

Comparison of Antimicrobial Stewardship and Infection Prevention and Control Activities and Resources Between Low-/Middle- and High-income Countries

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Background: The growth of antimicrobial resistance worldwide has led to increased focus on antimicrobial stewardship (AMS) and infection prevention and control (IPC) measures, although primarily in high-income countries (HIC). We aimed to compare pediatric AMS and IPC resources/activities between low- and middle-income countries (LMIC) and HIC and to determine the barriers and priorities for AMS and IPC in LMIC as assessed by clinicians in those settings.

Methods: An online questionnaire was distributed to clinicians working in HIC and LMIC healthcare facilities in 2020.

Results: Participants were from 135 healthcare settings in 39 LMIC and 27 HIC. Formal AMS and IPC programs were less frequent in LMIC than HIC settings (AMS 42% versus 76% and IPC 58% versus 89%). Only 47% of LMIC facilities conducted audits of antibiotic use for pediatric patients, with less reliable availability of World Health Organization Access list antibiotics (29% of LMIC facilities). Hand hygiene promotion was the most common IPC intervention in both LMIC and HIC settings (82% versus 91%), although LMIC hospitals had more limited access to reliable water supply for handwashing and antiseptic hand rub. The greatest perceived barrier to pediatric AMS and IPC in both LMIC and HIC was lack of educa-

tion: only 17% of LMIC settings had regular/required education on antimicrobial prescribing and only 25% on IPC.

Conclusions: Marked differences exist in availability of AMS and IPC resources in LMIC as compared with HIC. A collaborative international approach is urgently needed to combat antimicrobial resistance, using targeted strategies that address the imbalance in global AMS and IPC resource availability and activities.

Key Words: antimicrobial stewardship, infection prevention, low- and middle-income countries, antimicrobial resistance

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The increasing spread of antimicrobial resistance (AMR) is a global public health threat. The World Health Organization (WHO) has outlined a global action plan to address AMR,¹ highlighting the key roles of antimicrobial stewardship (AMS) and infection prevention and control (IPC) measures in confronting this problem.

AMS, through evidence-based interventions designed to optimize rational antimicrobial use, can decrease the rate of development and acquisition of AMR.^{2,3} Concurrently, the spread of AMR can also be prevented through effective IPC practices.⁴ AMR is higher in low- and middle-income countries (LMIC) than high-income countries (HIC),⁵ but to date, AMS and IPC efforts in children have largely concentrated in HIC. LMIC face unique challenges requiring special attention and context-appropriate responses. These include constraints in healthcare systems and diagnostic infrastructure,⁶ unregulated nonprescription availability of antibiotics leading to widespread antibiotic misuse which fuels AMR,⁷ limited access to quality-assured pharmaceuticals, higher patient-provider ratios and fewer resources and funding to instigate local AMR surveillance and control.⁸

There is paucity of information pertaining to children's healthcare and risk of AMR across LMIC settings. The aims of this global survey were to compare AMS and IPC resources and activities between LMIC and HIC as assessed by clinicians working in those settings.

METHODS

An online questionnaire relating to AMS and IPC resources and activities was developed by members of the World Society of Pediatric Infectious Diseases AMR Declaration Working Group. It was based on a previous survey developed for AMS resources in children⁹ and adapted with the support of the African Society for Pediatric Infectious Diseases to include questions relevant to LMIC settings and IPC (Supplemental Digital Content 1; <http://links.lww.com/INF/E515>). It was distributed to clinicians in September 2020 via professional networks and Twitter to members of the World Society of Pediatric Infectious Diseases regional member societies: African, Asian, Australasian, European, North American and South American pediatric infectious diseases societies. Responses were entered online directly via REDCap (Research Electronic Data

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Capture; Vanderbilt University, Nashville, TN),^{10,11} and the survey link was open until November 30, 2020. The analysis was limited to one respondent per hospital/healthcare setting. In cases of multiple respondents for the same institution, survey responses were amalgamated. Statistical comparisons were made with χ^2 test for categorical variables and *t* test for continuous variables. The classification of countries into LMIC and HIC by income was based on the 2020 World Bank classification.¹²

