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Antimicrobial resistance surveillance in low- and middle-income countries: Progress and challenges in eight South Asian and Southeast Asian countries

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REVIEW

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

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SUMMARY Antimicrobial resistance (AMR) is a serious global health threat and is predicted to cause significant health and economic impacts, 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 the high prevalence of resistance, but these data exhibit several shortcomings, such as a 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 Southeast Asian countries.

KEYWORDS AMR, LMICs, antibiotic resistance, resource-limited settings, surveillance

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, and 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 a lack of comprehensive population-based surveillance data from not just LMICs but also high-income countries (3). The World Bank estimates that by 2050, the world will lose up to 3.8% 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-pound 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 a lack of laboratory facilities or gaps in existing laboratories in quality assurance, skilled personnel, laboratory supplies, and data management (9, 10). These shortcomings lead to a lack of trust in laboratory results by clinicians and, thus, the underuse of microbiology laboratory services and lack of response to reported results (i.e., no deescalation or 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 (NAPs) 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 to and opportunities for conducting AMR surveillance, and progress in other efforts to tackle AMR in eight South and Southeast 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 the 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 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 gross domestic product (GDP) for these eight countries ranged from 2.3% in Bangladesh and Cambodia to 6.3% in Nepal (World Bank data [https://data.worldbank.org/indicator/SH.XPD.CHEX.GD.ZS?locations=BD-KH-IN-LA-NP-PK-TH-VN&name_desc=false]). In contrast to these eight countries, in 2016, the United States and the United Kingdom contributed 17% and 9.7% of their GDP, respectively, to health expenditure (World Bank data [https://data.worldbank.org/indicator/SH.XPD.CHEX.GD.ZS?locations=GB-US&name_desc=false]). In 2016, the government contribution to health expenditure ranged from 16% in Bangladesh to 76% in Thailand, whereas the government contribution for health expenditure in the United States and United Kingdom for 2016 was 50% and 80%, respectively (World Bank data [https://data.worldbank.org/indicator/SH.XPD.GHED.CH.ZS?locations=IN-LA-NP-PK-TH-VN-BD-KH-GB-US&name_desc=false]). As in the majority of LMICs, structures of health systems in these eight countries are mixed (13); health care services are provided by both the public and private sectors in various proportions (14–19). In Bangladesh, Cambodia, Laos, and Nepal, international development organizations also provide significant contributions for health care services (14, 20–22). The administration and implementation of health services in the public sector differ by country, which have either a centralized or decentralized structure (18, 21, 23–27). Having better governance and regulation, accreditation of health care organizations with adequately trained and certified health care staff, and lower patient load, the private sector has an edge over the public sector in imparting better health care services but may be accessible only to the wealthier part of the population. These factors have resulted in the expansion of the private sector, and in countries like India and Pakistan, health care delivery is dominated by the private sector (17, 28). However, in Thailand and Vietnam, the public sector dominates health care delivery. Since 2002, the Thai government has provided universal health coverage (18). The Vietnamese government is making efforts to

TABLE 1 Health systems overview in eight South Asian and Southeast Asian countries

