Antimicrobial resistance: A Commonwealth perspective

Fatima Mir, Farah Naz Qamar and Zulfiqar A. Bhutta

Infections, such as pneumonia, diarrhoea and malaria, account for over 30 per cent of under-five child deaths in the world (Walker et al., 2013). When under-nutrition, a known predictor of mortality, affects over half of under-five children, the contribution of antimicrobial resistance (AMR) to infection-related clinical outcomes becomes difficult to tease apart (Black et al., 2013). The impact of AMR is highest in poorer countries, where the infectious disease burden is large (due to poor hygiene, polluted water supplies, malnutrition and sub-optimal vaccination) and inappropriate antibiotic use is unchecked. Even in the highest-income countries, in the face of a dry new-antibiotic pipeline and rising resistance among nosocomial pathogens, continued efforts to contain AMR are essential. A global co-ordinated effort is now imperative and networks such as the Commonwealth of Nations, through which sovereign states can associate, and share resources and efforts towards common goals, can be useful conduits. This article deals with AMR trends reported among common childhood pathogens, case examples of successful containment strategies, and gaps in recommendations and ground realities in Commonwealth countries.

AMR trends and childhood diseases

Newborn sepsis

Recent studies reporting on aetiology and resistance trends in early and late onset newborn sepsis within Commonwealth Asia and Africa show similar gram-negative preponderance and resistance trends reported earlier in developing countries (Waters et al, 2011; Zaidi et al., 2009).[1] The use of Group B streptococci prophylaxis in the Americas has been linked to the increase in ampicillin resistant *E. coli* from 1988 to 2000.[2]

Pneumonia/meningitis

Epidemiologic data suggests that asymptomatic nasopharyngeal carriage of *Streptococcus pneumonia* may represent an important reservoir of resistant strains in the community. Most of the 156 million new pneumococcal pneumonia episodes each year occur in India (43 million), China (21 million), Pakistan (ten million) and Bangladesh, Indonesia and Nigeria (six million each; Rudan et al., 2008).[3]

Diarrhoeal and enteric pathogens

Vibrio cholerae, *Salmonella sp.*, *Shigella sp.*, *Escherichia coli* and *Campylobacter sp.* are endemic in Sub-Saharan Africa and South Asia with high rates of antimicrobial resistance.

Increasing *V. cholerae* resistance to not only the World Health Organization (WHO) recommended ciprofloxacin, but also other antibiotics including tetracycline, ampicillin, chloramphenicol, azithromycin and third generation cephalosporins, increases disease severity and complexity in addition to treatment costs.

Resistance to ciprofloxacin, among campylobacter jejuni, has been linked to injudicious use of floroquinolones in poultry (reservoir of organism; Laxminarayan et al., 2013). Rates from five to 38 per cent have been reported from Bangladesh, India and Ethiopia. Almost 60 per cent of *Salmonella enterica* serovar Typhi and Paratyphi isolates, from regions of highest disease burden (South/Central Asia and Africa) are multi-drug resistant (Kariuki et al., 2010; Ochiai et al., 2008). The global increase in multidrug resistance (resistance to ampicillin, chloramphenicol and co-trimaxazole) against *S. enterica* ser. Typhi is associated with greater severity and higher case-fatality rates (World Health Organization, 2009).

Improving and measuring antibiotic use

WHO recommends surveillance as a key strategy to address the growing global problems associated with AMR and extends systems support in the form of recommendations.

Supranational and national surveillance networks

Active supranational networks include Integrated Disease Surveillance and Response (IDSR), co-ordinated by the WHO regional office for Africa; the Red Latinoamericana de Vigilancia de la Resistencia a los Antimicrobianos (ReLAVRA), co-ordinated by the Pan American Health Organization; and the European Antimicrobial Resistance Surveillance Network. These systems help inform appropriate indicators (scientific, population and systems data) for an antibiotic resistance information database.