RESULTS

The survey was completed by 146 clinicians in 135 distinct hospitals/healthcare settings in 66 countries across 6 continents; 39 LMIC and 27 HIC (Fig. 1). Clinicians from more than 10 disciplines completed the survey, most commonly pediatric infectious diseases (ID) physicians/trainees (60/135, 44%), followed by general pediatricians/trainees (38/135, 28%). In both LMIC and HIC, participating healthcare settings were most frequently tertiary pediatric hospitals (38/89 [43%] and 29/46 [63%], respectively; Table 1). The pediatric team was a more likely to review over 50 patients per day in LMIC hospitals (42/89, 47%) than HIC hospitals (12/46, 26%; $P = 0.01$). Pediatric (including neonatal) hospital bed numbers were lower in LMIC than HIC (median 70 [interquartile range, 29–120] versus 145 [interquartile range, 51–300], respectively).

Antimicrobial Stewardship Resources

Formal AMS programs existed in fewer LMIC than HIC healthcare settings (37/89 [42%] versus 35/46 [76%], $P = 0.0001$; Fig. 2A). The majority of AMS programs in both LMIC and HIC formally included pediatric patients (86% and 89%, respectively). Within LMIC, these programs were predominantly available in tertiary pediatric hospitals and public hospitals in medium to large cities (26/32, 81%).

In LMIC healthcare settings, the most common personnel on AMS teams were general pediatricians (78/89, 88%), whereas in HIC settings these were pediatric ID and adult ID physicians (each 39/46, 85%; Fig. 2B). The greatest difference in personnel resources was the availability of AMS pharmacists: 15/89 (17%) in LMIC compared with 37/46 (80%) in HIC ($P < 0.001$). Within

nontertiary/noncity public hospitals in LMIC, the most common AMS personnel were general pediatricians (22/26, 85%).

Antibiotic Guidelines

Antibiotic guidelines were less frequently used in LMIC than in HIC healthcare settings (Fig. 3A), but the difference in specific guideline use was only significant in the highly specialized setting of hematology/oncology services, with guidelines for febrile neutropenia in 27/28 (96%) of healthcare settings in HIC, compared with 33/43 (77%) ($P = 0.04$) in LMIC.

Most hospital respondents in LMIC (72/80, 90%) were aware of the WHO Integrated Management of Childhood Illness guide; however, fewer than half of their hospital antibiotic guidelines were developed in line with the guide (36/80, 45%). Overall, 55/135 (41%) were aware of the WHO Access Watch Reserve classification of antibiotic choice and 28/135 (21%) were aware of the Australian and New Zealand Pediatric Infectious Diseases IV-oral guideline for antibiotic duration; proportions were similar for LMIC and HIC.

Review of Antimicrobial Prescribing

Over half of all facilities conducted AMS/ID rounds, although they were less likely to occur in LMIC than HIC (47/89 [53%] versus 37/46 [80%], $P = 0.002$). Moreover, AMS/ID rounds frequently occurred only in response to specific patient referrals, with unsolicited regular AMS rounds only occurring in 29/89 (33%) LMIC and 23/46 (50%) HIC facilities ($P = 0.04$).

Point-of-care interventions relating to antimicrobial prescribing—including review of choice, dose, duration, narrowing based on microbiology results, intravenous to oral switch—occurred at least sometimes in most hospitals (LMIC 71%–79% compared with HIC 84%–91%; Fig. 3B). The most common point-of-care intervention in LMIC hospitals was intravenous to oral switch (63/80, 79%) versus de-escalation based on microbiology results in HIC hospitals (39/43, 91%).