Country	Population (World Bank 2018)	Income category (World Bank 2018)	Health care delivery	Public health care delivery	Health expenditure as % of GDP, % government contribution in 2016 (World Bank 2016)
Bangladesh	161 million	Lower middle income	Public sector, private sector, and international development organizations (14); public health facilities account for 45,993 hospital beds, and private health care facilities account for 45,485 hospital beds (14)	The Ministry of Health and Family Welfare directs health care services with little decision power at the local level (23)	2.31, 16.42
Cambodia	16 million	Lower middle income	Public sector, private sector, international development organizations (15); approx 70% of the population seeks initial care from private providers (20)	The Ministry of Health is responsible for provision of health care services in the public sector, with responsibilities assigned to officials at provincial and district levels (15)	6.12, 21.81
India	1.3 billion	Lower middle income	Public sector and private sector (24); private health care providers treat 78% of outpatients and 60% of inpatients and account for 80% of urban health care (28)	Health initiatives are handled by individual states, and each state has its own health care delivery system (24)	3.51, 26.84
Laos	7 million	Lower middle income	Public sector and international development organizations (21); health care delivery system is mainly public, with recent emergence of a private sector (21)	The Ministry of Health is responsible for directing central services, whereas provincial- and district-level health services are under the jurisdiction of provincial governments (21)	2.36, 32.40
Nepal	28 million	Low income	Public sector, private sector, and international development organizations (16); greater than two-thirds of hospital beds contributed by the private sector (22)	Restructuring of the health care system is ongoing, with an aim to accelerate universal health coverage (25)	6.28, 18.58
Pakistan	197 million	Lower middle income	Public sector and private sector (26); two-thirds of health services are provided by the private sector (17)	Provincial governments are responsible for the majority of public health care delivery, and districts are mainly responsible for implementation (26)	2.86, 28.74
Thailand	68 million	Upper middle income	Public sector and private sector (18); public hospitals account for 75% of hospitals and 79% of beds, and private hospitals account for 25% and 21%, respectively (18)	The Ministry of Public Health is the principal agency that provides health care services, with local governments playing a limited role (18)	3.76, 75.95
Vietnam	95 million	Lower middle income	Public sector and private sector (19); the private sector accounted for 6% of health care facilities and 4% of hospital beds but provided more than 60% of outpatient services, mostly through private clinic services (19, 27)	As of 2015, 77% of the population is covered by national insurance and government is making efforts to achieve universal health coverage; public health care facilities are divided into central, provincial, district, and community levels with a hierarchical referral system (27)	5.66, 47.43

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 to 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, the assessment of laboratory capacity of 28 public hospitals in 2013 to 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 the 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 Southeast Asia (36). High bacterial disease burden imposes the need for robust AMR surveillance to inform empirical 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, and Pakistan) investigated the causes of community-acquired infections among 63,114 infants (0 to 59 months) (37). The mean incidences of bacterial and viral infections were 13.2 (95% credible interval [CrI], 11.2 to 15.6) and 10.1 (9.4 to 11.6) per 1,000 live births, respectively. Among children who died, 46% of cases 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 Southeast Asian countries (Indonesia, Thailand, and Vietnam) in 2014 and 2015 (38). The 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, an average of 123 (95% confidence interval [CI], 109.5 to 137.8) deaths per 100,000 occurred in children younger than 5 years due to lower respiratory tract infections and ranged from 113 (99 to 129.4) deaths per 100,000 in India to 157.7 (118.9 to 200.8) deaths per 100,000 in Pakistan (39). In four Southeast

Asian countries, the numbers of deaths in children younger than 5 years ranged from 7.8 (5.4 to 11.0) per 100,000 in Thailand to 285.2 (175.1 to 441.7) in Laos. Of these deaths in children younger than 5 years, 67% in South Asia and 68% in Southeast 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 number of deaths in children younger than 5 years due to lower respiratory tract infections was 3.4 (3.1 to 3.7) per 100,000 (39). In 2017, the incidence of meningitis due to 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 (per the Institute of Health Metrics Global Burden of Disease [http://vizhub.healthdata.org/gbd-compare]). However, mortality was higher for bacterial causes than for other causes (2.63 versus 1.36 deaths per 100,000 people). In Southeast 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 Southeast Asia compared to those of high-income countries could be partially 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 1-year-old children ranged from 45% in India to 98% in Bangladesh (Fig. 1A) [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 1-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/pneumoccocal-conjugate-vaccines-(pcv3)-immunization-coverage-among-1-year-olds-(-)]. In contrast, in 2015, among three high-income countries, Australia, the United States, and the United Kingdom, the Hib and PCV immunization coverage among 1-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 (Fig. 1), which may have impacted the burden of infection caused by these organisms. A recent review of studies published after 2011 in South and Southeast 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 Southeast Asia (44). Pathogenic organisms were isolated from 3,506 patients (9%; range, 1% to 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.

