

Antimicrobial Resistance Surveillance in Low- and Middle-Income Countries: Progress and Challenges in Eight South Asian and South East Asian Countries

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SUMMARY

Antimicrobial resistance (AMR) is a serious global health threat and is predicted to cause a significant health and economic impact, particularly in low- and middle-income countries (LMICs). AMR surveillance is critical in LMICs due to high burden of bacterial infections; however, conducting AMR surveillance in resource-limited settings is constrained by poorly functioning health systems, scarce financial resources, and lack of skilled personnel. In 2015, the United Nations World Health Assembly endorsed the World Health Organization's Global Action Plan to tackle AMR; thus, several countries are striving to improve their AMR surveillance capacity, including making significant investments and establishing and expanding surveillance networks. Initial data generated from AMR surveillance networks in LMICs suggest high prevalence of resistance, but these data exhibit several shortcomings such as lack of representativeness, lack of standardized laboratory practices and underutilization of microbiology services. Despite significant progress, AMR surveillance networks in LMICs face several challenges in expansion and sustainability due to limited financial resources and technical capacity. This review summarizes the existing health infrastructure affecting the establishment of AMR surveillance programs, the burden of bacterial infections demonstrating the need for AMR surveillance, and current progress and challenges in AMR surveillance efforts in eight South and South East Asian countries.

INTRODUCTION

Antimicrobial resistance (AMR) is recognized as a major threat to global public health. Drug-resistant bacterial infections (including tuberculosis) are estimated to cause at least 700,000 deaths globally each year (1, 2). Estimates predict that by 2050, approximately 10 million deaths will occur annually due to drug-resistant bacteria (including tuberculosis), malaria, HIV infections, with 90% of these deaths occurring in low- and middle-income countries (LMICs) in Africa and Asia. However, the scientific accuracy of these estimates has been questioned due to lack of comprehensive population-based surveillance data from not just LMICs but also from high income countries (3). The World Bank estimates that by 2050, the world will lose up to 3.8 percent of its annual gross domestic product (GDP) as a result of drug-resistant infections (4).

In 2015, the World Health Assembly endorsed the World Health Organization's (WHO's) Global Action Plan to tackle AMR (5). A key component of the Global Action Plan is to improve AMR surveillance capacity, especially in LMICs, with a 'One Health' approach, as drug-resistant organisms exist in humans, animals, food, and the environment (5). Several global funding initiatives aim to improve AMR surveillance in LMICs, including the 265 million GBP Fleming Fund (www.flemingfund.org), established by the government of the United Kingdom, to build capacity for AMR surveillance in LMICs.

LMICs exhibit a relatively high burden of infectious diseases (6, 7), but AMR data from these countries are limited (8). Conducting AMR surveillance has been challenging in LMICs due to lack of laboratory facilities or gaps in existing laboratories in quality assurance, availability of skilled personnel, laboratory supplies, and data management (9, 10). These shortcomings lead to a lack of trust in laboratory results by clinicians and thus, underuse of microbiology laboratory services and lack of response to reported results (i.e., no de-escalation, discontinuation of

antibiotic use). Early reports from LMICs indicate that antibacterial resistance is increasing and more common in LMICs than in high-income countries (11, 12). However, these data display several shortcomings such as lack of representativeness, lack of standardized laboratory practices and underutilization of microbiology services (3, 12).

As several countries have begun to develop National Action Plans consistent with the WHO Global Action Plan, understanding the human AMR surveillance efforts and progress in LMICs will be useful to address the challenges and provide guidance for other countries that are initiating these efforts. In this review, we discuss health systems, including laboratory capacity, bacterial disease burden substantiating the need for AMR surveillance, AMR surveillance progress, AMR status, shortcomings of AMR data, challenges and opportunities for conducting AMR surveillance, and progress in other efforts to tackle AMR in eight South and South East Asian countries. We conclude by identifying AMR surveillance guidelines suitable for resource-limited settings. A comprehensive review of the One Health approach for surveillance and efforts across sectors is beyond the scope of this article; this review is limited to discussion of AMR in bacteria (excluding mycobacteria) in humans.

OVERVIEW OF HEALTH SYSTEMS IN LMICS

The ability of a country to establish and strengthen AMR surveillance is influenced by several factors including the health system efficacy and resource availability. The majority of countries discussed in this review have relatively weak public health systems and very low government expenditure on health services. Brief demographic and health system information for each country are summarized in Table 1. In 2016, total health expenditure as a proportion of GDP for these eight countries ranged from 2.3% in Bangladesh and Cambodia to 6.2% in Nepal (World Bank Data 2016). In contrast to these eight countries, in 2016, the United States and the United

Kingdom contributed 17% and 9.7% of their GDP respectively, for health expenditure (World Bank Data 2016). In 2016, the government contribution for health expenditure ranged from 18% in Bangladesh to 78% in Thailand, whereas the government contribution for health expenditure in the United States and United Kingdom for 2016 was 82% and 80%, respectively (World Bank Data 2016). As in the majority of LMICs, health systems in these eight countries are mixed (13); healthcare services are provided by both the public and private sectors in varying proportions (14-19). In Bangladesh, Cambodia, Laos and Nepal, international development organizations also provide significant contributions for healthcare services (14, 20-22). Administration and implementation of health services in the public sector differ by country, which may have either a centralized or decentralized structure (18, 21, 23-27). Having better governance and regulation, accreditation of healthcare organizations with adequately trained and certified healthcare staff and less patient load, the private sector has an edge over the public sector in imparting better health care services but may only be accessible to the wealthier part of the population. These factors have resulted in expansion of the private sector, and in countries like India and Pakistan, healthcare delivery is dominated by the private sector (17, 28). In Thailand and Vietnam, the public sector dominates healthcare delivery, however. Since 2002, the Thai government has provided universal health coverage (18). The Vietnamese government is making efforts to achieve universal health coverage; as of 2015, 77% of the population is covered by national insurance (19).

OVERVIEW OF LABORATORY CAPACITY

Studies evaluating clinical microbiology laboratory capacity at the national scale in these eight countries are limited. The majority of these countries have weak laboratory capacity and infrastructure, especially in the public sector (29, 30). One exception is Thailand, which has a

comprehensive public laboratory network with good capacity (31), including approximately 1,000 laboratories (32). Except Cambodia, Laos, and Nepal, the countries have national bureaus of accreditation that accredit clinical laboratories according to international standards. The private sector accounts for the majority of clinical laboratories in South Asian countries. In India, 98% of the medical laboratories accredited by national accreditation organizations belong to the private sector (33). In 2012, Bangladesh had approximately 5,122 private laboratories (14) and Nepal had approximately 277 government laboratories and 1,300 private laboratories (34). However, for the majority of these laboratories, diagnostic microbiology services are absent or limited. One study in Pakistan assessed antimicrobial susceptibility testing (AST) capacity in 30 public and private microbiology laboratories in 2015–2016 and found low scores for quality assurance, microbial identification, and readiness for AMR surveillance. However, scores improved in select laboratories with additional training and mentoring (9). In Cambodia, assessment of laboratory capacity of 28 public hospitals in 2013–2014 revealed that most did not have quality management systems in place (35). The assessment revealed several deficiencies, such as a lack of training and awareness of quality control procedures, irregular power supply, poor quality reagents and supplies, and lack of standard management guidelines and financial resources for supplies. However, a repeat assessment of 15 laboratories in late 2015 showed improvements among those laboratories that implemented a mentored laboratory quality stepwise implementation (LQSI) program (35). This program involved training on use of the LQSI tool, which includes a stepwise plan for medical laboratories to implement a quality management system in compliance with the International Organization for Standardization (ISO) 15189 standard. The LQSI tool does not address specific components of AMR surveillance but focuses on overall quality assurance.

