REVIEW

Role of antibiotic stewardship in extending the age of modern medicine

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Antibiotic resistance is threatening modern medicine. Overuse and misuse of antibiotics is driving resistance to such an extent that we have entered the post-antibiotic era, where some multidrug- and pandrug-resistant bacterial infections are no longer treatable. If the situation is not reversed, 10 million people will die annually of drug-resistant infections by 2050. More than just a question of mortality, such infections are causing the closure of wards, cancellation of operations, and interference with other common medical procedures that rely on antibiotics for their success. The response to this crisis requires co-ordinated international action with increased surveillance of bacterial resistance, infection prevention, and antibiotic stewardship, i.e. access to affordable, quality-assured antibiotics prescribed appropriately. This review describes antibiotic stewardship at the individual patient and programmatic level, which must be adopted by every prescriber if we are to preserve modern medicine for future generations.

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Antibiotic overuse and misuse drives resistance

A common misconception suggests that antibiotic resistance (ABR) is a result of the introduction of antibiotics from the 1940s onwards. ABR is, however, an ancient phenomenon; bacterial resistance genes have been identified in ice samples dating back 30 000 years.[1] Naturally acquired bacterial resistance genes are propagated by the survival advantage they confer on bacteria in response to attack from naturally occurring antibacterial proteins produced by other bacteria and fungi. Resistance mechanisms may also be acquired through horizontal gene transfer of mobile genetic elements on plasmids (circular pieces of extrachromosomal DNA) that carry the resistance gene(s) between bacteria.[2] A bacterium that possesses a way of resisting an antibiotic attack has a survival advantage over bacteria that do not. In the presence of an antibiotic to which that bacterium is resistant, the resistant bacterium will be selected out in favour of bacteria that are sensitive to the antibiotic. Hence, Darwinian natural selection is being played out. The antibiotics first discovered by Fleming did not create ABR – their use has provided a survival advantage to resistant bacteria. It therefore follows that the more antibiotics one uses, the more resistance will develop.

This paradox threatens modern medicine, which relies so intimately on antibiotics for its successes. Estimates suggest that antibiotics have resulted in an additional 20 years of life expectancy.[3] The use of antibiotics to prevent surgical site infection enables safe surgical procedures that would otherwise carry significant morbidity and mortality.[4] Antibiotics form an integral part of the management of high-risk patients, such as the critically ill in intensive care units, those who are immunosuppressed as a result of transplantation, chemotherapy or HIV, and those with a broad spectrum of bacterial infection – from sepsis to septic shock. For every hour a person with septic shock is not being treated with an antibiotic to which the bacteria are sensitive, mortality increases by 7.8%.[5] Mortality from antibiotic-resistant compared with antibiotic-sensitive infections is increased, as is morbidity and length of hospital stay.[6] Furthermore, resistance comes with heavy financial costs to healthcare systems; second- and third-line antibiotics are more expensive.[7] Therefore, to limit resistance we face a critical balance between the need to use antibiotics as life-saving medicines and the need to ensure their appropriate use.

We are currently in a state of crisis. Overuse and misuse of antibiotics over the past 70 years has propelled us into a post-antibiotic era. Untreatable, pandrug-resistant bacterial infections are increasingly common,[8,9] and colonisation or infection with multidrug-resistant (MDR) bacteria has changed the risk profile of patients to such an extent that medical and surgical procedures may no longer be considered.[10] We have engendered this global disaster by disregarding the basic tenet of antibiotic prescribing, i.e. 'access not excess', and by forgetting that, ecologically, antibiotics are a common pooled resource whose use, and exclusion of use through resistance, affects the global population rather than merely our patients or ourselves. Also, individuals and populations travel, and with them resistant bacteria such as New Delhi metallobetalactamase-1-(NDM-1)[11] or *Klebsiella pneumoniae* carbapenemase (*kpc*)[12] in Gram-negative bacteria, which has ensured the global spread of MDR bacteria to new, susceptible populations. People in low- and middle-income countries (LMICs), where healthcare systems are already overstretched owing to the high burden of infection, are at an even greater disadvantage than those in high-income countries (HICs).