Facilities in LMIC were less likely to have a system for restricting use of broad-spectrum/expensive antimicrobials as compared with those in HIC (40/89 [45%] versus 30/46 [65%], $P = 0.03$). The most common intervention in both LMIC (25/40, 63%)

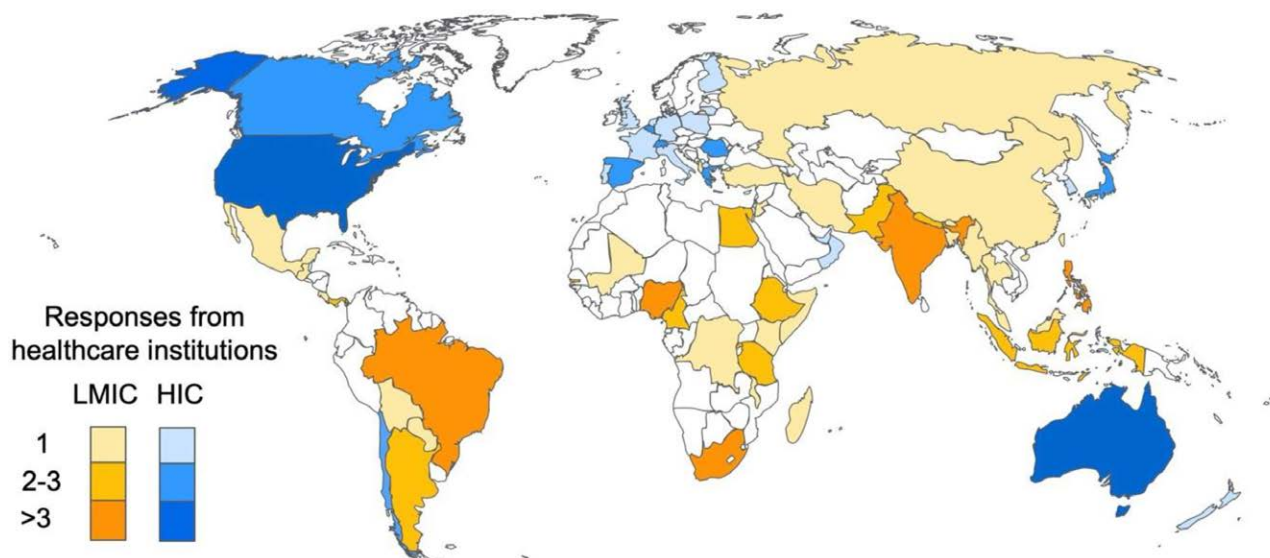


FIGURE 1. Global map of responses describing local healthcare institutions.

TABLE 1. Demographics of Respondents and Healthcare Settings

	LMIC						HIC				
	Overall N (%)	Pediatric hospital	Large/medium hospital	Small/rural hospital	Private hospital	Other	Overall N (%)	Pediatric hospital	Large/medium hospital	Small/rural hospital	Other
	n = 89	n = 38	n = 25	n = 3	n = 14	n = 9	n = 46	n = 29	n = 12	n = 2	n = 3
Role of responding clinician											
Pediatric ID physician/trainee	37 (42)	23	8	0	6	0	23 (50)	15	7	1	0
General pediatrician/trainee	24 (27)	8	7	2	5	2	14 (30)	10	1	1	2
Microbiologist	11 (12)	2	4	0	1	4	3 (7)	1	2	0	0
General practitioner/PHP	4 (4)	0	1	1	0	2	1 (4)	0	0	0	1
Neonatologist	3 (3)	2	0	0	1	0	2 (2)	2	0	0	0
General adult physician/trainee	0 (0)	0	0	0	0	0	1 (2)	0	1	0	0
General pediatric nurse	1 (1)	0	1	0	0	0	0 (0)	0	0	0	0
General pharmacist	1 (1)	0	0	0	1	0	0 (0)	0	0	0	0
Other*	8 (9)	3	4	0	0	1	2 (4)	1	1	0	0
Availability of speciality											
General pediatrics	83 (93)	35	24	3	13	8	43 (93)	27	11	2	3
General pediatric surgery	63 (71)	33	17	0	9	4	38 (82)	26	9	2	1
Hematology/oncology	43 (48)	27	6	0	7	3	28 (61)	23	5	0	0
Bone marrow transplant	15 (69)	12	1	0	1	1	20 (33)	19	1	0	0
Solid organ transplant	11 (12)	9	0	0	1	1	15 (33)	15	0	0	0
Cardiothoracic/neurosurgery	43 (48)	27	6	0	6	4	24 (52)	23	1	0	0
ICU (pediatric ± adults)	61 (69)	33	15	0	10	3	34 (74)	26	7	0	1
Neonatal ICU	55 (62)	31	13	1	5	5	35 (76)	25	9	0	1
Special care nursery	45 (51)	21	13	1	6	4	25 (54)	16	8	1	1
Obstetrics	47 (53)	20	14	3	6	4	24 (52)	13	9	1	1
Pediatric patients reviewed per day (N)†											
< 25	19 (21)	9	2	2	5	1	20 (43)	13	6	1	0
25–< 50	21 (24)	9	5	1	5	1	9 (20)	7	1	1	0
50–< 100	17 (19)	7	6	0	3	1	5 (11)	2	1	0	2
≥ 100	25 (28)	12	10	0	0	3	7 (15)	4	3	0	0