BURDEN OF BACTERIAL INFECTIONS

Bacterial Disease Burden in Community-Acquired Infections

Communicable diseases continue to be a major cause of morbidity and mortality in South and South East Asia (36). High bacterial disease burden imposes the need for robust AMR surveillance to inform empiric treatment regimens. Rigorous population-based epidemiological studies focused on the etiology of community-acquired infections in this region are limited. A recent prospective study carried out between 2011 and 2014 in three countries (Bangladesh, India, Pakistan) investigated the causes of community acquired infections among 63,114 infants (0-59 months) (37). The mean incidences of bacterial and viral infections were 13.2 (95% credible interval [CrI] 11.2–15.6) and 10.1 (9.4–11.6) per 1,000 live births, respectively. Among children who died, 46% of causes were attributed to possible serious infections, of which 92% were bacterial. Another recent prospective study investigated causes of community-acquired sepsis among 1,578 children and adults in three South East Asian countries (Indonesia, Thailand, and Vietnam) in 2014 and 2015 (38). Etiology of sepsis was identified in 56% of children and 48% of adults enrolled in the study. Viruses were identified in 29% of patients and bacteria in 27% of patients. Bacteremia accounted for 12% of cases in adult patients and 5% in pediatric patients. Among patients who died, 37% had a bacterial infection, while 11% had a viral infection.

In South Asia in 2015, on an average 123 (95% confidence interval [CI]; 109.5–137.8) deaths per 100,000 occurred in children younger than 5 years due to lower respiratory tract infections and ranged from 113 (99-129.4) deaths per 100,000 in India to 157.7 (118.9-200.8) deaths per 100,000 in Pakistan (39). In four South East Asian countries, the numbers of deaths in children younger than 5 years ranged from 7.8 (5.4–11.0) per 100,000 in Thailand to 285.2 (175.1–441.7)

in Laos. Of these deaths in children younger than 5 years, 67% in South Asia and 68% in South East Asia were attributed to two bacterial causes (*Streptococcus pneumoniae* and *Haemophilus influenzae* type b), whereas approximately 9% of deaths in both regions are attributed to two viral causes (respiratory syncytial virus and influenza). However, in high-income countries, the average numbers of deaths in children younger than 5 years due to lower respiratory tract infections was 3.4 (3.1-3.7) per 100,000 (39). In 2017, the incidence of meningitis due all causes in all age groups in South Asia was 77.4 cases per 100,000 people, whereas the incidence rate due to three (vaccine-preventable) bacterial causes (*S. pneumoniae*, *H. influenzae*, and *Neisseria meningitidis*) was 13 cases per 100,000 [as per the Institute of Health Metrics Global Burden of Disease (<http://vizhub.healthdata.org/gbd-compare>)]. However, mortality was higher for bacterial causes when compared with other causes (2.63 vs. 1.36 deaths per 100,000 people). In South East Asia, the incidence of meningitis due to three vaccine-preventable bacterial causes was 0.9 cases per 100,000, whereas in the United States and Western Europe the incidence was 0.24 and 0.25 cases per 100,000, respectively.

The high burden of respiratory tract infections and meningitis due to *H. influenzae* and *S. pneumoniae* in 2015 in South Asia and South East Asia compared to high-income countries could partially be attributed to low *H. influenzae* type b (Hib) and pneumococcal conjugate vaccine (PCV) immunization rates. In 2015, among the eight countries the Hib immunization coverage among one-year old children ranged from 45% in India to 98% in Bangladesh (Figure 1A) ([https://www.who.int/data/gho/data/indicators/indicator-details/GHO/hib-\(hib3\)-immunization-coverage-among-1-year-olds\(-\)](https://www.who.int/data/gho/data/indicators/indicator-details/GHO/hib-(hib3)-immunization-coverage-among-1-year-olds(-))). Similarly, in 2015 PCV immunization coverage among one-year old children ranged from 5% in Nepal (not introduced in India in 2015) to 80% in Pakistan (<https://www.who.int/data/gho/data/indicators/indicator-details/GHO/pneumococcal->

conjugate-vaccines-(pcv3)-immunization-coverage-among-1-year-olds-(-)). However, in 2015 among three high-income countries, Australia, the United States and the United Kingdom; the Hib and PCV immunization coverage among one-year old children was greater than 92%. Although, Hib and PCV immunization rates were low in 2015, the majority of the eight countries included in this review improved their immunization coverage in 2018 (Figure 1), which may have impacted the burden of infection caused by these organisms. A recent review of studies published after 2011 in South and South East Asia (Bangladesh, India, Nepal, Pakistan, Sri Lanka, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Thailand, and Vietnam) identified causes of acute febrile illness. Among 30 studies that included both adults and children and that included three or more pathogens, the most frequently reported causes of febrile illness were dengue (reported by 50% of studies) followed by bacterial infections: leptospirosis (27%), scrub typhus (23%), and typhoid (20%) (40).

Etiology of Community-Acquired Bacteremia

Understanding the epidemiology and microbial causes of community-onset bloodstream infections is vital for developing intervention strategies and for optimal clinical management (41). The substantial clinical impact, straightforward definition of bloodstream infections, straightforward interpretability of blood culture results, and increasing incidence of antibiotic resistance in community-acquired infections makes bloodstream infections a suitable primary target for AMR surveillance programs (42, 43). A systematic review of 17 studies published between 1990 and 2010 of 40,644 patients reported causes of bacteremia in febrile illness among hospitalized patients in South and South East Asia (44). Pathogenic organisms were isolated from 3,506 patients (9%; range 1–51%): of which 1,784 were from adults (1,784/14,386; 12%) and 1,722 were from children (1,722/26,258; 7%). In children, the most common pathogens were

Salmonella enterica serovar Typhi (25%), *S. pneumoniae* (12.8%), *H. influenzae* (8.4%), and *Staphylococcus aureus* (4.1%). Similarly, in adults, the most common pathogens were *S. Typhi* (29.6%), *S. aureus* (12.6%), *Escherichia coli* (12%), *Pseudomonas* spp. (10.2%), and *Klebsiella* spp. (7.6%). However, others cited concerns that the above review did not adhere to the strict definition of community-acquired infection and included hospital-acquired infections (45). For example, one study from India included in the above systematic review was based on microbiology laboratory data and did not define community- or hospital-acquired infections (46).

Evaluation of organisms causing community-onset bacteremia (defined as blood cultures obtained on admission or within 48 hours of admission to the hospital) among eight countries using studies published between 2010 and 2018 (42, 47-62) (Supplementary Table S1) indicated that among children (excluding newborns) and adults, *S. Typhi* is the most frequently reported cause of community-onset bacteremia in all four South Asian countries as well as in Cambodia and Laos (Table 2). However, in Thailand, the most frequent causes of community-onset bacteremia were *S. aureus* in children and *E. coli* in adults. *Burkholderia pseudomallei* was the second most frequently identified organism in hospitalized children and adults in Thailand. A study in Vietnam found that *K. pneumoniae* followed by *E. coli* were the most frequent causes of community-onset bacteremia in adults (62). Only one study investigated the causes of community-acquired infections among neonates in three countries (Bangladesh, India, and Pakistan) (37). Among 4,859 neonates with possible serious bacterial infections, 102 had clinically relevant pathogens isolated from blood cultures. *E. coli* (21%) was the most predominant pathogen followed by *Klebsiella* spp. (17%), *S. aureus* (12%), and group A *Streptococcus* (11%).