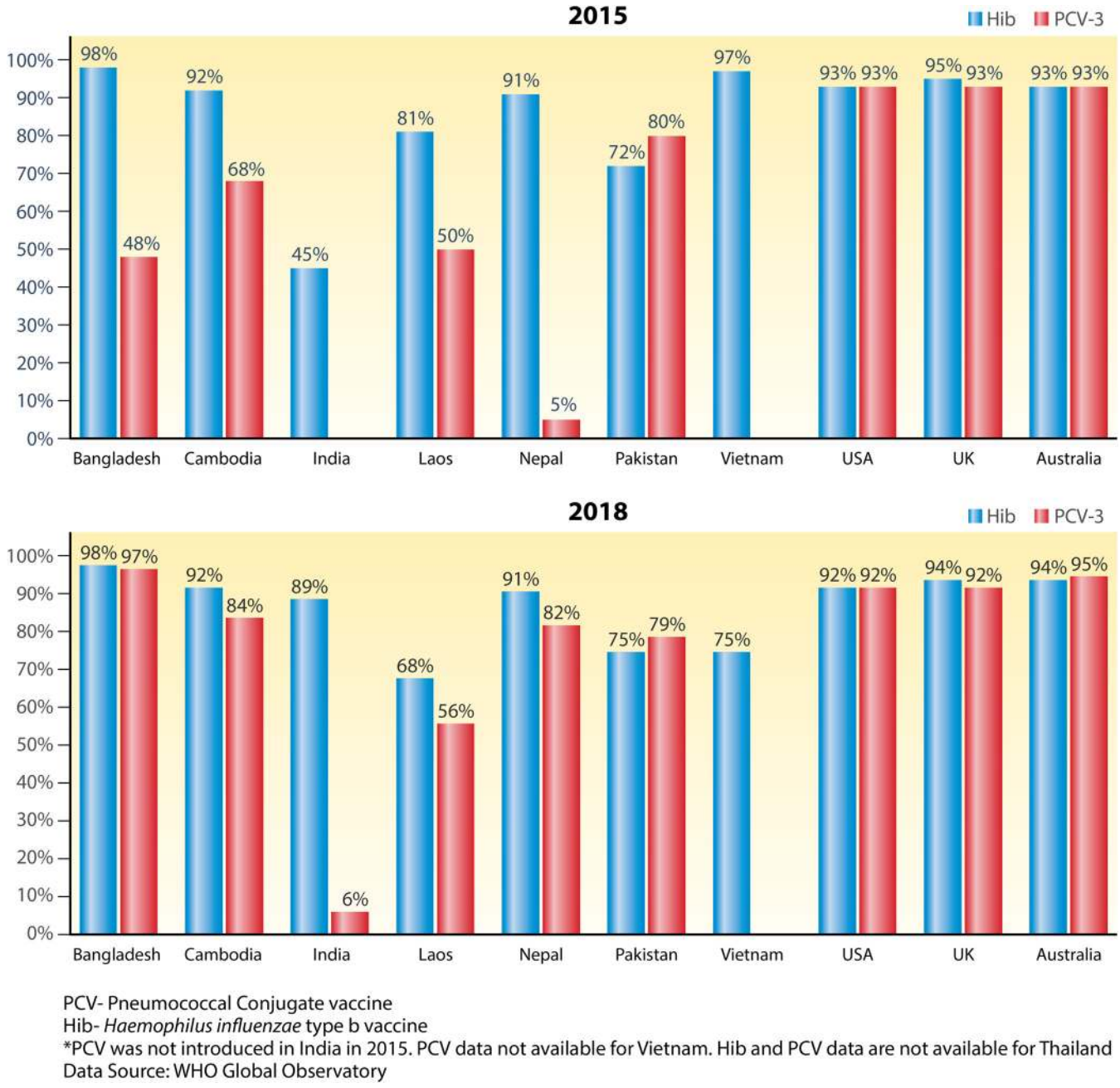

FIG 1 Hib and PCV immunization coverage in 10 countries in 2015 and 2018.