Microsoft Windows-based software (WHO Surveillance Software – WHONET) can be used to enter AMR data and, for countries with Laboratory Information Systems (LIS), import data from LIS through a WHO-developed BacLink data conversion facility. WHONET is currently used in over a hundred countries worldwide.

Programmes like SENTRY, The Surveillance Network (TSN), CIPARS, CNISP, the Canadian National Centre for Streptococcus and the Canadian Tuberculosis Laboratory Surveillance System are electronic surveillance databases that collect qualitative and quantitative AMR test results from participating clinical laboratories and co-ordinated surveillance studies.

Commonwealth Secretariat / Aizuddin Saad

Progress on rapid tests for HIV, malaria and TB has not been matched in point of care tests for respiratory infections, the leading reason for antibiotics over-prescribing

Establishment of good surveillance systems to monitor trends of antibiotic resistance and antibiotic use, like the National Antimicrobial Utilisation Surveillance Program (NAUSP) in Australia, can help curtail irrational antibiotic use. The NAUSP regularly reviews drug use also in the community, advises on changes in drug utilisation patterns, disseminates information on drug utilisation and contributes to educational initiatives that promote the quality use of medicines.

Country-based networks like the 'Pakistan Antimicrobial Resistance Network' (PARN) result from collaborations with global experts and create platforms for clinicians and technicians to gather and disseminate information on infection control and antimicrobial resistance burden in hospitals. Health professionals can improve empiric prescriptions, and track rates through accessing local hospital antibiograms and learn about standard operating procedures for performing antimicrobial sensitivities.

Australia has only recently allocated funds for the development of the Australian National AMR Prevention and Containment Strategy, despite early inroads in containment efforts. India stepped towards an action plan with the groundbreaking 'Chennai Declaration', while Canada and Malaysia are other countries in the Commonwealth network with active government engagement.

Regulation

To counter irrational use of antibiotics and its contributing role in AMR spread, essential drug lists and antibiotic policies are now in place in many Commonwealth countries, such as India, Tonga, Malaysia and Canada. Tanzania's Food, Drugs and Cosmetics Act 2003 ensures the quality, safety and efficacy of all medicines in circulation since preparation of guidelines in 1997. Australia's national medicines policy includes the Pharmaceutical Benefits Scheme (PBS), which facilitates access to certain prescribed medicines by subsidising costs and providing subsidies when hospitals supply medicines to patients.

Goel et al.'s framework of interventions to improve over-the-counter antibiotic misuse can serve as a guideline for ambulatory and hospital settings in developing countries (Goel et al., 1996). Variations between country-specific requirements for pharmaceutical companies looking to register drugs in Africa decrease easy access to appropriate drugs. Expert groups such as the Alliance for Prudent Use of Antibiotics unite antimicrobial taskforces in different countries, create a common forum for infection control surveillance teams the world over and ensure that uniform messages of containment are disseminated to check the spread of resistant organisms from hospitals to communities.

Improved access to BCG, diphtheria, pertussis, Hib and pneumococcal vaccines, available in most developing countries with GAVI support, impedes the spread of AMR by preventing diseases requiring antibiotic treatment.

In-patient and out-patient clinical settings

Antimicrobial stewardship (AMS) programmes (ASPs) aim to prevent or slow the emergence of antimicrobial resistance. For example, AMS is one of several initiatives undertaken by the Australian Commission on Safety and Quality in Health Care (ACSQHC) to ensure comprehensive actions are assumed in a nationally co-ordinated way by leaders and decision-makers in both public and private health systems. Reports from Africa demonstrate a 20 per cent decrease in the volume of antibiotics and concomitant increase in laboratory tests used, but no difference in inpatient mortality or 30-day re-admission rates with the use of ASP (World Health Organization, 2009). Boyles et al. observed a 20 per cent decrease in the volume of antibiotics used with a 35 per cent decrease in antibiotic costs upon the introduction of an antibiotic prescription chart and weekly antibiotic stewardship ward round in an academic teaching hospital in South Africa (Boyles, 2013).

