Multinational consensus antimicrobial stewardship recommendations for children managed in hospital settings

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Children are entitled to receive antibiotic therapy that is based on evidence and best practice, but might be overlooked in hospital programmes designed to achieve antimicrobial stewardship [AMS]. This failure to include children could be because children make up small proportion of patients in most hospitals, and are cared for by specialised paediatric staff. We reviewed the evidence and consulted experts in three global regions to develop ten recommendations for good-practice in hospital AMS programmes for children. We performed a review of scientific research, published between Jan 1, 2007, and Oct 17, 2019, concerning AMS, and formed a multinational expert group comprising members from the USA, Canada, the UK, Belgium, Switzerland, Australia, and Aotearoa New Zealand to develop the recommendations. These recommendations aim to help health-care workers who care for children in these regions to deliver best-practice care. We surveyed health-care workers with expertise in antibiotic therapy for children across these regions, and found that the recommendations were considered both very important and generally feasible. These recommendations should be implemented in hospitals to improve antibiotic therapy for children and to stimulate research into future improvements in care.

Introduction

Antimicrobials are essential for hospital care, including safe surgery, intensive care, cancer care, obstetrics, and neonatology, as well as treatment and prevention of infection in the community and in hospital. Overuse and misuse of these crucial drugs exerts selective pressure for antimicrobial resistance (AMR).[1,2] The global AMR crisis poses a threat not only to contemporary medical practice, but to our current way of life, with substantial attributable mortality and costs to society.[3] Antimicrobial stewardship (AMS) describes "a collective set of strategies to improve the appropriateness and minimise the adverse effects of antibiotic use including resistance, toxicity and costs…achieved by promoting the selection of the optimal antibiotic regimen, dose, duration and route of administration".[4] In hospitals, these strategies might be implemented collectively under AMS programmes, ideally with staff dedicated to overseeing them, formulary restrictions and guidelines, and audit and feedback for prescribers to optimise antimicrobial prescribing. Children are entitled to optimal use of antibiotics and other antimicrobials to treat infections, but as a minority and specialised population, especially outside dedicated children's hospitals, they might be overlooked or assigned low priority in hospital AMS programmes. Paediatric infections and antibiotic prescribing differ systematically from that in adults, and this must also be considered in providing AMS for children. In addition, long-term effects of antimicrobial prescribing in early life, including associations with obesity and inflammation, and alterations in the microbiome, with potential increased risk for viral and bacterial superinfections, are increasingly reported, adding additional need for careful stewardship in this population.[5–10] Infants younger than 3 months of age, but especially infants younger than 1 month of age (neonates), are particularly vulnerable to consequences of AMR, and resistant invasive bacterial infections, such as neonatal sepsis, are an increasing problem globally.[11,12] To address the need for consideration of best-practice paediatric AMS in the hospital setting, an international expert group was assembled in 2019 to develop recommendations.

These recommendations are intended for health-care providers caring for infants, children, and adolescents in hospital, both in the emergency department and for admitted patients. Compared with AMS in hospitals, provision of antimicrobials to children in primary care requires a different approach, including specific engagement with stakeholders from primary care; this topic was considered outside of the scope of these recommendations. These recommendations might have less relevance outside high-income global regions, due to differing health systems and resource constraints, but some elements and principles might remain applicable. These recommendations are, therefore, intended to support and supplement work undertaken by WHO,[13] the World Society for Pediatric Infectious Diseases,[14] and other groups to improve paediatric AMS globally, and to highlight the need for improving resourcing and research in low-income and middle-income countries.

The purpose of these multinational consensus recommendations is to enable clinicians to advocate for resources to deliver paediatric AMS in all hospitals that provide care for children; provide guidance for AMS teams to improve service delivery; provide guidance on prioritising elements of AMS strategy; and promote benchmarking of paediatric AMS programme delivery.