(10.2%), and *Klebsiella* spp. (7.6%). However, others cited concerns that the abovementioned 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 abovementioned 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 h of admission to the hospital) among the eight countries using studies published between 2010 and 2018 (42, 47–62) (see Table S1 in the supplemental material) 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

TABLE 2 Most frequent causes of community-acquired and hospital-acquired bacteremia in eight countries[a]

Country	Community-onset bacteremia organism(s)			Hospital-onset bacteremia organism(s)
	Newborns	Children	Adults	
South Asia regional study (Bangladesh, India, Pakistan)	*E. coli*, *Klebsiella* spp., *S. aureus*, GAS	NA[b]	NA	NA
Bangladesh	NA	*S.* Typhi	*S.* Typhi	NA
India	NA	*S.* Typhi, *S. aureus*, *E. coli*	*S.* Typhi, *S. aureus*, *E. coli*	*Acinetobacter* spp., *E. coli*, *Pseudomonas* spp., *S. aureus*, *Klebsiella* spp.
Nepal	NA	NA	*S.* Typhi	*Burkholderia cepacia*, *E. coli*, *Acinetobacter* spp., *Klebsiella* spp.
Pakistan	NA	*S.* Typhi, *E. coli*, *Pseudomonas* spp.		NA
Southeast Asia regional studies (Indonesia, Thailand, Vietnam)	NA	*S. aureus*, *S. pneumoniae*, *E. coli*	*E. coli*, *Klebsiella* spp., *Streptococcus suis*, beta-hemolytic *Streptococcus* spp.	NA
Cambodia	NA	*S.* Typhi, *S. aureus*, *E. coli*	*S.* Typhi, *S. aureus*, *E. coli*, *B. pseudomallei*	*K. pneumoniae*, *E. coli*, *A. baumannii*, *S. aureus*
Laos	NA	NA	*S.* Typhi, *E. coli*, *B. pseudomallei*	NA
Thailand	NA	*S. aureus*, *B. pseudomallei*, *Pseudomonas* spp.	*E. coli*, *B. pseudomallei*, *S. aureus*	*Acinetobacter* spp., *K. pneumoniae*, *S. aureus*, *E. coli*, *Pseudomonas* spp.
Vietnam	NA	NA	*K. pneumoniae*, *E. coli*, *S. maltophilia*, *Acinetobacter* spp.	*K. pneumoniae*, *E. coli*, *S. maltophilia*, *Acinetobacter* spp., *S. aureus*

[a]Organisms listed in order of frequency.
[b]NA, data not available.

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 HAIs

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 a higher prevalence of HAIs and SSIs than the United States 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 intensive care units (ICUs) was at least three times higher in developing countries (47.9 per 1,000 patient-days) than in the United States (13.6 per 1,000 patient-days). A more recent systematic review of HAIs in six Southeast Asian countries (Indonesia, Malaysia, the Philippines, Singapore, Thailand, and Vietnam) reported a pooled HAI prevalence of 9.0% (95% CI, 7.2% to 10.8%) (64). In Thailand, the pooled HAI prevalence was 7.1% (95% CI, 6.6% to 7.6%), and in Vietnam, the pooled HAI prevalence was 7.8% (95% CI, 7.2% to 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 an HAI prevalence of 29.5% (65). A study using a similar methodology for six pediatric ICUs

in Vietnam found an 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 Centers for Disease Control and Prevention (U.S. CDC) National Healthcare Safety Network (NHSN), despite a lower device utilization ratio in India. The central line-associated bloodstream infection (CLABSI) rates were at least five times higher in Indian ICUs than in the U.S. CDC/NHSN rates (67). Although multicenter 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 1,000 patient-days in Nepal (68). In Pakistan, a single pediatric ICU study reported a device-associated HAI incidence rate of 6.3 per 1,000 patient-days (69), whereas in Cambodia, the device-associated HAI incidence rate in one pediatric ICU was reported as 4.6 per 1,000 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 Southeast Asia region reporting causes of hospital-acquired bacteremia. The organisms causing hospital-onset bacteremia (defined as blood cultures obtained after 48 h of admission to a hospital) in eight countries determined using studies published between 2010 and 2018 (42, 50, 55, 56, 62, 70, 73–75) (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, the 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 a lack of or substandard infection control practices as well as the 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 health care facilities (79–81). Implementing IPC and ASPs can enhance the 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, and 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 the 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 health care institutions consistently recorded the incidence of health care-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 health care facilities (88) and ASP guidelines (89). These guidelines may help standardize IPC and ASPs across Indian hospitals, but most health care facilities face challenges in implementation due to hospital overcrowding, high 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 health care 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 postgraduation 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 nonprofit) in Kathmandu 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 (96) 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 (97). In another recent survey of 137 hospitals assessing ASPs, 32% of hospitals reported having a multidisciplinary antimicrobial stewardship team, but the implementation and quality of these programs were not assessed (98).