Bacterial Disease Burden in Hospital-Acquired Infections

Reported hospital-acquired infections (HAIs) include device-associated and surgical site infections (SSIs) that are mostly bacterial in nature. In a systematic review of HAIs, studies in LMICs reported higher prevalence of HAIs and SSIs when compared to the United States of America and European countries (63). The average prevalence of HAIs was 15.5% in LMICs, compared to 7.1% and 4.5% in Europe and the United States, respectively. HAI density in adults in ICUs was at least three times higher in developing countries (47.9 per 1,000 patient-days) compared to that in the United States (13.6 per 1,000 patient-days). A more recent systematic review of HAIs in six South East Asian countries (Indonesia, Malaysia, the Philippines, Singapore, Thailand, and Vietnam) reported a pooled HAI prevalence of 9.0% (95% CI, 7.2%–10.8%) (64). In Thailand, the pooled HAI prevalence was 7.1% (95% CI, 6.6%–7.6%), and in Vietnam, the pooled HAI prevalence was 7.8% (95% CI, 7.2%–8.4%). A recent study in Vietnam that used the European Center for Disease Prevention and Control (ECDC) point prevalence survey methodology and involved 15 adult ICUs in 14 tertiary care hospitals across the country found a HAI prevalence of 29.5% (65). A study using a similar methodology of six pediatric ICUs in Vietnam found a HAI prevalence of 33.1% (66). Although pooled HAI prevalence rates are not available for India, pooled device-associated infection rates in ICUs from 40 hospitals were much higher than those reported by the United States Center for Disease Control and Prevention (US CDC) National Healthcare Safety Network (NHSN), despite a lower device utilization ratio in India. The central line–associated blood stream infection (CLABSI) rates were at least five times higher in Indian ICUs when compared to the US CDC/NHSN rates (67). Although multi-center studies reporting HAIs in other countries were not published, a single-center study in an ICU reported a high device associated HAI incidence rate of 27.3 per

1000 patient-days in Nepal (68). In Pakistan, a single pediatric ICU study reported a device associated HAI incidence rate of 6.3 per 1000 patient-days (69), whereas in Cambodia, the device associated HAI incidence rate in one pediatric ICU was reported as 4.6 per 1000 patient-days (70).

Etiology of Hospital-Acquired Bacteremia

Although CLABSIs are primarily reported as hospital-acquired bacteremia cases (71), recent studies in the United States indicate that only 20% of hospital-acquired bacteremia cases were attributed to CLABSIs (72). We did not identify a systematic review that included data from multiple countries in the South Asia or South East Asia region reporting causes of hospital-acquired bacteremia. The organisms causing hospital-onset bacteremia (defined as blood cultures obtained after 48 hours of admission to a hospital) in eight countries determined using studies published between 2010 and 2018 (42, 50, 55, 56, 62, 70, 73-75) (Supplementary Table S2) are listed in Table 2. We identified very few or no studies from Bangladesh, Pakistan, and Laos that determined the causes of hospital-acquired bacteremia, indicating the need for more comprehensive studies in these areas. A retrospective study from 10 provincial hospitals in northeastern Thailand based on microbiology laboratory data from a total of 3,424 patients reported the following organisms as the most common causes of hospital-acquired bacteremia: *Acinetobacter* spp. (16.2%), *K. pneumoniae* (13.9%), *S. aureus* (13.9%), *E. coli* (12.6%), and *Pseudomonas* spp. (10.5%) (74). Overall, determination of causes of hospital-onset bacteremia in countries other than Thailand was limited by the small number of studies.

STATUS OF INFECTION PREVENTION AND CONTROL AND ANTIMICROBIAL STEWARDSHIP PROGRAMS

AMR in hospitals is augmented by lacking or substandard infection control practices as well as

overuse of antibiotics, which creates selection pressure for resistance (76, 77). Studies from LMICs indicate a positive impact of implementing infection prevention and control (IPC) measures (78) and antimicrobial stewardship programs (ASP) in healthcare facilities (79-81). Implementing IPC and ASPs can enhance utilization of diagnostic laboratory services and diagnostic stewardship which could aid AMR surveillance activities (82, 83). The status of IPC and ASP in eight countries is discussed below.

Bangladesh, Cambodia, Laos

Studies assessing IPC and ASPs are lacking. In Cambodia, IPC guidelines were developed in 2010 (84), but infection prevention activities are hindered due to lack of adequate funding for hospitals (85). In Laos, a national infection prevention and control strategy was developed in 2013, which includes details on establishing IPC measures (86).

India

A survey of 20 tertiary care hospitals representing different regions reported that written guidelines for ASP and IPC were available in 40% and 75%, of hospitals, respectively (87). However, only 60% of healthcare institutions consistently recorded the incidence of healthcare-associated infections, and only 25% analyzed antimicrobial usage data. Private hospitals performed better than public hospitals, mainly due to mandatory hospital accreditation requirements, which were more common in private institutions. In 2017, the Indian Council of Medical Research (ICMR) published IPC guidelines for healthcare facilities (88) and ASP guidelines (89). These guidelines may help standardize IPC and ASPs across Indian hospitals, but most healthcare facilities face challenges in implementation due to hospital overcrowding, low nurse/patient ratios, and lack of qualified personnel, including infectious disease specialists, microbiologists, and clinical pharmacologists (67, 87, 90, 91). A recent study involving 60

healthcare professionals in 51 hospitals assessed the role of infrastructure, manpower, and education and training in relation to ASP (92). The study found that 69% of respondents received some education and training in antimicrobial prescribing during pre- or post-graduation training, but a formalized teaching program encompassing various components of ASP is lacking. The study also highlighted the need for government endorsement of antimicrobial stewardship activities and lack of formal ASP in hospitals.

Nepal

A study in Nepal assessed IPC programs in 17 hospitals (five public, nine private, and three non-profit) in Kathmandu city in 2011(93). Manuals for infection control were present in 53% of the hospitals, but only two hospitals had up-to-date content. Similarly, infection control committees were established in 41% of the hospitals, but only two hospitals held regular meetings. None of the evaluated hospitals had an infection control team responsible for daily infection control activities. We did not find studies assessing ASPs in hospitals in Nepal.

Pakistan

In Pakistan, studies assessing IPC and ASPs are limited (94). Although national infection control guidelines were established in 2006 (95), implementation was poor (94). One study assessed IPC and ASPs in seven tertiary care hospitals in 2008 (100) and reported poor implementation of these programs despite their existence in a majority of hospitals. A recent study indicated a lack of familiarity with ASP among physicians working in public tertiary care hospitals (96). In another recent survey of 137 hospitals assessing ASPs, 32% of hospitals reported having a multi-disciplinary antimicrobial stewardship team, but the implementation and quality of these programs were not assessed (97).

Thailand

Thailand is one of the few countries that implemented IPC programs as a measure to improve quality of medical care as early as 1979 (98). A survey of 57 hospitals (including university, regional, provincial, district, and private) in 2002 indicated implementation of IPC in all evaluated facilities (99). In this survey, regular infection control committee meetings were reported in 75% of hospitals, and regular report of surveillance data was prepared in 77% of the hospitals. Overall, the survey indicated that the IPC quality required further improvement to its structure and process (99). In 2012, another study assessed ASPs in Thailand (100). Among the 204 hospitals assessed, 71% (144 hospitals) of these reported having ASP, and 51% of them undertook drug utilization evaluations. Implementation of ASP was more effective in teaching hospitals than non-teaching hospitals.

Vietnam

In 1997, the Ministry of Health (MoH) developed a national IPC program (101), and in 2009, in partnership with WHO, the MoH announced new IPC guidelines (102) with the aim of improving infection control capacity and ensuring that health-related activities result in safer care for all patients, staff, and visitors. A study assessed IPC in 51 public hospitals in Northern Vietnam by conducting surveys in 2005 and 2007. The authors observed improvement in tertiary care hospitals, and infection control committees were established in most district hospitals, but implementation was constrained by lack of financial resources. The authors also observed that several guidelines were outdated and unsuitable for most hospitals. The Medical Services Administration within the MoH is responsible for implementation of ASP in hospitals with technical support from the WHO country office in Vietnam (www.unv.org/sites/default/files/special_calls/VNMR000065.pdf). A recent national survey on

implementation of ASP conducted by the MoH indicated that approximately 50% of hospitals do not have a committee to implement ASPs. In 2019, the Vietnam WHO ASP indicated that they aim to include activities involving access to quality-assured and affordable antibiotics in the community and in hospitals.