Methods

Steering committee

A steering committee was formed in 2019, comprising paediatric AMS physicians, AMS pharmacists, and nurses from three global regions, namely, Australia and Aotearoa

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See Online for appendix

New Zealand, USA and Canada, and Europe, with a chair for each region (BM, JN, and SP, respectively). Initially BM, JN, and SP discussed the scope of the project and formed a steering group, comprising multidisciplinary paediatric AMS professionals, including paediatric infectious diseases physicians, pharmacists, and nurses. These participants were sought via informal calls for interest and direct approach within each chair's regional AMS networks, including the European Society of Clinical Microbiology and Infectious Diseases' Study Group for Antimicrobial Stewardship for Europe, the Sharing Antimicrobial Reports for Pediatric Stewardship Collaborative, the Canadian Paediatric Society in North America, and the Australian and New Zealand Paediatric Infectious Diseases Group in Australia and Aotearoa New Zealand. These global regions have broadly similar capacity to undertake paediatric AMS policy improvements and shared goals among paediatric AMS experts, despite systemic differences in health policy.

Supporting literature review

A literature review was conducted to support this project, modelled on scoping review methods to identify evidence for paediatric AMS programmes and intervention benefits,[15] as well as consider evidence gaps. The search was conducted in 2019 by the steering group regional chairs, and was supported by British Society for Antimicrobial Chemotherapy staff. The review, which included research published between Jan 1, 2007, and Oct 17, 2019, identified literature concerning AMS policies and interventions for hospitalised children, with study outcomes including antimicrobial appropriateness, guideline compliance, antimicrobial consumption, antimicrobial cost, patient safety, and antimicrobial resistance.

Consensus process for good-practice recommendation development

The steering group chairs collaborated to develop ten recommendations and proposed these to the steering group, informed by the literature review process and drawing on the collective experience of leading paediatric AMS programmes, as well as research and practice improvement efforts. The steering group provided feedback on these recommendations, which were used by the chairs to revise the recommendations.

Revised recommendations (panel) were embedded in an electronic survey (appendix pp 11–22) using REDCap (hosted at University of New South Wales, Sydney, NSW, Australia). Surveys were sent via email to targeted distribution lists from pre-existing networks of paediatric AMS practitioners and experts in paediatric AMS

Panel: **Paediatric antimicrobial stewardship good-practice recommendations**

Section 1: all children admitted to hospital should have access to optimal antimicrobial management

Recommendation 1: guidelines
Hospitals should provide prescribers with access to current, evidence-based, endorsed antimicrobial guidelines suitable for paediatric patients

Recommendation 2: expert advice
Hospitals should ensure prescribers have access to expert advice in paediatric infection management. This could be provided through local personnel or networks of care

Recommendation 3: education
Hospitals should provide access to education on management of common infections in children and AMS for prescribers and other clinicians

Section 2: all hospitals that provide care to children should explicitly include children in AMS strategies

Recommendation 4: representation
AMS committees within hospitals that care for both adults and children should include representatives from the paediatric service. Paediatric hospitals that have AMS committees should include representatives from infectious diseases or microbiology, pharmacy, and other clinician groups relevant to that hospital

Recommendation 5: access to data
AMS committees should have access to prescribing data and data on local antimicrobial resistance in children. For quantitative antimicrobial use in children, if available, this should be measured in days of therapy per 1000 bed days or per 1000 patient days

Recommendation 6: AMS reporting
Hospitals should ensure antimicrobial prescribing for children is audited periodically and reported to relevant stakeholders within the hospital

Recommendation 7: funding
Hospitals should have access to government funding and appropriate resources to undertake AMS for children

Recommendation 8: inclusion
Hospitals that care for adults and children, and have access to funding for AMS, should include provision of AMS for children

Section 3: networks should be created to support hospitals in providing paediatric AMS

Recommendation 9: access to networks
Hospitals should have access to regional or national networks, or both, for benchmarking of paediatric AMS indicators and sharing of practice improvements

Recommendation 10: incentives
Hospitals should be provided with incentives to promote paediatric AMS, with requirements for national reporting or accreditation, or both, and with explicit criteria

The full survey and explanatory notes and examples for each recommendation are found in appendix pp 11–22. AMS=antimicrobial stewardship.

networks in Australia and Aotearoa New Zealand, USA and Canada, and Europe. Respondents were asked to rate all ten recommendations in terms of importance and feasibility using a five-point Likert-type scale, as shown in the figure. Respondents were also asked to provide details of perceived barriers to implementation. This survey component was considered optional. The survey also asked respondents their profession type and country of practice, but did not collect any identifying information. For this reason, the plan was to analyse completed surveys only.