Thailand

Thailand is one of the few countries that implemented IPC programs as a measure to improve the quality of medical care as early as 1979 (99). A survey of 57 hospitals (including university, regional, provincial, district, and private) in 2002 indicated the implementation of IPC in all evaluated facilities (100). In this survey, regular infection control committee meetings were reported in 75% of hospitals, and regular reports of surveillance data were prepared in 77% of the hospitals. Overall, the survey indicated that the IPC quality required further improvement to its structure and process (100). In 2012, another study assessed ASPs in Thailand (96). Among the 204 hospitals assessed, 71% (144 hospitals) of these reported having ASP, and 51% of them undertook drug utilization evaluations. The implementation of ASP was more effective in teaching hospitals than nonteaching hospitals.

Vietnam

In 1997, the Ministry of Health (MoH) developed a national IPC program (101), and in 2009, in partnership with the 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 a lack of financial resources. The authors also observed that several guidelines were outdated and unsuitable for most hospitals. The Medical Services Administration within

TABLE 3 Antimicrobial surveillance network status in eight countries

Country	No. of surveillance sites	AST guidelines followed and EQA status[a]	National reference laboratory	Other NAP documents[b]	Data reported to GLASS[c]
Bangladesh	16 (8 hospitals, 8 OPDs[d])	CLSI with partial EQA	Selected	NCC, NFP, and NAP in place	No
Cambodia	8 (hospitals)	CLSI, EUCAST with full EQA	Selected	NCC, NFP, and NAP in place	No
India	55 (hospitals)	CLSI, EUCAST with partial EQA	Selected	NCC, NFP, and NAP in place	Partial (21/55 sites)
Laos	Not established	Not applicable	Selected	NCC, NFP, and NAP in place	No
Nepal	42 (21 hospitals, 21 OPDs)	CLSI with partial EQA	Selected	NCC and NAP in place, NFP appointment in progress	Some (15 sites)
Pakistan	9 (7 hospitals, 2 OPDs)	CLSI with full EQA	Selected	NCC, NFP, and NAP in place	Some (6 sites)
Thailand	74 (hospitals)	CLSI with full EQA	Selected	NCC, NFP, and NAP in place	Some (4 sites)
Vietnam	16 (hospitals)	CLSI with full EQA	Selected	NCC, NFP, and NAP in place	Not enrolled

[a]AST, antimicrobial susceptibility testing; CLSI, Clinical and Laboratory Standards Institute; EQA, external quality assurance; EUCAST, European Committee on Antimicrobial Susceptibility Testing.
[b]NAP, national action plan on antimicrobial resistance; NCC, national coordinating center; NFP, national focal point.
[c]GLASS, Global Antimicrobial Surveillance System (World Health Organization).
[d]OPDs, outpatient departments.

the MoH is responsible for the 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 the 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 and analysis and the 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 ICMR established an AMR surveillance network in 2013 and has collected data since 2014. In 2014, four tertiary care hospitals selected as nodal centers not only contributed antimicrobial susceptibility data but also were designated to undertake molecular epidemiology research. In 2017, six other regional tertiary care hospitals were added to the network;

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, resulting in a total of 20 hospitals in the network. In addition to ICMR, the National Centers 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 the 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, the Fleming Fund partnered with the Laotian 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 the abovementioned species, multidrug-resistant [MDR] *Acinetobacter* spp., MDR *Klebsiella* spp., and methicillin-resistant *S. aureus* [MRSA] were added) (109).

Pakistan

Efforts to establish an AMR surveillance program in Pakistan were initiated in 2015, with the National Institute of Health designated 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.