Laboratory support

Most laboratories with culture-based tests are not available beyond big cities in developing countries. Poor yield from paediatric blood samples and the inherent added cost has perpetuated physician practice of deferring blood cultures in practice, and treating empirically. WHO provides expertise on capacity-building in laboratories for developing countries. Available kits for rapid screening for resistant clones within laboratories need to be integrated in existing laboratory systems. Though much has been done in terms of rapid tests for HIV, malaria and Tuberculosis, there has been very little progress in validated point of care (POC) tests for bacterial infections, especially respiratory infections (RTIs) which continue to be the leading reason for over-prescribing antibiotics. An important context to consider is neonatal sepsis where the rapid emergence of extended spectrum beta-lactamase (ESBL) organisms has compromised first line empiric regimens and is already making indents in second and third line antibiotics. Okeke et al. (2011) have documented the roadblocks in developing and implementing diagnostics, and the need for developing diagnostics that provide information on antibacterial susceptibility.

Figure 1 Action plan to address antibiotic resistance containment

Health system blocks

Taskforce (federal/central command)
Can counter issues like devolution, corruption, and disconnect between policy-makers and stakeholders

LEADERSHIP / GOVERNANCE

SYSTEMS SUPPORT

Education

Syllabi
- Undergraduate
- Postgraduate
- Veterinary science

Patient education
- Appropriate health seeking
- Measures to prevent infection
- Advocacy for immunisation

Drug regulation
- Pharmacovigilance
- Veterinary Review Board
- Regulation of antibiotics in agriculture
- Drug quality and availability

Improved diagnostics
- Availability of microbiology lab services
- Quality assurance
- Timely surveillance reports reports

Data cell

Planning for:
- Evaluating programme
- Evaluating intervention

Fund raising advocacy
- Meeting stakeholders
- Appraisal of progress
- Engaging media

SYSTEMS STRENGTHENING

Finance

Medical products, technology strengthening

Antibiotic stewardship
- Lab capacity
- Point of care diagnostics
- Restrict second line drug availability without prescription
- Tracing prescription trends electronically

Vaccination

Workforce strengthening

Training and career tracks
- Lab personnel
- Hospital admin
- Physicians / nurses
- Private practitioners
- Veterinarians
  - Public sector
  - Private sector
  - Inter-sectoral

Information and research strengthening

Hardware
Software
Maintenance
Team (ICT/statistician/researcher/clinician/microbiologist/economist)
Local research
- Facility based
- Community based

Service delivery

Primary

IMNCI; point of care diagnostics; appropriate prescriptions through training

Secondary

Infection Control Committee (ICC); use of diagnostics to support diagnosis

Tertiary

ICC; surveillance; tracking and reporting

Formulary restrictions

Changing hospital antibiotic use is a problem of great complexity; however, some success has been reported from countries in the Commonwealth. Jaggi et al. (2012) found that the implementation of an antibiotic policy decreased ESBLs by four per cent (*E. coli* and Klebsiella) and carbapenem-resistant Pseudomonas by 40 per cent. Restriction on Linezolid prescriptions in Karachi Pakistan decreased drug use and related cost in a tertiary hospital in Karachi (Ahsan et al., 2011). Marshall et al. (2006) analysed the impact of limited floroquinolone disbursement on antibiotic resistance rates in Ontario Canada on community-acquired pathogens.

Research and education

Research, hospital-based and otherwise, continues to support evidence-based customised solutions to AMR. Periodic audits, in the absence of a co-ordinated data flow system, or simple interventional studies help.

Knowledge about antibiotics stewardship varies significantly among prescribers. Training should extend beyond young and seasoned clinicians to pharmacists, veterinarians, laboratory technicians, agriculturists and animal breeders. Pharmacists need appropriate training in antibiotics and AMR containment too. Educating general practitioners on generic medicines may be another step towards better use of antibiotics.