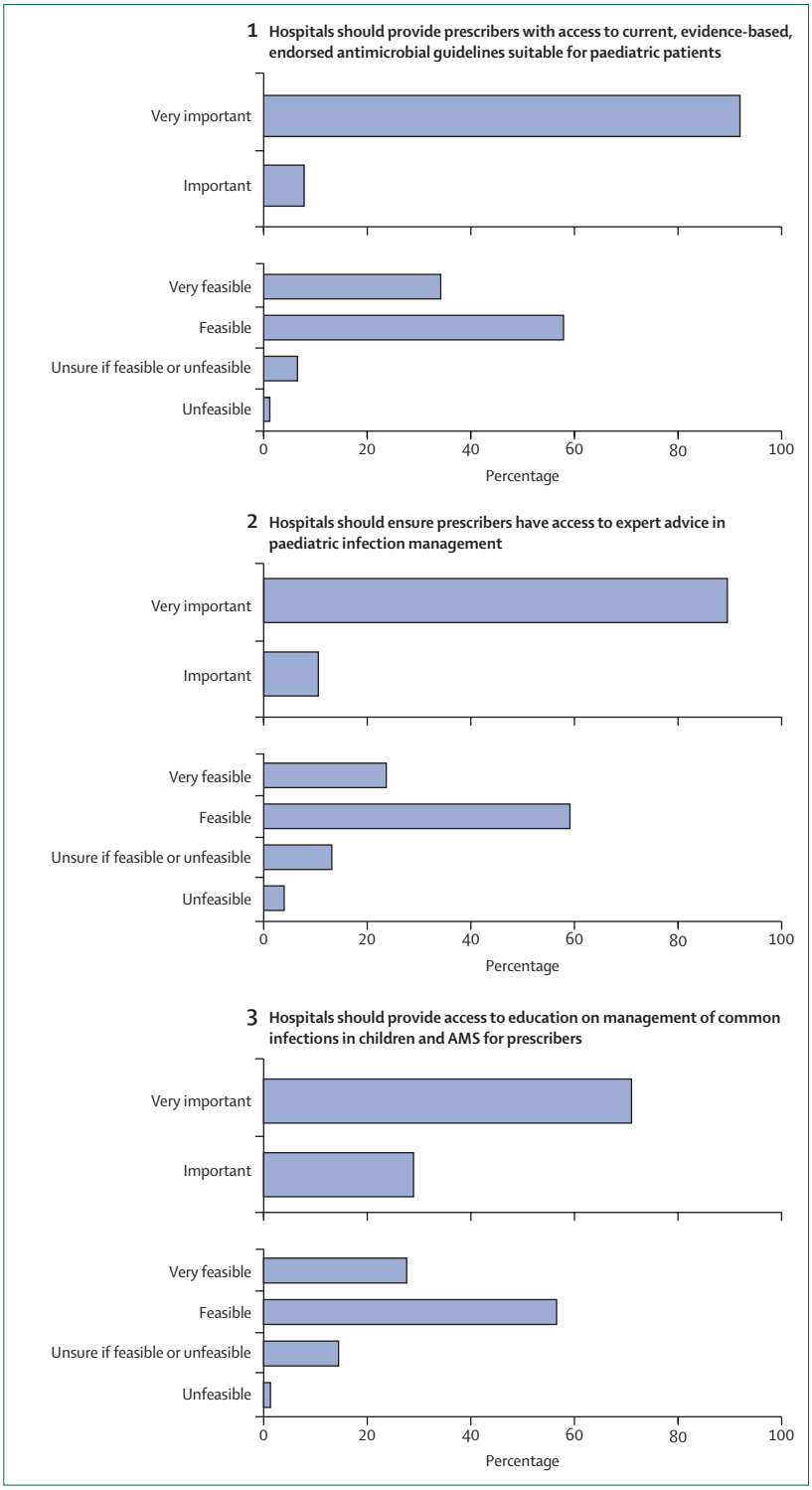
Recommendations in the guidelines were separated into three sections Section one: all children admitted to hospital should have access to optimal antimicrobial management; section two: all hospitals that provide care to children should explicitly include children in AMS strategies; and, section three: networks should be created to support hospitals in providing paediatric AMS. Notes and examples clarifying each recommendation were provided in the survey (appendix pp 11–22). The steering group did not set criteria for acceptance of recommendations a priori, but planned to review survey responses and resolve by consensus on the publication of recommendations, with revision if required, based on feedback received.