CURRENT STATUS OF NATIONAL AMR SURVEILLANCE PROGRAMS

Following the United Nations World Health Assembly resolution on AMR, AMR surveillance efforts have been initiated in several countries and are in various stages of development in the eight countries described in this review (Table 3). Countries with existing surveillance systems, such as Thailand, are expanding their AMR surveillance network, while networks in Laos and Bangladesh are in the initial stages of development. The WHO launched the Global Antimicrobial Surveillance System (GLASS) (12) to facilitate a standardized approach for AMR surveillance globally. GLASS provides surveillance and laboratory guidance, tools, and support to national AMR surveillance systems with the aims of standardizing approaches for data collection, analysis, and sharing of data globally. GLASS also provides the list of antibiotics that should be reported for each pathogen. Below, we discuss the progress in each country in establishing and developing AMR programs.

Bangladesh

Efforts to establish a national AMR surveillance program were initiated in 2016. The Institute of Epidemiology Disease Control and Research is the nodal center for conducting surveillance (103). Ten hospitals were selected to conduct surveillance activities across eight divisions of the country; data collection is ongoing (103).

Cambodia

Efforts to establish a national AMR surveillance program were initiated in 2014. Currently, eight sentinel sites have been selected, and data collection is ongoing (12, 104).

India

In the last few years, India has taken steps to develop a human AMR surveillance network, and significant progress was reported recently (105). The Indian Council of Medical Research (ICMR) established an AMR surveillance network in 2013 and has collected data since 2014. In 2014, four tertiary care hospitals selected as nodal centers contributed not only antimicrobial susceptibility data but were also designated to undertake molecular epidemiology research. In 2017, six other regional tertiary care hospitals were added to the network, and thus, 10 tertiary care hospitals contributed to AMR data in 2017 (106). In 2018, 10 additional regional tertiary care hospitals were added to the AMR surveillance network to result in a total of 20 hospitals in the network. In addition to ICMR, the National Center for Disease Control (NCDC) also initiated AMR surveillance in 13 public teaching hospitals across India, which report antimicrobial susceptibility data for selected pathogens (107).

Laos

In 2018, The Ministry of Health launched an AMR surveillance program with support from WHO and the Korea International Cooperation Agency (KOICA) (<http://www.wpro.who.int/laos/mediacentre/releases/2018/20180712-launch-of-ars-program-in-laopdr/en/>). The National Center for Laboratory and Epidemiology will function as the coordinating body for the national AMR surveillance system. Surveillance sites have not yet been selected. More recently, Fleming Fund partnered with the Loatian government to build an

AMR surveillance system (<http://www.flemingfund.org/publications/new-partnership-between-lao-pdr-and-the-fleming-fund/>).

Nepal

An AMR surveillance program was initiated in 1999 with The National Public Health Laboratory and the Epidemiology and Disease Control Division functioning as the national coordinating laboratory and the national focal point for the program, respectively (108). Initially, nine hospital laboratories participated in the surveillance and monitored five pathogens: *Vibrio cholerae*, *Shigella* spp., *S. pneumoniae*, *H. influenzae*, and *Neisseria gonorrhoeae*. By 2002, *Salmonella* spp. and extended spectrum beta-lactamase producing (ESBL) *E. coli* were added to the surveillance list. In 2017, AMR surveillance efforts were expanded to include a total of 21 hospital laboratories and 10 pathogens [in addition to above, multidrug-resistant (MDR) *Acinetobacter* spp., MDR *Klebsiella* spp., and MRSA were added] (109).

Pakistan

Efforts to establish an AMR surveillance program were initiated in 2015, with National Institute of Health designated as the nodal center. Currently, nine laboratories (seven hospitals and two outpatient facilities) participate in the surveillance (12, 110). AMR data collection from the selected sites is ongoing. AMR data collection from the selected sites is ongoing.

Thailand

Thailand is among the few countries in South East Asia with an established AMR surveillance system, which continues to expand its network. The National AMR Surveillance Center at the National Institute of Health was established in 1997 with support from the WHO and has collected data since 1998 (<http://narst.dmsc.moph.go.th/>). The National AMR Surveillance Center has been designated as a WHO Collaborating Centre for AMR Surveillance for the South-

East Asia region since 2005 (http://apps.who.int/whocc/Detail.aspx?cc_ref=THA-71&cc_code=tha&). In 1998, 28 hospitals contributed data; this number increased to 85 hospitals in 2018 (<http://narst.dmsc.moph.go.th/antibiograms/2018/12/Jan-Dec2018-Blood.pdf>). Yearly cumulative AMR data have been updated regularly on a public website since 1998.

Vietnam

The Vietnam Resistance project (VINARES) was an AMR surveillance network established in 2012 in collaboration with the Minister of Health, the Vietnamese Infectious Diseases Society, Oxford University Clinical Research Unit, and Linköping University in Sweden (111). This network was recognized as the national AMR surveillance network in 2016 by the Ministry of Health and includes 16 central and provincial hospitals, and further development is supported by various foreign development partners through the Fleming Fund and the Global Health Security Agenda (112). All 16 hospitals participate in an external quality assurance program through the United Kingdom National External Quality Assessment Service. In 2018, a reference laboratory was established that will conduct training and perform confirmatory testing and molecular resistance mechanisms research (112).

CURRENT AMR SITUATION

For AMR surveillance, GLASS focuses on common human bacterial pathogens, namely *E. coli*, *K. pneumoniae*, *Acinetobacter baumannii*, *S. aureus*, *S. pneumoniae*, *Salmonella* spp., *Shigella* spp., and *N. gonorrhea*. GLASS also provides a list of antibiotics for which susceptibility should be reported for each pathogen. Recently, WHO published the list of priority pathogens considered to pose the greatest threats to human health in order to promote research and development of new antibiotics (113, 114). Based on the associated need for new antibiotics, the pathogens were divided into critical, high, and medium priority. Critical pathogens include

carbapenem-resistant *A. baumannii*, *Pseudomonas aeruginosa*, and Enterobacterales including ESBL producers. High priority pathogens include organisms such as fluoroquinolone-resistant *Salmonella* spp., MRSA, and vancomycin resistant enterococci (VRE). Except for *P. aeruginosa*, all other bug-drug combinations are also included in GLASS. Below, we discuss resistance statistics of critical and high-priority pathogens obtained from blood cultures in the eight South and South East Asian countries. The resistance statistics of the eight countries featured in this review and three high-income countries (Australia, Canada and United Kingdom) are summarized in Figure 2.

Bangladesh

A recent systematic review of 42 studies published between 2004 and 2018 reported resistance rates for various pathogens in Bangladesh (115). However, this study reported resistance rates of all specimens combined and blood culture isolates were not reported separately. The median carbapenem (imipenem) resistance rates among *Acinetobacter* spp. and *Pseudomonas* spp. were 27.3% (range, 5% to 65.5%) and 13.5% (range, 5.4% to 29.5%), respectively. The median ceftriaxone resistance rate among *E. coli* was 59% (range, 41.7% to 81.8%), and the median carbapenem resistance rate among *Klebsiella* spp. was 7.7% (range, 0% to 41.9%). For *Salmonella* spp. (including *S. Typhi* and *S. Paratyphi*), the median ciprofloxacin resistance rate was 32.6% (range, 4% to 84.5%). The median percentage of MRSA was 46.7% (range, 44.1% to 68.1%), and vancomycin resistance among *Enterococcus* spp. was 0% (range, 0% to 27.3%). Only two studies published between 2010 and 2018 included bloodstream infections (116, 117). A single tertiary care hospital study (117) from 2005 to 2014 that reviewed blood stream infections, reported several resistance rates. Carbapenem (imipenem) resistance among *Acinetobacter* spp. increased from 39% in 2010 to 64% in 2014, whereas carbapenem resistance

among *Pseudomonas* spp. decreased from 29% in 2010 to 16% in 2014. Among *E. coli*, ceftriaxone resistance increased from 34% in 2005 to 75% in 2014, while carbapenem resistance among *Klebsiella* spp. increased from 0% in 2005 to 46% in 2014. Ciprofloxacin non-susceptibility among *Salmonella* spp. (*S. Typhi* and *S. Paratyphi*) increased from 90% in 2005 to 98% in 2014. The proportion of MRSA (based on ceftriaxone susceptibility) was 43% in 2010 and 45% in 2014. Vancomycin resistance in *E. faecium* was not reported in the study.