Global response to antibiotic resistance

An international response is required to answer this crisis. The World Health Organization (WHO), whose previous calls for action went largely unheeded,[13,14] has developed a draft global action plan (GAP) as a result of wide stakeholder consultation that will be presented at the 68th World Health Assembly in Geneva, Switzerland in May 2015 for adoption.[15] GAP mandates member states to produce national strategic plans to combat antimicrobial resistance (AMR), with specific emphasis on antibacterial resistance.[16,17] Simply put, there are three fundamental pillars of any strategy that must be strengthened to combat ABR. Firstly, through strengthened surveillance and reporting, we need to learn what the resistance profile of the bacteria in our local environment (community and healthcare settings) is to enable

appropriate choice of an antibiotic that will be active against a given infection. Secondly, when a bacterium that requires treatment is identified or an empiric antibiotic(s) is needed before its identification, we must optimise the use of that antibiotic to maximise its action (antibiotic stewardship (ABS)). Lastly, we need to prevent infection before it occurs by attending to social determinants that drive infectious diseases, such as water supply and sanitation, and increase access to and coverage with vaccines. Rigorous infection control practice in healthcare settings to prevent transmission of resistant bacteria from patient to patient must be adopted, chief among which is rigorous hand hygiene. Infection prevention as it relates to ABR is comprehensively reviewed in this CME series by Brink[18] and Whitelaw.[19]

The required response is as pertinent to animal and agricultural sectors as it is to human health. As an estimated 80% of all antibiotic use is in animals[20] and its association with acquisition of resistant bacteria by humans is becoming increasingly clear,[21] we disregard the impact of antibiotic use in the animal sector at our peril. However, for the purposes of this review, I concentrate on the essential elements of ABS as it relates to bacterial infections other than tuberculosis in humans.

Antibiotic stewardship at the individual patient level

At an individual patient level, a single fundamental question needs to be asked before any antibiotic is prescribed: 'Does this patient have a bacterial infection that requires an antibiotic?' (Fig. 1.) While particularly pertinent to primary care prescribers and the continued unnecessary use of antibiotics for viral upper respiratory tract infections (URTIs), it applies equally to febrile patients admitted to healthcare institutions at all levels. The identification of intensive care patients in the public and private sectors in South Africa (SA) who were on up to 10 different antibiotics concurrently, testifies to this and the need to realise that collective action is needed.[22]

Although simpler for patients with a clear source of infection, the question of whether a patient has a bacterial infection becomes more complex when related to an undifferentiated fever, i.e. one that lacks a clear site of origin. Fear of missing a bacterial infection is a strong motivator for prescribing antibiotics,[23] whereas having access to diagnostic tests, ideally those at point-of-care (POC) to help differentiate the cause of fever, increases appropriate antibiotic use.[24,25] Access to a POC malaria rapid diagnostic test in Zambia led to a four-fold reduction in inappropriate antimalarial prescribing, and a five-fold increase in the appropriate use of antibiotics for pneumonia.[25] Furthermore, when diagnostic and resistance information is provided in a single test, not only may a diagnosis be established, but the time to appropriate antibiotic use reduced. The automated real-time nucleic acid amplification system Xpert MTB/RIF, which can confirm the presence of tuberculosis and its sensitivity to rifampicin within 2 hours, is one such example.[26] Similarly, rapid POC or close to POC non-culture-based tests for antibiotic-resistant bacteria other than *Mycobacterium tuberculosis* are urgently needed, particularly in LMICs with poor access to assured quality diagnostic services.

When the source of infection is clear, but the microbial aetiology is not, biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) may be useful tools for specific infections. Both CRP[27,28] and PCT[29,30] have demonstrated utility in differentiating bacterial from viral acute respiratory infection (ARI) in developed countries, and for PCT its use has been estimated to confer substantial economic gains (USD1.6 billion (ZAR18.8 billion) savings if used across the US health sector) in HICs.[31] In a high tuberculosis-prevalence country such as SA, the utility of CRP and PCT is less clear for ARI, as both are increased in tuberculosis. Furthermore, in a resource-challenged healthcare setting, PCT, which currently costs in excess of ZAR300 per test, is costly, particularly when used incorrectly.[32]

Once the decision has been made to treat with an antibiotic, it is imperative that, whenever possible, adequate specimens are sent to the laboratory to enable identification of the bacteria causing infection and, critically, its sensitivity profile to antibiotics (the antibiogram) before the antibiotic is administered. The likelihood of adverse effects of broad-spectrum antibiotics, whose use is commonly indicated at the start of treatment, is greater than those of directed, narrow-spectrum antibiotics that can be used once sensitivities are known. An antibiogram is a prerequisite for safe de-escalation from a broad- to narrow-spectrum antibiotic. Without it, the prescriber runs the risk of