Literature review

The initial literature review yielded 1181 articles. Title screening identified 594 relevant articles, after excluding duplicates and case reports. Two authors (SP and BM) independently screened the abstracts, and where necessary the full text, of 594 articles and found 126 relevant articles for inclusion (SP and BM screened the articles and resolved disagreements by consensus, with a third author [JN] to resolve disputes where consensus could not be reached. The third author resolution process did not need to be implemented). Search results and exclusions are shown in the appendix (p 1).

Of the 126 included articles, 51 described an intervention relating to paediatric AMS, and five relevant systematic reviews were identified. The remaining article types and further results are listed in the appendix (p 2). AMS criteria or themes reported in the 51 intervention studies are listed in table 1, and details of each intervention study are listed in the appendix (pp 3–10). These publications generally reported that paediatric AMS interventions were beneficial, commonly regarding reduction of antimicrobial consumption or improvement in quality of use, including broad-spectrum antibiotic use. However, most studies that reported on AMS interventions and programmes were retrospective studies or uncontrolled before and after prospective studies, with attendant limitations with respect to internal and external validity and risk (appendix pp 5–8; tables 1, 2).

Five systematic reviews on paediatric AMS incorporating hospitalised children were identified (table 2).



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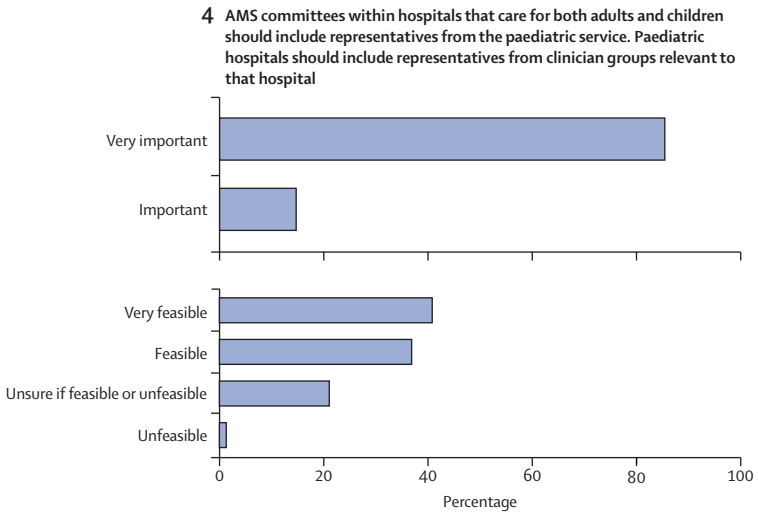
These systematic reviews are characterised by a range of methods, studies included, and outcomes reported. In general, the reviews report beneficial effects from paediatric AMS programmes, implemented mainly in



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inpatient settings only, mostly in reducing excessive antimicrobial use. Randomised controlled trial data are scarce. Further details of each included review are listed in table 2.

The reviewers concluded that existing evidence establishes that paediatric AMS programmes have been shown to provide various benefits for children. Studies were heterogeneous in terms of structure and outcome, and did not provide sufficient guidance on optimal AMS programme structure, performance indicators or resourcing, or clarify which outcomes should be measured.

There is a need for broadly applicable indicators against which paediatric AMS programmes and interventions can be benchmarked. This need for indicators is relevant for clinical practice and future research. Because the reviewers were not able to identify this in the literature, they concluded there was a need for an expert consensus approach initially to construct recommendations, although these must be informed by evidence where and when available. This informed our decision to survey experts.

Targeted survey of recommendations

Surveys of the ten recommendations, with supporting notes and examples (appendix 5–8) were sent to targeted distribution lists from February to March, 2021. There were 119 total entries and 76 completed survey responses. Of completed surveys, 26 (34%) were from Australia or Aotearoa New Zealand, 40 (53%) were from the USA or Canada, eight (11%) were from Europe, and two (3%) did not include details for country. The response rate was variable: 26 (72%) of 36 in Australia and Aotearoa New Zealand, 40 (6%) of 699 in USA and Canada, and eight (6%) of 135 in Europe. Respondents were mainly paediatric infectious diseases physicians (n=40; 53%) and AMS pharmacists (n=25; 33%); the remainder (n=11; 15%) included paediatric trainees and other professionals. Survey respondents generally rated all ten recommendations as important or very important. The recommendations were also generally rated as feasible or very feasible by more than 50% of respondents (figure), except for recommendations seven and ten, relating to funding and incentives for hospitals to undertake paediatric AMS. Less than 10% of respondents (figure) reported any of the ten recommendations as unfeasible, except for recommendation five (access to data), where eight (11%) respondents indicated poor feasibility. Results for each recommendation on importance and feasibility are provided in detail in the figure.