Cambodia

A recent systematic review of 24 studies published between 2000 and 2018 reported resistance rates for selected pathogens in Cambodia (118). The median resistance rates, calculated by combining all specimens, were reported in this study. Considering studies which included only blood culture isolates, the carbapenem (meropenem) resistance rate among *A. baumannii* was 12% (45, 55), and the carbapenem resistance rate in *Pseudomonas* spp. was 7% (55). Third or fourth generation cephalosporin resistance among *E. coli* blood culture isolates was 47% (45, 55, 57), whereas the carbapenem resistance rate among *K. pneumoniae* was less than 1% (45, 55). For *Salmonella* spp. (*S. Typhi* and *S. Paratyphi*), the ciprofloxacin resistance rate was 67%, with a 100% resistance rate reported in *S. Typhi* (55, 119, 120). The percentage of MRSA among *S. aureus* blood culture isolates was 15% (55, 57).

India

ICMR published its first comprehensive report on AMR data from its surveillance network for the year 2017 (106). The carbapenem (meropenem) resistance rate among *A. baumannii* was 73%, whereas the rate among *P. aeruginosa* was 30%. The cefotaxime resistance rate among *E. coli* was 77%, whereas the carbapenem (meropenem) resistance rate for *Klebsiella* spp. was 59%. For *Salmonella* spp. (*S. Typhi* and *S. Paratyphi*), the ciprofloxacin resistance rate was 39%.

In 2017, the MRSA proportion was 32%, and the vancomycin resistance rate among *E. faecium* was 17%. Resistance rates reported by the NCDC AMR surveillance network among the blood culture isolates from 2017 were similar to those reported by the ICMR network (107). The rate of carbapenem (imipenem) resistance among *Acinetobacter* spp. was 58%, whereas the rate for *P. aeruginosa* was 30%. The cefotaxime resistance rate among *E. coli* isolates was 81%, the carbapenem (imipenem) resistance rate among *Klebsiella* spp. was 44%, and the ciprofloxacin resistance rate among *Salmonella* spp. (*S. Typhi* and *S. Paratyphi*) was 27%. The MRSA proportion among *S. aureus* was 57%. Vancomycin resistance among *Enterococcus* spp. was not reported. Other recent studies utilizing laboratory data from several private sector hospitals reported similar resistance rates (121, 122).

Laos

Studies reporting resistance rates are limited in Laos. One retrospective study examined resistance patterns among bacteremic isolates of hospitalized infants for a 12-year period (2000–2011) (123). Among 11 *E. coli* isolates observed during the study period, 33% were resistant to ceftriaxone. Carbapenem susceptibility was not tested for *K. pneumoniae* isolates. None of the 39 *S. aureus* isolates investigated were MRSA. Another study reported resistance rates in community-acquired bacteremia pathogens (124) but did not report rates for WHO critical and high-priority pathogens.

Nepal

Resistance data for the WHO critical and high-priority pathogens were not available for blood culture isolates from the surveillance network. A recent study investigated the MDR proportions in bacteremia cases in a single tertiary care hospital over a period of 23 years (from 1992–2014); this study revealed a significant increase in the proportion of MDR in non-*Salmonella*

Enterobacterales, other Gram-negative organisms, and Gram-positive organisms over time. However, individual antibiotic susceptibilities were not reported (125). In this study, the MDR non-*Salmonella* Enterobacterales, other Gram-negative organisms, and Gram-positive organisms accounted for 80%, 69%, and 70% of the isolates, respectively, in 2014. Among studies examining *Salmonella* spp. (*S. Typhi* and *S. Paratyphi*) resistance rates in bacteremia isolates between 2012 and 2017, the rate of ciprofloxacin non-susceptibility ranged from 25% to 94% (126-135). A limited number of studies examined the resistance rates of other organisms isolated from blood cultures (132-136). Among these studies, which were conducted between 2012 and 2016, third-generation cephalosporin resistance among *E. coli* ranged from 0% to 60% (132-136), and the proportion of MRSA ranged from 25% to 40% (132, 134-136). Carbapenem resistance among *Klebsiella* spp., *Acinetobacter* spp., and *Pseudomonas* spp. was reported in only one study (132) at rates of 29%, 18%, and 20%, respectively.

Pakistan

Data from six surveillance sites from 2016–2017 submitted to WHO GLASS (12) revealed the following resistance patterns among blood culture isolates: the rates of carbapenem resistance among *Acinetobacter* spp. and *K. pneumoniae* were 65% and approximately 40%, respectively. The rate of ceftriaxone resistance in *E. coli* was approximately 85%, whereas the rate of ciprofloxacin non-susceptibility among *Salmonella* spp. (*S. Typhi* and *S. Paratyphi*) was 95%. The percentage of MRSA among *S. aureus* isolates was 65%. Resistance data from blood cultures collected from a large private laboratory network in Pakistan were reported to a global repository, ResistanceMap, and revealed similar results (<https://resistancemap.cddep.org/>). In 2015, the carbapenem resistance rate among *K. pneumoniae* was 42%, and the ceftriaxone resistance rate among *E. coli* was 90%. Similarly, the rate of ciprofloxacin non-susceptibility

among *S. Typhi* was 95%. The percentage of MRSA among *S. aureus* was 43%. Vancomycin resistance among *E. faecium* was not reported. A group of 12 hospitals also report their cumulative antibiograms voluntarily through a website (<https://parn.org.pk/antimicrobial-data/>), but they do not consistently provide yearly reports and do not report by specimen site.

Thailand

Among blood culture isolates, several resistance patterns were observed in critical and high-priority pathogens (<http://narst.dmsc.moph.go.th/antibiograms/2017/12/Jan-Dec2017-Blood.pdf>).

Among *A. baumannii* isolates, the rate of carbapenem (imipenem) resistance increased from 5% in 2000 to 55% in 2017, whereas the rate of carbapenem (imipenem) resistance among *P. aeruginosa* decreased from 16% in 2000 to 13% in 2017. The cefotaxime resistance rate among *E. coli* increased from 7% in 2000 to 39% in 2017. Similarly, carbapenem (imipenem) resistance among *K. pneumoniae* increased from 0% in 2000 to 9% in 2017. Among *S. aureus* isolates, the MRSA proportion decreased from 35% in 2000 to 9% in 2017. The rate of vancomycin resistance among *E. faecium* increased from 5% in 2000 to 8% in 2017.

Vietnam

Data collected from the VINARES AMR surveillance network for 2013 and 2016 were reported to ResistanceMap (<https://resistancemap.cddep.org/>). Recently, resistance rates from this network were also published for the years 2012–2013 (137). For *A. baumannii* blood culture isolates, the rate of carbapenem (meropenem) resistance increased from 51% in 2013 to 61% in 2016, whereas the rate of carbapenem (imipenem) resistance among *P. aeruginosa* was 36% in 2016. The cefotaxime resistance rate among *E. coli* isolates increased from 64% in 2013 to 71% in 2016. Similarly, the carbapenem (meropenem) resistance rate among *K. pneumoniae* increased from 22% in 2013 to 24% in 2016 (<https://resistancemap.cddep.org/>). Among *S. aureus* isolates,

the MRSA proportion increased from 46% in 2013 to 73% in 2016. The rate of vancomycin resistance among *E. faecium* isolates was 27% in 2016.

The AMR data for the WHO priority pathogens from three high-income countries (Australia, Canada, and United Kingdom) with good health systems show lower resistance rates especially among Gram-negative organisms when compared to the eight countries included in this review. Brief AMR trends among the WHO priority pathogens for three high-income countries are discussed below.