*One critical care clinician, others not specified.

†Total inpatients and outpatients reviewed by respondent's team per day.

ICU indicates intensive care unit; ID, infectious diseases; PHP, primary healthcare provider.

and HIC (23/30, 77%) settings was pre-approval of restricted antibiotics. The second most common intervention (18/40, 45%) in LMIC settings was limiting prescribing of restricted antibiotics to certain physicians (eg, named or a designated level of seniority). Whereas in HIC, regular audits of restricted drug use and accountability to hospital management were more common (12/30, 40%). These systems were reported as mostly working in 73% of all settings.

Audits of antibiotic use for pediatric (including neonatal) patients were less common in LMIC than HIC healthcare settings (42/89 [47%] versus [67%], $P = 0.03$). Where conducted, having at least an annual review was less common in LMIC settings (20/42 [48%] versus 23/32 [74%], $P = 0.02$).

Antibiotic Availability

Substantial differences existed in the reported availability of antibiotics between LMIC and HIC (Fig. 3C). For the sickest patients, intravenous antibiotics were only reliably available in 50/80 (62%) LMIC hospitals versus 36/43 (84%) HIC hospitals ($P = 0.01$). Likewise, broad-spectrum antibiotics (such as beta-lactam/beta-lactamase inhibitors) were always available in only 28/80 (35%) LMIC hospitals compared with 28/43 (65%) HIC hospitals ($P = 0.001$). For 12/80 (15%) LMIC facilities, antibiotics were frequently not available.

The WHO recommends that only antibiotics on the Access list¹³ be used for empirical treatment (amikacin, amoxicillin, amoxicillin + clavulanic acid, ampicillin, benzylpenicillin, cefalexin, cefazolin, chloramphenicol, clindamycin, cloxacillin/flucloxacillin, doxycycline, gentamicin, metronidazole, nitrofurantoin, penicillin V, spectinomycin and trimethoprim/sulfamethoxazole). Empirical

first-line antibiotics were limited to WHO Access antibiotics in approximately half of LMIC (48/89, 54%) and HIC (22/46, 48%) healthcare settings ($P = 0.45$). Reliable availability of these antibiotics was less common in LMIC (26/89, 29%) versus HIC settings (22/46, 48%; $P = 0.03$).

Infection Prevention and Control Resources

IPC resources were uniformly lower in LMIC than HIC settings. A formal IPC program/team existed in 52/89 (58%) LMIC healthcare settings and in 40/46 (89%) HIC settings ($P = 0.001$; Fig. 2A), although most IPC programs included pediatric patients.

Infection control practitioners were the most common personnel on IPC teams in both LMIC (37/89, 42%) and HIC (33/46, 72%) facilities (Fig. 2C).

Infection Control Interventions

IPC interventions (eg, by infection control nurses) included promoting and auditing hand hygiene, surveillance of healthcare-associated infections and managing outbreaks. Similar proportions of LMIC and HIC facilities reported that these activities occurred at least sometimes (Fig. 4A). In all healthcare settings, promoting hand hygiene with education and posters was the most common IPC intervention: 73/89 (82%) in LMIC and 42/46 (91%) in HIC.