Thailand

Thailand is among the few countries in Southeast Asia with an established AMR surveillance system, and it continues to expand its network. The National AMR Surveillance Center at the National Institutes 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 a WHO Collaborating Centre for AMR Surveillance for the Southeast Asia region since 2005. 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. gonorrhoeae*. GLASS also provides a list of antibiotics for which susceptibility should be reported for each pathogen. Recently, the WHO published a 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 priorities. 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 those involving *P. aeruginosa*, all 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 Southeast Asian countries. The resistance statistics of the eight countries featured in this review and three high-income countries (Australia, Canada, and the United Kingdom) are summarized in Fig. 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* isolates 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 bloodstream 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* isolates, 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 nonsusceptibility 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 that included only blood culture isolates, the carbapenem (meropenem) resistance rate among *A. baumannii* isolates 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* isolates was less than 1% (45, 55). For *Salmonella* spp. (*S.* Typhi and *S.* Paratyphi), the ciprofloxacin resistance rate was 67%, with a 100%

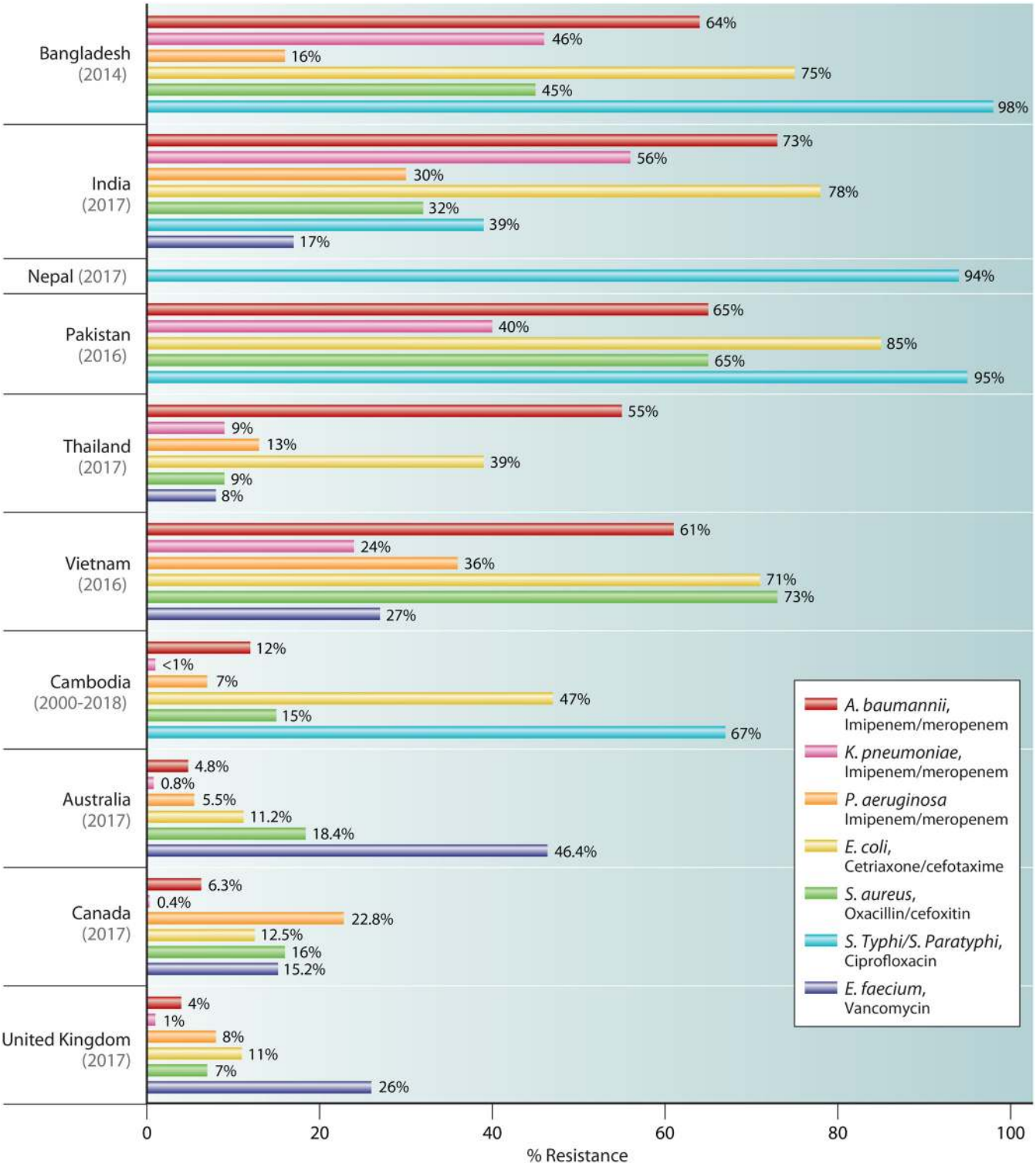

FIG 2 Antimicrobial resistance prevalence among bacteria listed in the World Health Organization's priority pathogens list in seven South and Southeast Asian countries, Australia, Canada, and the United Kingdom. Data for Laos were not available.

resistance rate reported in *S.* Typhi (55, 119, 120). The percentage of MRSA among *S. aureus* blood culture isolates was 15% (55, 57).

India

The 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* isolates was 73%, whereas the rate among *P. aeruginosa* isolates was 30%. The cefotaxime resistance rate among *E. coli* isolates 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* isolates 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* isolates 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 in Laos are limited. One retrospective study examined resistance patterns among bacteremic isolates of hospitalized infants for a 12-year period (2000 to 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 to 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 nonsusceptibility 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* isolates 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 to 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* isolates were 65% and approximately 40%, respectively. The rate of ceftriaxone resistance in *E. coli* isolates was approximately 85%, whereas the rate of ciprofloxacin nonsusceptibility 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 car-