Australia

The Australian Group on Antimicrobial Resistance (AGAR) has been reporting AMR surveillance data on blood culture isolates from 36 public and private laboratories across Australia yearly since 2014 (138). In 2017, carbapenem (meropenem) resistance among *A. baumannii* was 4.8%, whereas carbapenem (meropenem) resistance among *P. aeruginosa* was 5.5%. In 2017, the ceftriaxone resistance rate among *E. coli* isolates was 11.2% and the carbapenem (meropenem) resistance rate among *K. pneumoniae* was 0.8%. Among *S. aureus* isolates, the MRSA proportion was 18.4% in 2017. The rate of vancomycin resistance among *E. faecium* isolates was 46.4% in 2017.

Canada

The Canadian Antimicrobial Resistance Alliance (CARA) has been reporting AMR surveillance data from all specimens since 2009 (<http://www.can-r.com/index.php>). CARA collects AMR data from 10 to 15 hospital sites from eight provinces across Canada (139). In 2017, carbapenem (meropenem) resistance among *A. baumannii* was 6.3%, whereas carbapenem (imipenem) resistance among *P. aeruginosa* was 22.8% (<http://www.can-r.com/index.php>). The ceftriaxone

resistance among *E. coli* isolates increased from 5.7% in 2009 to 12.5% in 2017. Carbapenem (imipenem) resistance rate among *K. pneumoniae* was 0.4% in 2017. Among *S. aureus* isolates, the MRSA proportion decreased from 21.1% in 2009 to 16% in 2017. The rate of vancomycin resistance among *E. faecium* isolates was 15.2% in 2017.

United Kingdom

The United Kingdom reports AMR surveillance data for selected pathogens isolated from blood and cerebrospinal fluid cultures to EARS-NET since 2001 (140). For *Acinetobacter* spp., carbapenem (imipenem/meropenem) resistance was 3% in 2012 and 4% in 2017, whereas the rate of carbapenem (imipenem/meropenem) resistance among *P. aeruginosa* was 8% in 2017 (140). The cefotaxime/ceftriaxone resistance among *E. coli* isolates increased from 1% in 2001 to 11% in 2017. Carbapenem (imipenem/meropenem) resistance rate among *K. pneumoniae* was 1% in 2017. Among *S. aureus* isolates, the MRSA proportion decreased from 47% in 2001 to 7% in 2017. The rate of vancomycin resistance among *E. faecium* isolates was 26% in 2017.

SHORTCOMINGS OF THE AMR DATA GENERATED

Gathering evidence of pathogen susceptibility to antimicrobials and the burden of drug-resistant infections through surveillance is a key goal of the WHO Global Action Plan and is included as a priority in most National Action Plans on AMR. Collection of surveillance data is crucial to generating evidence for use by local clinicians to develop empiric treatment guidelines.

Furthermore, surveillance data can aid early detection of emergence and transmission of resistance in human pathogens and can also be used to establish benchmarks to assess the impact of interventions to curb resistance, guide policy recommendations, and assess changes over time (12). However, representative population data, along with key epidemiological information and adequate diagnostic service utilization, are crucial for developing policy recommendations and

treatment guidelines at the national level using AMR surveillance data (141). Although significant progress has been made regarding AMR surveillance, and initial data suggests high prevalence of resistance among bacterial pathogens among South and South East Asian countries, there are several shortcomings of data generated by the AMR surveillance networks, as outlined below.

Representativeness

Current sites involved in surveillance are primarily tertiary care hospitals or regional hospitals; secondary care and primary care centers are poorly represented. The majority of tertiary care hospitals are national referral centers and cater to patients from different regions, without specific population catchment areas (42). Thus, resistance rates may be overestimated (142, 143) when academic tertiary care centers alone are included, as these centers harbor very sick patients, a large proportion of whom may be transferred from other hospitals and may have been treated with antibiotics before admission (144). Studies comparing resistance rates in tertiary vs. secondary care or primary care hospitals are limited. Only one study in the United States reported no significant differences in resistance rates between large tertiary care and small community hospitals (145), but the ability to generalize these results to other high-income and LMICs is unknown. Similarly, public sector hospitals are more highly represented in the AMR sites despite that the majority of healthcare is provided through the private sector in South Asian countries (33, 146-149). National drug policies often define the types of antibiotics prescribed in public hospitals, and thus differences in antibiotic consumption (150) could influence AMR rates in public and private hospitals.

Community- vs. Hospital-Acquired Infections

The primary methodology undertaken by the countries is passive surveillance of laboratory-based data from isolates, combining both community- and hospital-acquired infections. Several studies reported higher resistance rates for organisms isolated from bloodstream infections among hospital-acquired/healthcare-associated infections when compared to community-acquired infections (151-160). Countries are preparing standard treatment guidelines with empirical antibiotic choices based on the data collected through their AMR surveillance network (161). The need for narrow-spectrum antibiotics may be underestimated when the origin of infection is unknown, leading to unwanted use of broad-spectrum antibiotics and increasing antibiotic resistance. Although WHO GLASS recommends collecting clinical-epidemiological metadata along with laboratory data, the majority of countries do not collect this information. This is also true for most data collected in multi-country surveillance efforts, such as the European Antimicrobial Surveillance Network (EARS-NET) (162)) and the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) (163). Among the five countries (Bangladesh, India, Nepal, Pakistan, and Thailand) that submitted data to WHO GLASS for 2016–2017, only Thailand reported (12, 42) whether isolates were obtained from community- or hospital-acquired infections. Using the difference between the date of sampling and date of admission alone as a proxy for differentiating between community- and hospital-acquired infection is inadequate, as the majority of surveillance sites are tertiary care referral centers, and patients are transferred from regional or secondary care hospitals. In one study, using the date of admission alone as criteria resulted in designation of 10% of hospital-acquired infections as community-acquired and resulted in an increase in the prevalence of community-

acquired MRSA from 0% to 9% and an increase in the prevalence of community-acquired ceftriaxone-resistant *E. coli* and *K. pneumoniae* from 19.3% to 38.5% (42).

Threshold for Obtaining Cultures

Organism resistance profiles can be influenced by the timing of diagnostic cultures. It is ideal to obtain cultures prior to administration of antimicrobial therapy, but in LMICs, it is common practice to utilize diagnostic microbiology services only after patients fail to improve on broad-spectrum antibiotic therapy (164, 165), a practice which could inflate AMR rates (166). The decision of clinicians to refrain from using diagnostic microbiology services is attributed to negative perceptions of the laboratory, including slow turn-around time and poor accuracy of laboratory tests (167). Blood culture rates could serve as indirect measures of utility of diagnostic microbiology services in hospitals (168). It is unknown if there is a preference among clinical scenarios for obtaining cultures. For example, it is possible that patients with multi-organ failure and admitted to ICUs or patients with hospital-acquired infections are more likely to have blood cultures compared to patients with community-acquired infections. Considering thresholds for blood culture rates (169), developing standard guidelines for obtaining cultures from patients from AMR surveillance sites (diagnostic stewardship) could overcome some of these limitations. However, some degree of hesitation regarding diagnostic cultures could also be related to insurance and cost.

Data Quality

The quality of data generated from AMR surveillance networks is dependent on laboratory practices (use of internal and external quality assurance and control, quality management systems, accreditation), clinical sampling methodology, and consistent use of microbiology laboratories for infectious disease diagnostics (170). Practices that influence AMR surveillance

data quality include reporting on key bug-drug combinations, defining MDR, inclusion of appropriate specimens, and reporting clinically inappropriate bug-drug combinations (170). Variability in these areas result in difficulties in data interpretation and comparison (171, 172). To overcome these issues, a group of researchers recently developed a checklist that provides a framework for consistent reporting (170). These limitations could be minimized as more countries enroll in GLASS, which provides surveillance and laboratory guidance, the tools and support that aim to standardize data collection process.