Recommendations

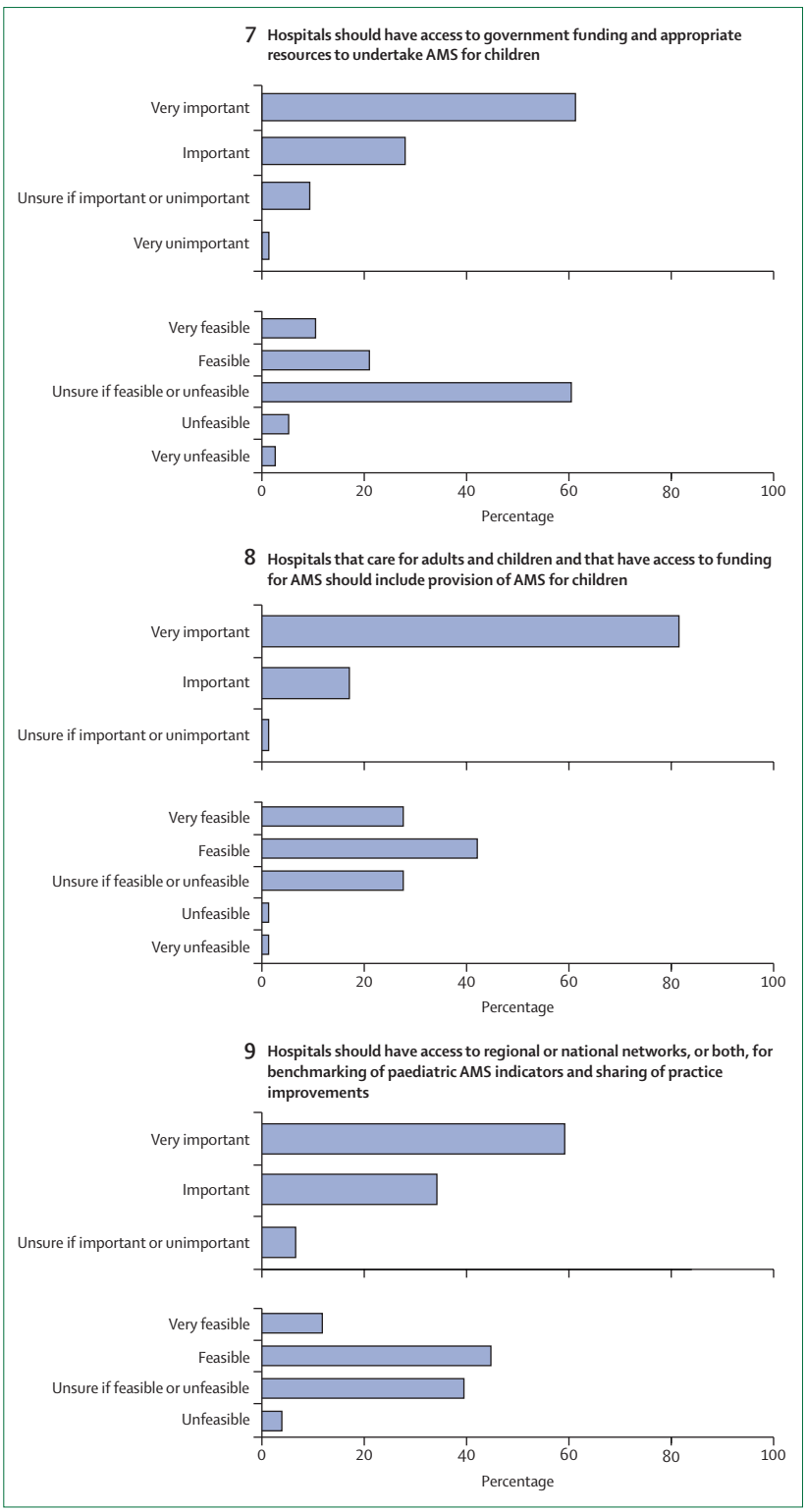
The recommendations in this Review are the culmination of an evidence-based and consensus-led process undertaken to set new benchmarks for paediatric AMS.