Equipment and Consumable Resources

Most LMIC hospitals reported shortages of equipment and consumables either often or always (Fig. 4B). Shortages included, sinks near patient beds, a reliable and continuous water supply for handwashing, antiseptic hand rub near patient beds, disposable gloves, full personal protective equipment (PPE), boxes for used

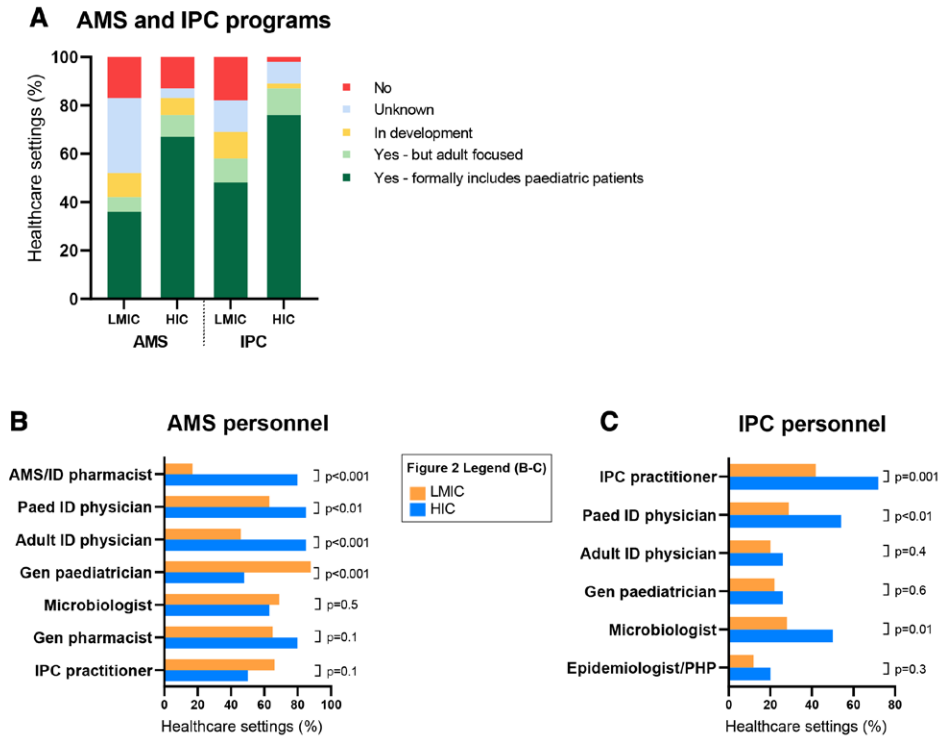


FIGURE 2. Access to AMS and IPC programs and personnel. Proportion of LMIC and HIC healthcare settings with (A) a formal AMS program or IPC program; (B) types of AMS and (C) types of IPC personnel.

sharps near blood-taking and daily cleaning in patient areas. These deficits were very occasionally noted in HIC hospitals.

Reuse of equipment, including oxygen masks (39%), nasal prongs (25%), PPE (20%), endotracheal tubes (11%), nasogastric tubes (9%) and syringes (8%), was common in LMIC healthcare settings (Fig. 4C). Three LMIC healthcare settings had no protocol for cleaning equipment. In HIC, PPE was reused in 15% of healthcare settings and the remainder in up to 4% of settings. Nasogastric tubes were not reused in HIC healthcare settings.

A minimum distance between pediatric beds/neonatal cots was maintained less often in LMIC than HIC hospitals (45/80 [56%] versus 34/43 [79%], $P=0.01$). The most common minimum distance was 1 meter (range 1–3 meters) in LMIC hospitals. In

HIC hospitals, single-patient rooms were most commonly reported, and the same distance range (1–3 meters) for those not in separate rooms.

Microbiology Resources

Most hospitals had access to laboratory services for microbiology cultures: 70/80 (88%) LMIC and 40/43 (93%) HIC hospitals (Table 2). An onsite microbiology laboratory was available more frequently in HIC (36/43, 84%) than LMIC (53/80, 66%) hospitals ($P = 0.03$). HIC had no restrictions on testing, whereas some LMIC had to send samples to an off-site laboratory (6/70, 9%) or had restrictions on which patients/samples to test because of capacity and cost (11/70, 16%). For hospitals with microbiology