CHALLENGES AND OPPORTUNITIES AHEAD FOR AMR SURVEILLANCE EFFORTS

Funding

For establishment of AMR surveillance programs, many countries receive external funding and support through agencies such as WHO, US CDC, and Fleming Fund. Bangladesh, India, Laos, Nepal, Pakistan, and Vietnam have been awarded Fleming Fund country grants to initiate or strengthen AMR surveillance activities (<https://www.flemingfund.org/regions-countries/>). However, going forward, the sustainability of the network and continued training depends on internal government funding and sustained support from policy makers, which represents a major challenge (105, 173). Eight countries included in this review have developed National Action Plans, but the majority of these countries have not identified funding sources for implementation of these programs (174). In addition to sustainability, expansion of surveillance sites is required for more accurate representation in the generated data.

Standardization of Laboratory Practices and Diagnostic Stewardship

One of the benefits of establishing an AMR surveillance network is standardization of laboratory procedures across hospitals in the network. However, effective AMR surveillance programs not

only require standardized laboratory procedures but a thorough implementation of diagnostic stewardship (83, 175), which includes all stages of diagnostic practice beginning from procedures that guide specimen selection and collection to reporting and interpretation of results. For example, ideally two or more sets of blood cultures should be obtained before antibiotic administration (176), but this practice is a challenge even in developed countries. However, for the majority of the eight countries in this review, constraints may include costs, reimbursement for microbiological diagnostic testing, supply chain for consumables, transportation of samples, and lack of staff awareness and training (43). External quality assurance schemes for all laboratories involved in AMR surveillance is also challenging. The above constraints could hamper oversight of quality assurance by national reference laboratories.

Electronic Data Capturing

Electronic capture of microbiology laboratory data remains a challenge in these countries (105), and use of Information and Technology (IT) for AMR surveillance is limited (177). The barriers to electronic capture include lack of data standards, lack of trained local and national IT workforces, technical problems, and system interoperability (177). Laboratories often rely on paper-based data capture, with limited use of laboratory information management systems (LIMS). LIMS are used in private sector hospitals or large university hospitals that do not participate in AMR surveillance (33, 177). WHONET software provides an “off the shelf” platform for standardized capture, quality control, and analysis of pathogen and antimicrobial susceptibility (AST) data (178). WHONET software is available in many languages and is periodically updated. BacLink, an associated tool, provides linkage to existing LIMS and laboratory instruments (178). However, for the many laboratories without such systems or

sufficient IT support, appropriate human resource allocation is required for manual data entry (105).

Clinical and Epidemiological Data Capturing

WHO GLASS encourages collection of clinical and epidemiological data along with microbiology data to improve the utility of information generated by surveillance. However, collecting this type of information requires significant time and resources, as experienced by a hospital in Thailand that captured data compatible with WHO's GLASS (42). This hospital decided to activate the GLASS protocol for only a 6-month period every other year. Considering this experience in Thailand, which has more resources than many other LMICs, implementing the full GLASS protocol would likely be challenging for other countries, as evidenced by other countries not submitting clinical or epidemiological data to GLASS (12). Laboratory-based surveillance data generated from tertiary care hospitals will be biased for use in developing national antibiotic guidelines but will be valuable for monitoring resistance trends and emergence of novel resistance (30).

Public Health Laboratories Role in AMR surveillance

The WHO advocated Integrated Disease Surveillance and Response (IDSR) approach for surveillance of communicable diseases for LMICs in 1998 (179). IDSR is implemented by 46 countries in the Africa region whereas only few countries (India, Indonesia, Sri Lanka, Thailand) in the South East Asia region attempted to implement IDSR (180). One component of IDSR implementation involved establishing and strengthening laboratory capacity and accordingly several countries in the Africa region established national reference and regional public health laboratories. These laboratories are involved in surveillance of epidemic prone and other bacterial pathogens causing meningitis, sepsis and diarrhea (181). This existing laboratory

network could be utilized for AMR surveillance activities in individual countries. However, proficiency testing between 2011 and 2016 for identification and AST of 13 bacterial pathogens in 81 laboratories across 45 African countries showed acceptable scores for microbial identification but poor scores for AST (181). Although there is a huge opportunity to take advantage of existing public health laboratory networks for AMR surveillance, there is a need for capacity building of these existing laboratories.

Opportunities from the Private Sector

The private sector is a significant contributor to healthcare delivery, especially in South Asian countries. Several private sector hospitals have well-equipped laboratories with automated methods for organism identification and antimicrobial susceptibility testing as well as functioning LIMS (33, 177). In addition, some of these laboratories are accredited by national and international agencies, which serves as a proxy for data quality. Data generated from these laboratories could be used for AMR surveillance activities, as in South Africa, where public (182) and private sector (183) data are collected and reported. However, limitations to this approach include access, cost, and representativeness of the data from private laboratories.

CURRENT STATUS OF EFFORTS TO TACKLE AMR IN HUMAN HEALTH

Endorsement of the WHO Global Action Plan on AMR by the World Health Assembly led to initiation of efforts to tackle AMR in several member states. Several countries have begun creating and implementing programs to control AMR in human, animal, and environmental sectors. WHO created a database (184) to track the status of AMR efforts in individual countries since 2017 through a self-assessment questionnaire (185). For the eight countries in this review, progress on AMR National Action Plans, infection prevention in healthcare facilities, antimicrobial use surveillance efforts, and optimization of antimicrobial use in humans are

described in Table 4 (source: World Health Organization, <https://amrcountryprogress.org/>).

While Thailand and Pakistan have approved and implemented action plans on AMR, national action plans have not yet been fully approved in Nepal, Laos or Cambodia, and implementation is pending in India, Bangladesh and Vietnam. Monitoring of consumption and rational use of antimicrobials has only been initiated in Thailand, but still not in a systematic way. National infection prevention and control programs have been implemented in selected healthcare facilities from Laos, Cambodia and Vietnam, but not in the rest of countries. Programs to promote the appropriate use of antimicrobials have been implemented in Thailand and, partially, in India and Vietnam, but not in other countries included in this review.

AMR SURVEILLANCE GUIDELINES FOR RESOURCE LIMITED SETTINGS

The WHO has developed systems for regional (e.g., CAESAR) (163) and global (GLASS) AMR surveillance. These surveillance systems provide detailed guidance on data requirements, data collection and management, selection of laboratories, patient populations and establishment, maintenance and improvement of national AMR networks. The overarching aim of these systems is to standardize data collection to enable data compilation and comparison globally. In addition to guidance on data collection, the CAESAR point-of-principle project (186) and the GLASS manual provide a detailed set of protocols and standard operating procedures for specimen collection, identification of bacteria and antimicrobial susceptibility testing that could be used at the individual laboratory level. However, there are three major differences between the two surveillance systems. First, CAESAR focuses only on invasive isolates obtained from blood and cerebrospinal fluid cultures, whereas GLASS includes isolates obtained from blood, urine, faeces, urethral and cervical specimens. Second, CAESAR and GLASS focus on different pathogens: CAESAR includes *S. pneumoniae*, *S. aureus*, *E. faecalis*, *E. faecium*, *E. coli*, *K.*

pneumoniae, *P. aeruginosa* and *Acinetobacter* spp., whereas GLASS does not include the enterococci and *P. aeruginosa* and instead includes *Salmonella* spp., *Shigella* spp. and *N. gonorrhoeae*. Third, CAESAR requires individual isolate level data submission whereas GLASS also allows submission of aggregated data.