There remains a paucity of evidence surrounding paediatric AMS programmes compared with adult

programmes. Additionally, the quality of evidence for AMS interventions in general remains poor, with few controlled studies and few studies reporting clinical or microbiological outcome data, despite recommendations for improvement.[21,22] In our review of the research published between 2007 and 2019, we identified 126 relevant articles, but no consistent evidence or guidelines for AMS best practice in children. A search of the National Library of Medicine using PubMed for the same period identified more than 7500 articles relating to AMS. The vast majority were applicable to adult, rather than paediatric, AMS. Gaps in knowledge around paediatric AMS include methods for programme implementation and approval processes.[23,24] Determination of which AMS interventions are most effective to reduce errors and save costs in paediatric hospital and general hospital contexts is also needed. For example, AMS programmes need to consider all aspects of appropriate prescribing, but programme leaders might have to choose whether to focus on pathogen–drug mismatches, dose optimisation, antimicrobial de-escalation, or intravenous-to-oral antibiotic conversion efforts, depending on local needs.[25,26] Uncertainty and variability also exist in programmatic implementation strategies—eg, dedicated rounds by AMS experts, preapproval systems versus post-prescription review or combined approaches, and the value of computerised decision support systems and other structural aids.[27–30] All AMS programmes must ultimately be in service of patient safety, aiming to improve clinical outcomes for patients and their communities.[31,32]

These recommendations are practical in nature and support optimal management of infection, ensuring that children are considered within wider hospital AMS strategies. They also require that regional or national networks are used to support AMS in local hospitals. The recommendations can be used together as a benchmarking tool and present a powerful approach to driving change.[33] The recommendations are applicable for children admitted to both specialist children's hospitals and general hospitals and might be used to set standards for AMS provision to children in hospital. The recommendations have potential implications for accreditation of hospitals, regional AMS network practices, and national standards to benchmark hospital paediatric AMS. Implementation of improved paediatric AMS at several levels is also supported by examples of good-practice, provided alongside the recommendations (appendix 11–22).

Although there has been comparatively little focus on children in national AMS strategies,[34,35] these recommendations could be embedded within national AMS strategic plans, to facilitate improved funding and improved quality of paediatric AMS services and accompanying research to achieve these goals. These recommendations could also support generation of better-quality evidence for paediatric AMS programmes and their implementation by providing a common framework and incentives for conducting research and quality-improvement studies in this field.



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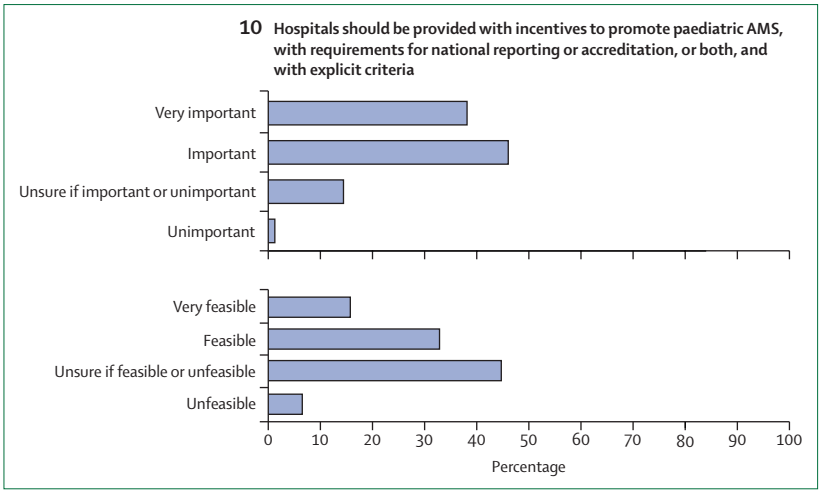

Figure: **Importance and feasibility survey responses for paediatric antimicrobial stewardship good-practice recommendations**
Absolute number varied by recommendation. AMS=antimicrobial stewardship. DOT=days of therapy.