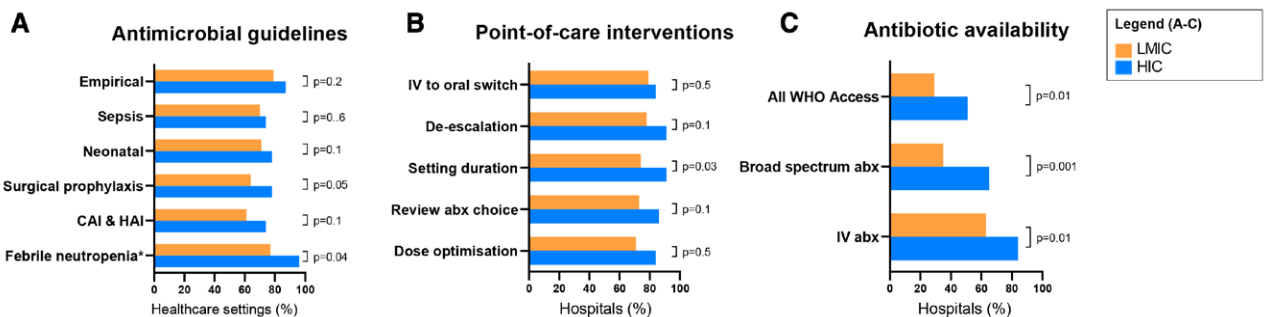


FIGURE 3. Specific AMS resources and interventions: (A) Use of antimicrobial prescribing guidelines in all healthcare settings; (B) Use of point-of-care interventions relating to antimicrobial prescribing in children in hospitals; (C) Reliable antibiotic availability for children in hospitals. Abx, antibiotic; CAI & HAI, guidelines differentiating between community-acquired infections and hospital-acquired infections. *In healthcare settings with hematology/oncology services.

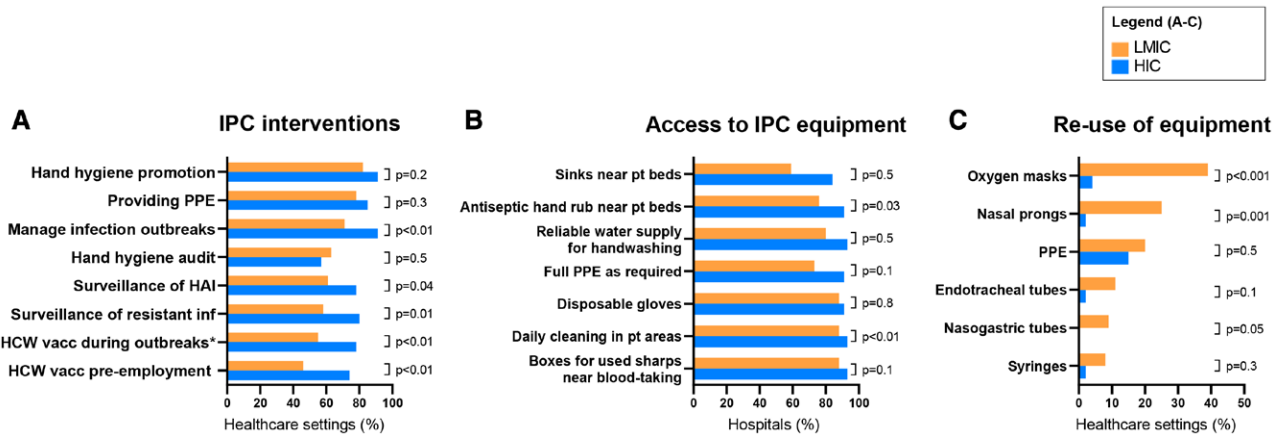


FIGURE 4. Specific IPC resources and interventions: (A) IPC interventions for children; (B) Access to IPC equipment; (C) Reuse of healthcare equipment. HAI, hospital, acquired infections; HCW, healthcare worker; inf, infection; pt, patient; vacc, vaccination. *Seasonal outbreaks.

capabilities, blood culture results were notified to the treating clinician within 24 hours of a positive result in 24/40 (60%) and within 48 hours in 39/40 (98%) HIC hospitals. In LMIC hospitals, in contrast, only 15/67 (22%) received notification within 24 hours and 43/67 (64%) within 48 hours (both $P < 0.001$). Patients more frequently self-funded microbiology investigations in LMIC than HIC hospitals (33/70 [47%] versus 1/40 [3%], $P < 0.001$).