bapenem resistance rate among *K. pneumoniae* isolates was 42%, and the ceftriaxone resistance rate among *E. coli* isolates was 90%. Similarly, the rate of ciprofloxacin nonsusceptibility among *S.* Typhi isolates was 95%. The percentage of MRSA among *S. aureus* isolates was 43%. Vancomycin resistance among *E. faecium* isolates 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 in Thailand, 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* isolates decreased from 16% in 2000 to 13% in 2017. The cefotaxime resistance rate among *E. coli* isolates increased from 7% in 2000 to 39% in 2017. Similarly, carbapenem (imipenem) resistance among *K. pneumoniae* isolates 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* isolates 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 and 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* isolates 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* isolates 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 the United Kingdom) with good health systems show lower resistance rates, especially among Gram-negative organisms, than 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* isolates was 4.8%, whereas carbapenem (meropenem) resistance among *P. aeruginosa* isolates 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* isolates 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* isolates was 6.3%, whereas carbapenem (imipenem) resistance among *P. aeruginosa* isolates 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. The carbapenem (imipenem) resistance rate among *K. pneumoniae* isolates 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 has reported 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* isolates was 8% in 2017 (140). The cefotaxime/ceftriaxone resistance among *E. coli* isolates increased from 1% in 2001 to 11% in 2017. The carbapenem (imipenem/meropenem) resistance rate among *K. pneumoniae* isolates 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. The collection of surveillance data is crucial to generating evidence for use by local clinicians to develop empirical treatment guidelines. Furthermore, surveillance data can aid the early detection of the emergence and transmission of resistance in human pathogens and also can 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 suggest the high prevalence of resistance among bacterial pathogens in South and Southeast 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 versus 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 countries and LMICs is unknown. Similarly, public sector hospitals are more highly represented in the AMR sites despite the majority of health care being 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; thus, differences in antibiotic consumption (150) could influence AMR rates in public and private hospitals.

Community- versus 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/health care-associated infections than 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 the 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 multicountry 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 to 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 the criteria resulted in the 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 the 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 that 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 turnaround time and poor accuracy of laboratory tests (167). Blood culture rates could serve as indirect measures of the 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 multiorgan failure and admitted to ICUs or patients with hospital-acquired infections are more likely to have blood cultures than 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 also could 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, and 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, the inclusion of appropriate specimens, and reporting clinically inappropriate bug-drug combinations (170). Variability in these areas results 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 the data collection process.