Considering the variation in availability of resources and capacity in LMICs to implement all components of GLASS an early Fleming Fund–supported activity developed a roadmap, including suggested case definitions, for LMICs to implement WHO’s GLASS (187). This roadmap allows flexibility of the different health systems but incorporates standardized core processes that ensure data validity and comparability. The roadmap recommends establishing a sentinel AMR surveillance system with gradual increase in the number of sentinel sites and their scope with the long-term aim of obtaining high quality and representative AMR data. It describes the required essential AMR surveillance activities at national and individual sentinel site levels. This includes establishing a National Coordinating Center (NCC) for AMR surveillance with Ministry of Health engagement and also establishing a National Reference Laboratory (NRL). The NCC provides leadership in addition to training and quality assurance for clinical, laboratory and data surveillance procedures. The individual sentinel site functions include maintaining quality assurance in clinical surveillance, proper collection and transport of specimens, identification and antimicrobial susceptibility testing, and data management. Finally, the roadmap also offers extended and advanced functions for AMR surveillance systems at the national and individual sites once the core processes are fulfilled. Following the appropriate situational analysis, these templates may be used by countries to develop their own surveillance protocols, as was recently completed for Cambodia (188). In addition to these resources, guidelines for establishing and strengthening ASPs in resource-limited settings were recently

published by WHO (189) and others (190); these guidelines will facilitate AMR surveillance efforts.

CONCLUSION

The eight LMICs described in this review experience a high bacterial infectious disease burden, highlighting the need to establish and strengthen AMR surveillance systems. Significant progress has been achieved in AMR surveillance efforts in recent years, but these efforts are in different stages in each country. Addressing weak public health systems, poor laboratory infrastructure, inadequate government healthcare spending, and insufficient skilled human resources are crucial to strengthening AMR surveillance. Establishing and strengthening IPC and ASPs in healthcare facilities in these countries will aid AMR surveillance by improving diagnostic stewardship. Although high AMR rates are reported in these countries, these data are biased due to underuse of microbiology services; lack of accompanying clinical metadata and denominators; lack of representativeness, standardized laboratory practices, and diagnostic stewardship; and poor data quality. Partnership with WHO and enrolling into GLASS could minimize some of these limitations if the challenges in laborious data entry can be addressed. Initiatives such as the Fleming Fund that aims to improve laboratory infrastructure in LMICs are also improving the collection and quality of evidence, however financial investment by individual countries is essential for sustainability of these efforts. Considering the significant role of the private sector in healthcare delivery in some of these countries, public-private partnerships in AMR surveillance could be considered to improve the representativeness of the AMR data collected and to address the variation in AMR rates due to differing antibiotic prescribing practices. Ultimately, strong leadership and financial commitment from policy makers determines the

added value, robustness, and sustainability of the AMR surveillance systems and the data they generate.

ACKNOWLEDGMENTS:

We thank Suraj Pant (Data and Policy Analyst at Acumen LLC, Washington D.C., USA) for creating Figure 1. RVD was PI on a Fleming Fund pilot grant for Vietnam and participated in several Fleming Fund events as a speaker. All other authors declare no relevant conflicts of interest. The manuscript was edited by the Scientific Editing Service supported by the Institute of Clinical and Translational Sciences at Washington University (NIH CTSA Grant UL1 TR002345).

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Figure 1 Legend:

Hib and PCV immunization coverage in 10 countries in 2015 and 2018

Figure 2 Legend:

Antimicrobial resistance prevalence among bacteria listed in World Health Organization's priority pathogens list in Seven South and South East Asian countries, Australia, Canada and the United Kingdom*

*Data for Laos not available

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Sumanth Gandra received his medical degree from Osmania Medical College, India. Following his residency in University of Illinois College of Medicine at Peoria, he completed a fellowship in infectious diseases at the University of Massachusetts Medical School, Worcester, MA. He then joined the Center for Disease Dynamics, Economics & Policy in Washington, DC where he worked on expanding a global repository of antimicrobial resistance data. He collaborated with several institutions especially in low and middle-income countries to collate antimicrobial resistance data. He completed fellowship in medical microbiology at the University of Chicago/NorthShore Health System. He is currently an Assistant Professor of Medicine in the Division of Infectious Diseases at the Washington University School of Medicine in St. Louis, MO. His research interests include understanding drivers of antibiotic use, molecular epidemiology, burden, transmission dynamics of antimicrobial resistance in healthcare settings and in the community in India and other resource limited settings.

Gerardo Alvarez-Uria is a clinician working in rural India, who is passionate about infectious diseases research in resource-poor settings. After receiving his medical degree in Oviedo (Spain), he moved to Barcelona to complete his General Internal Medicine Residency and his PhD in Infectious Diseases. He also completed a Diploma in Tropical Medicine & Hygiene (Liverpool University) and Master Degrees in Applied Statistics and Healthcare Administration. While working in UK and Spain, his research focused on hepatitis viruses, and non-tuberculous mycobacteria in HIV patients. Since 2009, he has been working for an NGO called Rural Development Trust in Anantapur (Andhra Pradesh, India). He is the Director of the Hospital for Infectious Diseases and of the field program for HIV and tuberculosis. Since coming to India, his research has focused on the cascade of care of HIV patients, diagnosis and treatment of tuberculosis, and the epidemiology of antimicrobial resistance in developing countries.

Paul Turner is a clinical microbiologist and director of the Cambodia Oxford Medical Research Unit (COMRU), based at Angkor Hospital for Children, Siem Reap. COMRU is a component of the Mahidol Oxford Tropical Medicine Research Unit, one of the Wellcome Africa and Asia Programmes. He is an associate professor at the Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford. He leads research on pneumococcal colonization and disease, the nasopharyngeal microbiota, pediatric invasive bacterial infection epidemiology and antimicrobial resistance. His non-research work focuses on capacity development for diagnostic microbiology in low-resource settings.

Jyoti Joshi is Head - South Asia at the Center for Disease Dynamics, Economics & Policy and an Adjunct Professor at Amity Institute of Public Health, Amity University, Noida, India. She is a medical doctor with specialization in Community Medicine and Infectious diseases. She worked with government health programs for more than 18 years and her research areas of interest are antimicrobial resistance (AMR), vaccines & infectious diseases and health systems. As the South Asia lead for the Global Antibiotic Research Partnership (GARP) project, she supported the development and establishment of in-country policy analysis and policy development capacity to address AMR in low and middle- income countries in Asia. She also worked with World Health Organization to undertake the country case study (Nepal) and develop global guidance for taking National Action Plans for AMR from paper to implementation by integrating AMR sensitive and AMR specific approaches within existing health programs.

Direk Limmathurotsakul received his medical degree from Chulalongkorn University, Thailand. He completed his Master's in Medical Statistics from London School of Hygiene & Tropical Medicine and PhD in Life and Biomolecular sciences from Open University, UK. He is the Head of Microbiology at Mahidol-Oxford Tropical Medicine Research Unit, Mahidol University. Antimicrobial resistance is also one of Direk's main research areas. By integrating routinely collected data from a range of databases, he estimated that around 19,000 excess deaths are caused by multidrug-resistant bacteria in Thailand each year. From 2014 to 2016, he led a large epidemiological study to determine the causes of community-acquired sepsis in Thailand, Vietnam and Indonesia. He also visited the microbiology laboratories of all 13 study sites. He showed that under-use of bacterial cultures is a critical issue in low and middle-income countries, and that may lead to an underestimate and underreporting of the incidence of antimicrobial-resistant infections.

Prof. H. Rogier van Doorn is a clinical microbiologist from the Netherlands (University of Amsterdam). Rogier moved to Viet Nam in 2007, where he first headed the Emerging Infections group and led research programmes on influenza and hand, foot and mouth disease at the Oxford University Clinical Research Unit (OUCRU), in Ho Chi Minh City. In 2015 he became director of the OUCRU unit in Hanoi which leads a multidisciplinary research on antimicrobial resistance, that includes the entire spectrum from laboratory diagnostics, clinical and community intervention trials, public engagement, implementation research to policy influencing with the responsible Ministries. He was principal investigator of the Fleming Fund Viet Nam pilot grant and helped establish a surveillance network for antimicrobial resistance of 16 hospitals that was given National status by the Ministry of Health Viet Nam, and a reference laboratory for antimicrobial resistance at the National Hospital of Tropical Diseases.