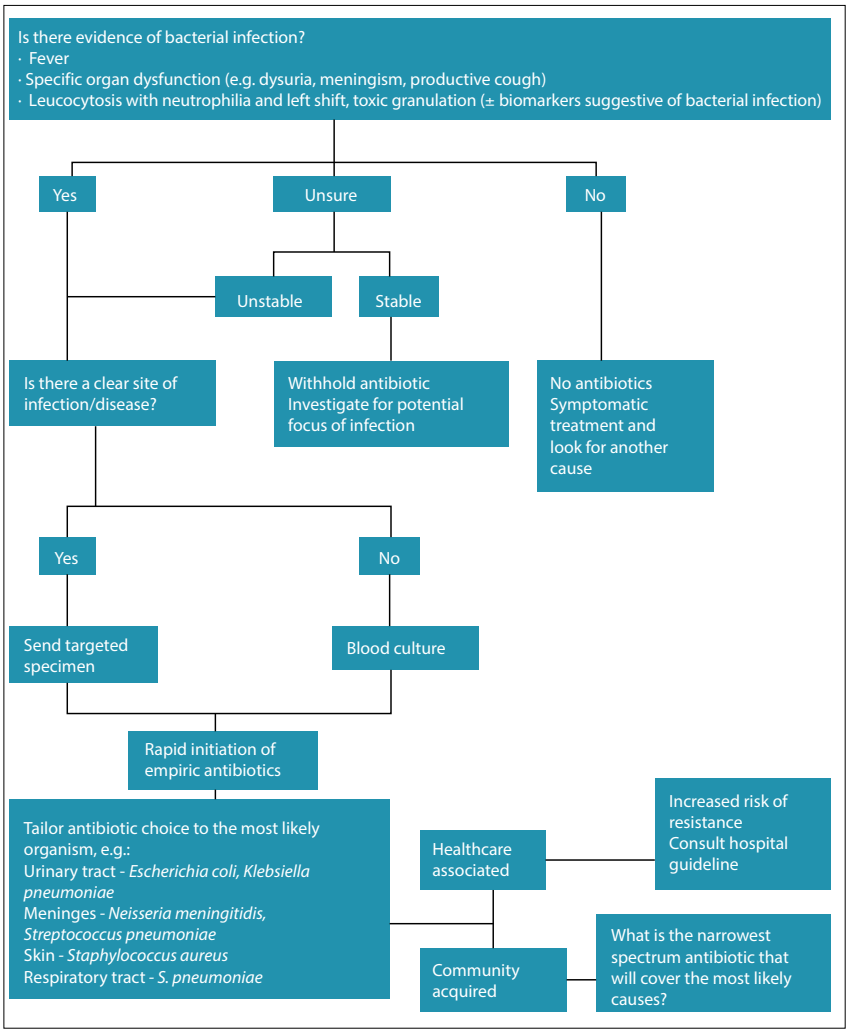

Fig. 1. Algorithm to determine whether a patient has a bacterial infection.

using a resistant or partially active antibiotic, which may negatively affect the patient's treatment. Whenever possible, a specimen from the probable site of infection should be sent to the laboratory. If no focus is evident, one or more correctly taken blood cultures are required (Fig. 1).[33] For blood cultures, the volume of blood inoculated is critical in determining yield. In an unselected cohort of adult patients requiring blood culture in the Emergency Department at Groote Schuur Hospital, Cape Town, all cultures were negative if <2 mL of blood were inoculated. The yield doubled if 10 - 12 mL were inoculated compared with 2 - 8 mL (T Boyles – personal communication).

Once appropriate cultures have been sent, considering the checklist presented in Box 1 can optimise prescribing. The empiric choice of an antibiotic is determined by the probable identity of the infecting organism and the likelihood of it carrying a resistance gene. For example, Gram-negative Enterobacteriaceae (*Escherichia coli* and *Klebsiella pneumoniae*) commonly cause urinary tract infections (UTIs); therefore, an antibiotic with a spectrum of activity against Gram-negative bacteria is advised. Resistance to commonly used Gram-negative antibiotics for UTI in community-acquired infections in SA is generally still low, but does vary geographically. Therefore, an antibiotic such as an aminoglycoside or ciprofloxacin would be an acceptable empiric choice. However, in SA, hospital-acquired UTI due to Enterobacteriaceae is characterised by high levels of extended-spectrum beta-lactamase production, rendering many resistant to first-line antibiotics, and forcing the use of second-line, broader-spectrum antibiotics.