More HIC than LMIC hospitals reported having a strategy to address increasing AMR (24/40 [60%] versus 26/70 [37%], $P = 0.02$). Globally, these strategies commonly included strengthening AMS services and IPC activities to reinforce guidelines, education and surveillance.

Education About Antibiotic Use and Infection Control in Children

Regular or required education on best practice in antimicrobial prescribing occurred in 15/89 (17%) LMIC and 13/46 (28%) HIC healthcare settings ($P = 0.1$). Within LMIC settings, 80% of regular antimicrobial and 73% of IPC education occurred in tertiary pediatric hospitals or large/medium public hospitals. Regular or required education on best practice in infection control was more common in both settings and occurred in 22/89 (25%) LMIC healthcare settings and 21/46 (46%) HIC settings ($P = 0.01$).

Respondents from 24/89 (27%) LMIC settings and 28/46 (61%) HIC settings ($P = 0.0001$) were aware of public health campaigns or messaging around antibiotic use or infection control aimed at the general public in their countries. Globally, these were most commonly World Antibiotic Awareness Week, Antibiotic Information Day, Ministry of Health campaigns through print, broadcast and social media.

Barriers to Progress

The two most common perceived barriers to AMS for pediatric patients in both healthcare settings were (1) lack of education about antibiotics and (2) lack of support and enforcement from hospital management. In LMIC, an additional barrier was lack of acknowledgment by senior doctors of the importance of AMS. In HIC, the next most commonly reported barrier was lack of personnel resources to prioritize AMS.

The three most common perceived barriers to infection control for pediatric patients encountered in healthcare settings were identical in both settings: (1) lack of education about infection control, (2) lack of personnel to address this as a priority and (3) lack of support from senior hospital clinicians to change practice. The most significant barrier identified in both LMIC and HIC settings was lack of resources. In LMIC, these resources were personnel/

Table 2. Access to Microbiology Laboratory Services

	LMIC Hospitals, N (%)	HIC Hospitals, N (%)	P Value
	n = 80	n = 43	
Availability of culture types			
Urine	69 (86)	40 (93)	0.03
Cerebrospinal fluid	62 (78)	40 (93)	< 0.01
Blood	67 (84)	40 (93)	0.02
Notification of positive blood culture result			
Within 24 h	15/67 (22)	24/40 (60)	< 0.001
Within 48 h	43/67 (64)	39/40 (98)	< 0.001
Antibiotic susceptibility testing			
Always/usually	59 (74)	38 (88)	< 0.01
Restricted to sample type/patient group	8 (10)	2 (5)	0.5
Occasionally/never	3 (4)	0 (0)	0.6
Cascade reporting	38 (48)	29 (67)	< 0.01
Periodic updates of local antibiogram	36 (45)	35 (81)	< 0.001

equipment/microbiology laboratory, and in HIC they were personnel and dedicated time.

DISCUSSION

This is the first international survey of AMS and IPC resources and activities for children.

Although substantial gaps were identified in both LMIC and HIC, there was significant disparity in these critical healthcare activities between these settings. Formal AMS and IPC programs existed in significantly fewer LMIC healthcare settings, magnifying the specific challenges faced by AMS and IPC implementation in pediatrics. Unique challenges for AMS in children include quantifying antimicrobial use (due to weight- and age-based dosing) and defining outcome measures of effectiveness.¹⁴ Likewise, standard IPC measures designed for adult care are not necessarily transferrable to neonatal and pediatric populations without addressing differences in pathophysiology of healthcare-associated infections (eg, differences in immunity, device utilization, family-centered care environment).^{15,16}

The most common AMS personnel were general pediatricians in LMIC and pediatric/adult ID subspecialists in HIC settings. This disparity reflects differences in resourcing for personnel and the consequent need for healthcare staff in LMIC to cover multiple different roles. In contrast to the expense of employing subspecialists, antimicrobial guidelines are relatively inexpensive. However, guidelines tended to be less commonly used in LMIC than HIC, despite reducing inappropriate antimicrobial prescribing in these settings.^{17–19} There was relatively low awareness of the existence of national/international guidelines for antibiotic choice and duration. Other reasons may relate to difficulties in developing local guidelines without robust local susceptibility data, uncertainty in adapting national or WHO guidelines or inadequate dissemination. This needs further exploration.

