers, surveillance sites run by other GDD programs (eg, Influenza, One Health, and Refugee Health), and affiliated surveillance networks (eg, the Eastern Mediterranean Acute Respiratory Infections Surveillance (EMARIS) sites established by the GDD Regional Center in Egypt, the World Health Organization's Eastern Mediterranean Regional Office, and its member states). Likewise, the sites are well poised to evaluate new diagnostic testing technologies, including multiple pathogen assays like the TaqMan array card (TAC), which tests for a variety of pathogens with one specimen [29]. Technologies like TAC allow archived specimens collected over multiple years to be tested at one time, presenting the possibility to rapidly characterize a vast array of ARI etiologies in multiple geographic locations with varied ecologic and demographic features. Using well-characterized clinical, demographic, and geographic information, the IEIP population-based surveillance sites are able to describe seasonality, risk factors, and spectrum of disease of newly identified pathogens.

CONCLUSIONS

This journal supplement highlights the value of population-based surveillance systems such as those initiated or catalyzed by GDD IEIP sites. This multicountry network of population-based surveillance sites provides a platform to test a variety of interventions in settings where ecology, economics, ethnicity, politics, predominant co-morbidities and co-infecting pathogens, and behavior vary, thereby providing a useful tool to design optimal intervention strategies targeted to each setting. GDD IEIP surveillance data also provides a stimulus for more urgent development of novel vaccines and therapeutics for RSV and other diseases by demonstrating their burden and severity and are poised to assess the effectiveness, acceptance, and value of these tools compared with other prevention strategies. Given the consistency in laboratory testing methods, the approach to surveillance of respiratory infections undertaken by GDD IEIP sites enables comparison of the burden of RSV disease and its epidemiology among the 6 geographically and sociopolitically diverse countries. Longitudinal surveillance data from these sites, combined with those from GDD Influenza Program sites, will add to the global understanding of RSV-associated mortality

and risk factors for severe disease and death in low- and middle-income countries, result in better descriptions of RSV seasonality, and inform intervention strategies to mitigate the burden of RSV-associated disease. The IEIP-run surveillance sites are well positioned to serve as platforms for future RSV vaccine efficacy or effectiveness studies in low- and middle-income countries, and to evaluate the utility and feasibility of RSV prophylaxis in these settings. Ultimately, the evidence generated by studies from GDD IEIP surveillance sites can inform countries' determinations of their public health priorities and generate the political will to implement effective prevention and control measures, through evidence-based policy change.

Notes

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