The optimal dose of an antibiotic depends on a number of factors, including the pharmacodynamic and pharmacokinetic properties associated with individual antibiotics, the patient's body weight, renal function, and, less commonly, hepatic function. Dosing of many antibiotics is weight dependent, e.g. vancomycin (Box 2), whose dosing frequency must be guided by therapeutic drug monitoring. A lack of attention to weight-based dosing and renally determined dosing frequency represents a common antibiotic prescribing pitfall. Pharmacokinetics play an especially important role in the critically ill patient in whom the volume of distribution may increase, augmented renal clearance may be present, and hypoalbuminaemia may alter the ratio of bound v. unbound antibiotic. Hence, dose must be carefully considered to optimise the effect of the antibiotic, particularly in those who are critically ill.

For many prescribers, determining the duration of an antibiotic course is a matter of what is familiar or easy, and bears little or no relation to trial evidence or national guidelines. Therefore, many antibiotic courses are prescribed for ≥1 week. For example, experience from our ABS programme at Groote Schuur Hospital indicated that the vast majority of patients in the Emergency Department who were prescribed ceftriaxone received a prescription for an antibiotic for 2 weeks, irrespective of the indication (M Mendelson – unpublished observations). Unfortunately, a strong evidence base for antibiotic duration is often lacking, meaning that decisions are based not on randomised controlled trials, but on small observational studies or expert opinion. In SA, the Essential Drugs List (EDL) and Structured Treatment Guidelines (STGs)[34]

Box 1. Checklist for optimal antibiotic prescribing

1. Drug – which is the narrowest spectrum antibiotic that I can use to treat this bacterial infection?
2. Dose – many antibiotics require weight-based dosing and their dosing depends on renal and/or hepatic function
3. Dose frequency – dependent on the half-life of the drug and whether the action of the antibiotic depends on the time above the MIC or the area under the concentration/time curve. Calculation of the dosing frequency may require therapeutic drug monitoring, such as for vancomycin or aminoglycosides
4. Duration – should be dictated by evidence from randomised controlled trials whenever possible. Expert opinion from national and international guidelines should be consulted where evidence is weak
5. Route – most antibiotics have good oral bioavailability, but some infections will require intravenous therapy either for the whole or part of the course
6. De-escalation – applies to the spectrum of antibiotic use and route of administration. All attempts to convert early from parenteral to oral use should be made

MIC = minimum inhibitory concentration.

Box 2. Vancomycin dosing

All patients should be weighed and GFR estimated

All patients should receive a loading dose of 25 - 30 mg/kg

All subsequent doses should be 10 - 15 mg/kg (unless inadequate trough levels achieved)

Dosing interval and measurement of trough concentrations depends on eGFR

eGFR (mL/min)	Dosing interval (hours)	Measurement of trough concentrations
>80	12	Before 3rd dose
50 - 79	24	Before 3rd dose
55 - 49	36	Before 2nd dose
25 - 34	48	Before 2nd dose
<25, haemodialysis or chronic ambulatory peritoneal dialysis	When trough level <15 μg/mL	3 days after loading dose

Aim for trough concentration of 10 - 20 μg/mL, except for osteitis or endocarditis, or if MIC >1 μg/mL, when trough should be 15 - 20 μg/mL

If trough is too low – increase the dose

If trough is too high – increase the dosing interval

eGFR = estimated glomerular filtration rate.

Box 3. Criteria for switching from parenteral to oral antibiotic route[61,62]

1. No indication requiring long-term parenteral antibiotic use: endocarditis, meningitis, central nervous system infection, osteomyelitis, prosthetic material infection, *Staphylococcus aureus* bacteraemia, undrained or undrainable abscess and neutropenic fever
2. Patient is able to take oral medications and lacks indications of potential malabsorption
3. An alternative oral antibiotic is available
4. Temperature <38°C for ≥24 hours
5. Clinically improving or remaining stable

may guide prescribers. The SA Antibiotic Stewardship Programme (SAASP) guidelines for antibiotic prescribing in adults,[35] which is aligned to the EDL and STGs, provide an algorithmic approach to prescribing and further information on treatment duration. It is now available as the 'SAASP' App across platforms.