There was decreased availability of the WHO Access Watch Reserve approach to antibiotics in LMIC than HIC settings. In fact, the reliable availability of WHO Access (essential and widely available) antibiotics was limited to one-third of LMIC healthcare settings, with fewer than half of LMIC settings conducting audits of antibiotic use in children. This highlights the importance of balancing improved access with avoiding excess use, especially for children and neonates.²⁰ These factors must be addressed, if the WHO target is to be reached redirecting use of access antibiotics to more than 60% of all antimicrobials.¹³

Microbiology services are considered fundamental to AMS²¹ with the majority of LMIC hospitals in this survey having access to bacterial culture (although still not all). However, the extent of this access is questionable. Limitations included that 1 in 6 hospitals had restrictions on sample processing due to capacity or cost, delays in clinician notification of results and patients needing to self-fund investigations. Improving the effectiveness of culture results requires not only access to a microbiology laboratory but improvements in systems and resources.

The most common IPC intervention in both LMIC and HIC was promoting hand hygiene, which has a strong evidence-base in reducing healthcare-associated infections and the transmission of resistant pathogens.²² There is room for improvement, however, as almost 1 in 5 pediatric healthcare settings in LMIC and HIC were not promoting this inexpensive effective strategy. In addition, LMIC hospitals had access to fewer resources such as sinks near patient beds and reliable water supply to support effective hand hygiene. A major difference between LMIC and HIC was the reuse of equipment. Limited resources necessitate pragmatic reuse of essential equipment, but this needs to be supported by reliable systems such as sterilization if spread of infection is to be prevented.

The most commonly perceived barrier to both AMS and IPC for children in LMIC (as well as in HIC) was lack of education. This was reflected in a woeful lack of sustained education on best practice in antimicrobial prescribing or infection control, although LMIC settings were even more limited than HIC. Education and training are important tools to improve awareness and understanding of AMR in the WHO Global Action Plan.¹ Educational activities are necessary to sustain any behavioral changes, especially where there is high turnover of healthcare personnel.²³ This is an area in desperate need of improvement if any strategies in AMS and IPC are to be sustained. Innovative and combination strategies could be effective, but the key is strong and ongoing support from senior clinicians and healthcare executives.^{24,25}

Our study has several limitations. Respondents were sourced through professional pediatric infectious diseases associations, the survey was distributed in English and participation was voluntary, all introducing potential selection bias in both respondents and most likely to access some resources. English not being the first language of respondents may have influenced interpretation of some questions and the accuracy of the self-reporting was not verified. Also, the survey was conducted during the coronavirus disease 2019 pandemic which affected regions at different stages around the world but may have increased focus on IPC strategies, although possibly predominantly adult-focused. The pandemic continues to unmask many weaknesses in healthcare systems and overburden many countries' healthcare infrastructure, impacting AMS/IPC programs, personnel, antibiotic supply chains and resources.²⁶

The marked imbalance between LMIC and HIC in pediatric AMS and IPC resources and activities calls for a collaborative international approach to combat AMR, a global public health problem. Because of perceived lower morbidity and mortality from AMR in children, they are being left behind in efforts to improve AMS and IPC effectiveness. However, success stories such as childhood vaccination show the impact of strong leadership and international collaboration. A key priority identified from this survey in all settings, but especially LMIC, is the implementation of systematic, ongoing, management-supported education programs in AMS and IPC. Additionally, given the quantitative and qualitative disparity between LMIC and HIC, an important next step would be a cost-effectiveness analysis of all AMS/IPC interventions to determine the greatest impact for children with limited resources. Concerted efforts, supported by HIC, will be needed to increase advocacy, facilitate inexpensive approaches to reliable antibiotic access and improved sanitation standards for healthcare facilities, in addition to expanding logistical access to microbiology. International organizations can share resources, establish research partnerships, develop specialist training of healthcare professionals and facilitate access to national/international professional networks, to support implementation of context-specific AMS and IPC strategies with global impact.

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