CHALLENGES AND OPPORTUNITIES AHEAD FOR AMR SURVEILLANCE EFFORTS

Funding

For the establishment of AMR surveillance programs, many countries receive external funding and support through agencies such as the WHO, U.S. 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 policymakers, 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 the implementation of these programs (174). In addition to sustainability, the 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 the standardization of laboratory procedures across hospitals in the network. However, effective AMR surveillance programs require not only standardized laboratory procedures but also 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 the 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-described constraints could hamper the oversight of quality assurance by national reference laboratories.

Electronic Data Capturing

The electronic capture of microbiology laboratory data remains a challenge in these countries (105), and the 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 the 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 the emergence of novel resistance (30).

Public Health Laboratory Role in AMR Surveillance

The WHO advocated the Integrated Disease Surveillance and Response (IDSR) approach for the surveillance of communicable diseases for LMICs in 1998 (179). IDSR is implemented by 46 countries in the Africa region, whereas only a few countries (India, Indonesia, Sri Lanka, and Thailand) in the Southeast 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 the 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 the 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 health care 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 serve 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 (183)-sector 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

The endorsement of the WHO Global Action Plan on AMR by the World Health Assembly led to the 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. The 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 health care facilities, antimicrobial use surveillance efforts, and the optimization of antimicrobial use in humans are described in Table 4 (sourced from the World Health Organization at 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. The 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 health care facilities in Laos, Cambodia, and Vietnam but not in the rest of the 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 the establishment, maintenance, and improvement of national AMR

TABLE 4 Currents status of efforts in eight countries to tackle AMR in the human sector

Country	NAP on AMR	National monitoring system for consumption and rational use of antimicrobials	National infection prevention and control program	Programs to promote the appropriate use of antimicrobials
Pakistan	Implemented with funding sources, monitoring and evaluation process in place	Designed but not implemented	None	Developed but not implemented in health care settings
India	Approved by government, including GAP objectives, operational plan, and monitoring system	Designed but not implemented	Available but not fully implemented	Implemented in some health care facilities, and guidelines for appropriate use of antimicrobials are available
Nepal	Developed but not fully approved yet	None	None	Developed but not implemented in health care settings
Bangladesh	Approved by government, including GAP objectives, operational plan, and monitoring system	Designed but not implemented	Available but not fully implemented	None or weak
Laos	Under development	None	Available and implemented in selected health facilities with monitoring and feedback in place	None or weak
Cambodia	Developed but not fully approved yet	None	Available and implemented in selected health facilities with monitoring and feedback in place	None or weak
Vietnam	Approved by government, including GAP objectives, operational plan, and monitoring system	Designed but not implemented	Available and implemented in selected health facilities with monitoring and feedback in place	Implemented in some health care facilities, and guidelines for appropriate use of antimicrobials are available
Thailand	Implemented with funding sources, monitoring and evaluation process in place	Initiated, but there is no systematic monitoring of antibiotic use in health care settings	Available but not fully implemented	Implemented in most health facilities nationwide with monitoring and surveillance

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, fecal, 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 the submission of aggregated data.

Considering the variation in the 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 for the 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 a

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, the 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 can 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 the WHO (189) and others (190); these guidelines will facilitate AMR surveillance efforts.

CONCLUSIONS

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 health care spending, and insufficient skilled human resources is crucial to strengthening AMR surveillance. Establishing and strengthening IPC and ASPs in health care 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 the underuse of microbiology services; the lack of accompanying clinical metadata and denominators; the lack of representativeness, standardized laboratory practices, and diagnostic stewardship; and poor data quality. Partnership with the WHO and enrolling in GLASS could minimize some of these limitations if the challenges in laborious data entry can be addressed. Initiatives, such as the Fleming Fund, that aim to improve laboratory infrastructure in LMICs are also improving the collection and quality of evidence; however, financial investment by individual countries is essential for the sustainability of these efforts. Considering the significant role of the private sector in health care 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.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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