Conferences, research and idea exchanges on AMR containment provide an opportunity to multiple stakeholders – like public health experts, clinicians/prescribers, pharmaceutical companies, governments, agriculturists, veterinarians and information technologists – to assemble and network in one setting.

Gaps in governance, service delivery and research

Figure 1 shows a schematic approach to a national AMR containment strategy. Though most developed countries within the Commonwealth have AMR action plans in place, centrally co-ordinated programmes are essential for relevant data collection and timely feedback loops.

The Commonwealth can provide a platform for sharing experiences and positively campaigning for cross-ministry engagement on matters of drug regulation (animal farming and agriculture) and access to appropriate drugs for human use. It is also a viable forum for collaboration on systems research regarding appropriate means to implement ASP and formulary restrictions in hospitals and ambulatory settings, along with effective modalities for training ASP teams in resource-poor and developed settings.

Acknowledgment

Dr Fatima Mir and Dr Farah Naz Qamar received research-training support from the National Institute of Health's Fogarty International Center. We would like to thank Dr Anoosh Mian for her help with literature research.

Endnotes

1 Antigua and Barbuda in the Commonwealth Caribbean reports gram positive (GP) predominance among newborn sepsis pathogens: coagulase negative staphylococci (31.7 per cent), *Klebsiella* sp. (22.0 per cent), *E. coli* (9.7 per cent). *Streptococcus* sp. (7.3 per cent) and Group B streptococci (2.4 per cent).

2 In Commonwealth Asia and Africa, resistance ranges among newborn sepsis pathogens like Enterobacteriaceae (*Klebsiella* sp. and *E. coli*) are: 87.5–100 per cent (ampicillin), 21.8–70 per cent (gentamicin), 36–92 per cent (cefotaxime), 8.8–30 per cent (amikacin), 13–48 per cent (ciprofloxacin) and 0–5.7 per cent (imipenem). Almost one-third of community-acquired Enterobacteriaceae, have been reported as extended spectrum beta lactamase-producing strains (Chandel et al., 2011). *Pseudomonas* sp. and *Acinetobacter* sp. resistance ranges are: 56–90 per cent (gentamicin), 14–36 per cent (ceftazidime), 18–36 per cent (ciprofloxacin) and zero to 27 per cent (colistin, imipenem). Methicillin-resistant *S. aureus* (MRSA) ranges from ten to 50 per cent in Asia, but most gram-positive organisms in England were susceptible to the combination of penicillin or flucloxacillin with gentamicin, except for CoNS (Vergano et al., 2011).

3 The Asian Network for Surveillance of Resistant Pathogens (ANSORP) reports a 4.6 per cent prevalence of penicillin-nonsusceptible pneumococci (PNSP), among non-meningeal isolates, with low resistance to ceftriaxone (3.7 per cent) but high resistance to macrolides: erythromycin (72.7 per cent), azithromycin (69.7 per cent) and clarithromycin (68.9 per cent; Kim et al., 2012).

References

Ahsan, S. M., Sheikh, A. L., Mehmood, F. and Ali, F., 2011. *Rationalizing the use of linezolid through antibiotic stewardship program in a tertiary care hospital in Pakistan* [poster]. 2011 International Pharmaceutical Federation (FIP) Congress Hyderabad India.

Black, R. E., Victora, C. G., Walker, S. P. et al., 2013. 'Maternal and child under nutrition and overweight in low-income and middle-income countries'. *The Lancet*, 382(9890), pp. 427–451.

Boyles, T. H., Whitelaw, A., Bamford, C. et al., 2013. 'Antibiotic stewardship ward rounds and a dedicated prescription chart reduce antibiotic consumption and pharmacy costs without affecting inpatient mortality or re-admission rates'. *PLOS ONE*, 8(12), e79747.

Chandel, D. S., Johnson, J. A., Chaudhry, R. et al., 2011. 'Extended-spectrum beta-lactamase-producing Gram-negative bacteria causing neonatal sepsis in India in rural and urban settings'. *Journal of medical microbiology*, 60(4), pp. 500–507.