	Number of studies identified
Impact of antimicrobial stewardship programmes	28
Antimicrobial consumption	28
Antimicrobial policy introduction	14
Appropriateness or guideline compliance	13
Safety related to antimicrobials or antimicrobial stewardship programme	7
Antimicrobial programme acceptance	6
Antimicrobial costs	5
Education or training programmes	5
Multiresistant organisms	4
Medication errors	3
Electronic prescribing	2
Utility of a diagnostic test	1
Infectious disease consultations	1
Antimicrobial stewardship programme staffing	1
Total	51

Detail on studies is provided in the appendix (pp 3–10). *Themes were not mutually exclusive.

Table 1: **Studies reporting interventions and themes* involving paediatric inpatient antimicrobial stewardship, 2007–19**

	Number of studies	Major conclusions
Patel et al (2007)[16]	28	The majority (21 of 28) of studies reported positive outcomes; there was considerable risk of bias and heterogeneity between included studies.
Smith et al (2015)[17]	17	The use of antimicrobial stewardship programmes and interventions reduced prescribing costs, antimicrobial use, and errors.
Araujo da Silva et al (2018)[18]	9	Studies reported a reduction in antibiotic use; prospective audits of antimicrobial use were the most common core component of antimicrobial stewardship programmes; intensive care unit impact data were absent.
Godbout et al (2018)[19]	17	Inpatient antimicrobial stewardship programmes reduced antimicrobial use without short-term safety concerns; interrupted time series analysis was common; control group data and randomised trials were absent; data on neonatal intensive care and haematology and oncology populations were absent.
Grammatico-Guillon et al (2019)[20]	21	Paediatric antimicrobial stewardship programmes (mostly inpatient) reduced antimicrobial consumption; most studies used descriptive analyses in retrospective before-and-after studies, lacked control groups, and rarely examined the effect of programmes on antimicrobial resistance.

Table 2: **Systematic reviews of paediatric inpatient antimicrobial stewardship 2007–19**

There are other paediatric AMS recommendations in the global literature, including the American Academy of Pediatrics policy statement.[36] Unlike our recommendations, the American Academy of Pediatrics' inpatient and outpatient proposals focus on the US setting and are not formulated in a way to allow for benchmarking across hospitals or international borders. Other notable contributions include the Dutch consensus report on human resources for AMS[37] and two landmark guidelines and policy statements[23,38] by influential American bodies such as the Infectious Diseases Society of America. However, none of these other recommendations are specific to paediatric AMS or contain sufficient detail about AMS in children.[23,38] We are unaware of any other international recommendations similar in nature and scope to our recommendations presented here, which specifically consider paediatric AMS programmes and allow for benchmarking to support minimum standards and facilitate improvement.

Limitations of these recommendations include their application to hospital-based rather than community-based prescribing stewardship. Most antimicrobial prescribing occurs in community settings, especially for upper respiratory tract infections.[39,40] Similar efforts to provide standards and programmes to improve AMS for children in primary care are also needed, but require adaptation of implementation methods and engagement of different stakeholders, including primary care practitioners.[41] Children in hospital merit specific AMS interventions because they are the most unwell and most clinically vulnerable children. The hospital provides the highest-risk setting for children to be infected with drug-resistant organisms, due to frequent antimicrobial use, comorbidities, and potential for nosocomial spread of organisms, despite the amount of antimicrobial prescribing in community settings.[34]

Recommendations five, seven, and ten, relating to access to data, funding, and incentives for paediatric

AMS, respectively, merit particular comment. These recommendations were considered important, but respondents noted challenges with relation to feasibility. The authors accept that current systems in many settings do not allow for these recommendations to be implemented immediately or easily. In the USA, hospital funding structures are not conducive to government funding to support AMS of any type, let alone paediatric-specific considerations. We consider, however, that these recommendations remain valuable to stimulate efforts to improve practice. Survey respondents considered them important, and our steering group concluded the status quo is not acceptable. This means these recommendations might be used to advocate for improvements, as well as measuring current standards.

Although our steering group, who are coauthors on this Review, represent opinion leaders in our regions, our survey responses from a much broader group interested in paediatric AMS were low in the USA, Canada, and European regions. The survey was conducted during the COVID-19 pandemic, and it was difficult for all but the most engaged clinicians to respond to additional surveys during this time. The steering group has broad representation from key clinician-researchers and opinion leaders representing those regions, however, and we judge these people well placed to speak on behalf of local clinicians.

Another limitation of these recommendations is that they were primarily developed for implementation within high-income settings, meaning that they cannot necessarily be applied to hospital settings globally. Unfortunately, the threat of AMR remains significantly higher in low-income and middle-income countries, often with fewer resources to undertake AMS activities to combat AMR and unequal access to life-saving medicines, which might thus be a higher priority. There is an urgent need for the international community to support global efforts to reduce AMR—including development of appropriate guidelines for prescribing and AMS—and promote equitable and appropriate antimicrobial use for children wherever they live.[42] Some of the recommendations presented here might be applicable to garner support for those efforts. In many countries, children from Indigenous communities are disproportionately affected by infections and the effects of antimicrobial resistance, and this underscores a need to engage with community leaders to develop targeted solutions to local antimicrobial stewardship problems.[43] There are legitimate concerns about data access and reporting requirements to implement locally adapted AMS for children. This potentially applies to hospital settings, especially those without electronic medical records and non-academic community hospitals. Analysis of perceived barriers to feasibility (also collected in this survey) requires more detailed discussion and will be presented in an upcoming report, along with suggestions for strategies to overcome these barriers.

Conclusions

These ten recommendations are current, expert-led consensus on achievable benchmarks for AMS in hospitalised children. We advise that these should be adapted, implemented broadly, and reviewed with further research to improve the assessment and provision of antimicrobials in children. Some recommendations may be aspirational benchmarks right now, even in some well resourced settings, but we believe they are ultimately attainable and urgently needed.[44] These recommendations have been endorsed by the Australian and New Zealand Paediatric Infectious Diseases Group, the European Society of Clinical Microbiology and Infectious Diseases Study Group for Antimicrobial Stewardship, the British Society for Antimicrobial Chemotherapy, and the Pediatric Infectious Diseases Society. These are representative expert groups in infectious diseases and AMS across three continents, and we plan for broader consultation with and endorsement by other international groups in the future.

Contributors

BM conceived and coordinated the project overall, coordinated the steering group contributors from Aotearoa New Zealand and Australia, independently reviewed the supporting literature, disseminated, and analysed the survey, and wrote and edited the recommendations and manuscript. JN conceived the project, coordinated the steering group contributors from the USA and Canada, supervised the project, disseminated the survey, and reviewed and edited the recommendations and manuscript. SP conceived the project, coordinated the steering group contributors from Europe, supervised the project, independently reviewed the supporting literature, disseminated the survey, and reviewed and edited the recommendations and manuscript. PAB, ED, JB, PDC, MS, TZ, KT, EM, RFH, and ACT reviewed and edited the recommendations and manuscript.

Declaration of interests

BM has received grants from the Sydney Children's Hospital Foundation and the National Health and Medical Research Council; holds an unpaid role on data safety monitoring board of the Pragmatic Adaptive Trial for Respiratory Infections in Children trial; and was a Board Director of the Australasian Society for Infectious Diseases from June, 2018–June 2022. JN has received a grant from Agency for Healthcare Research and Quality. JB has received grants from the European & Developing Countries Clinical Trials Partnership, Horizon 2000, Swiss National Science Foundation, National Institute for Health and Care Research, and Wellcome Trust; has received consulting fees from Shionogi and Sandoz, in addition to paid speaking events on behalf of Pfizer, Sandoz, and Bayer; and has also held unpaid positions on advisory boards for independent data monitoring committees for the Boost–EBOC trial, the Avenir trial, and the Lakana trial, and the trial steering committee for the cASPerCF trial, in addition to unpaid roles for SwissPedNet and the Penta Foundation. PDC has received grants from the Research Foundation–Flanders and the Belgian Healthcare Knowledge Centre, and has received payments for speaking engagements at the Congress of the European Society for Development, Perinatal, and Pediatric Pharmacology. KT has received payments for consultation from Avir Pharma and Wolter Kluwer. RFH declares a position as Committee Chair of the Pediatric Infectious Diseases Society. ACT has received grants from the Agency for Healthcare Research and Quality and the Cystic Fibrosis Foundation; has received payment from PBS for consultation and from the Pediatric Infectious Diseases Society for lectures; and is a committee chair of the Paediatric Infectious Diseases Society. All other authors declare no competing interests.

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