Goel, P., Ross-Degnan, D., Berman, P. and Soumerai, S., 1996. 'Retail pharmacies in developing countries: A behavior and intervention framework'. *Social Science and Medicine*, 42(8), pp. 1155–1161.

Jaggi, N., Sissodia, P. and Sharma, L., 2012. 'Control of multidrug resistant bacteria in a tertiary care hospital in India'. *Antimicrobial resistance and infection control*, 1(1), p. 23.

Kariuki, S., Revathi, G., Kiiru, J. et al., 2010. 'Typhoid in Kenya is associated with a dominant multidrug-resistant *Salmonella enterica* serovar Typhi haplotype that is also widespread in Southeast Asia'. *Journal of clinical microbiology*, 48(6), pp. 2171–2176.

Kim, S. H., Song, J. H., Chung, D. R. et al., 2012. 'Changing trends in antimicrobial resistance and serotypes of Streptococcus pneumoniae isolates in Asian countries: An Asian Network for Surveillance of Resistant Pathogens (ANSORP) study'. *Antimicrobial agents and chemotherapy*, 56(3), pp. 1418–1426.

Laxminarayan, R., Duse, A., Wattal, C. et al., 2013. 'Antibiotic resistance-the need for global solutions'. *The Lancet infectious diseases*, 13(12), pp. 1057–1098.

Marshall, D., Gough, J., Grootendorst, P. et al., 2006. 'Impact of administrative restrictions on antibiotic use and expenditure in Ontario: Time series analysis'. *Journal of health services research and policy*, 11(1), pp. 13–20.

Ochiai, R. L., Acosta, C. J., Danovaro-Holliday, M. C. et al., 2008. 'A study of typhoid fever in five Asian countries: Disease burden and implications for controls'. *Bulletin of the World Health Organization*, 86(4), pp. 260–268.

Okeke, I. N., Peeling, R. W., Goossens, H. et al., 2011. 'Diagnostics as essential tools for containing antibacterial resistance'. *Drug resistance updates: Reviews and commentaries in antimicrobial and anticancer chemotherapy*, 14(2), pp. 95–106.

Rudan, I., Boschi-Pinto, C., Biloglav, Z., Mulholland, K. and Campbell, H., 2008. 'Epidemiology and etiology of childhood pneumonia'. *Bulletin of the World Health Organization*, 86(5), pp. 408–416.

Vergnano, S., Menson, E., Kennea, N. et al., 2011. 'Neonatal infections in England: The NeonIN surveillance network'. *Archives of disease in childhood Fetal and neonatal edition*, 96(1), F9–F14.

Walker, C. L., Rudan, I., Liu, L. et al., 2013. 'Global burden of childhood pneumonia and diarrhoea'. *The Lancet*, 381(9875), pp. 1405–1416.

Waters, D., Jawad, I., Ahmad, A. et al., 2011. 'Aetiology of community-acquired neonatal sepsis in low and middle income countries'. *Journal of global health*, 1(2), pp. 154–170.

World Health Organization, 2009. *Community-Based Surveillance of Antimicrobial Use and Resistance in Resource-Constrained Settings: Report on five pilot projects*. Geneva: World Health Organization.

Zaidi, A. K., Thaver, D., Ali, S. A. and Khan, T. A., 2009. 'Pathogens associated with sepsis in newborns and young infants in developing countries'. *The Pediatric infectious disease journal*, 28(Supplement 1), S10–18.

For full references contact corresponding author Fatima Mir at fatima.mir@aku.edu.

FATIMA MIR and **FARAH NAZ QAMAR** are assistant professors in the Department of Paediatrics and Child Health, Division of Women and Child Health, Aga Khan University, Pakistan. **ZULFIQAR A. BHUTTA** is the founding director of the Center of Excellence in the Division of Women and Child Health, Aga Khan University; the Robert Harding inaugural chair in Global Child Health, Hospital for Sick Children, Toronto; and co-director of the SickKids Center for Global Child Health.