The route of administration of an antibiotic depends on the site of infection, how rapidly high drug levels need to be achieved, and ability of a patient to absorb an oral antibiotic. Some infections, such as bacterial meningitis, osteomyelitis or endocarditis, require high levels of antibiotic to be delivered to the site of infection, and necessitate parenteral antibiotics for all or the majority of the course. De-escalation to an oral antibiotic is a key principle of stewardship, as this obviates the need for vascular access and enables removal of a peripheral or central line. This reduces the risk of central line-associated bloodstream infections (CLABSI) or its peripheral counterpart. Prevention of CLABSI reduces morbidity, length of hospital stay and, ultimately, mortality.[36] Box 3 gives guidance for safe de-escalation from the parenteral to oral route.

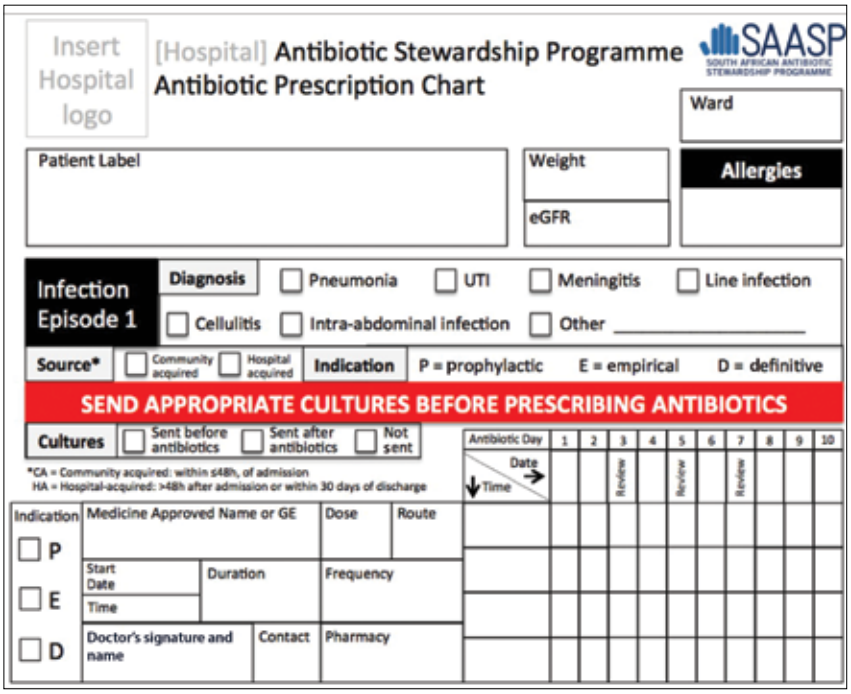

Fig. 2. South African Antibiotic Stewardship Programme prescription chart.

Antibiotic stewardship at the programmatic level

At a programmatic level, interventions to reduce antibiotic prescribing and improve microbial outcome tend to be either restrictive (limit how a prescriber prescribes) or persuasive (advise the prescriber or give feedback about how they prescribed).

Approximately 80% of antibiotics used in humans are prescribed in primary care.[37,38] The success of interventions at the community level depends in part on the barriers to change in that particular community and differs in countries and across borders. A meta-analysis of 39 studies of interventions to improve antibiotic prescribing in ambulatory patients concluded that multi-faceted interventions are most effective at achieving overall reduction in use, while printed educational material or feedback and audit were of little value.[39] Interactive educational sessions outperformed the didactic approach, and collaborative educational meetings between different groups involved in prescribing, i.e. a multidisciplinary community stewardship approach, showed promising reductions in antibiotic prescribing.[40] Combining teaching of primary care clinicians in enhanced consulting skills and the introduction of POC CRP into their practices, had an additive effect on appropriate, safe antibiotic prescribing, which was cost-effective.[28,41] The use of delayed prescriptions effectively reduced antibiotic use without increasing mortality.[42-44] All of these interventions are potentially transferable to LMICs, including SA.

Successful interventions to reduce prescribing in hospitalised patients have also been the subject of a Cochrane review.[45] Poor study designs in many investigations limited the number of studies included in the analysis to 20%. There were no direct comparative studies between persuasive and restrictive interventions, but a meta-analysis of interrupted time series studies allowed comparison. Interestingly, restrictive interventions (compulsory order forms, expert approval, removal by restriction and review and change) were more effective than persuasive (dissemination of educational material, reminders, audit and feedback, and educational outreach) interventions in the first 6 months; yet, there was no difference in the longer term at 12 and 24 months. Whether combinations of intervention type would have a sustained effect needs to be investigated.

It is notable that none of the studies included in the Cochrane review was from Africa. ABS has only recently been formally introduced in SA as a change mechanism, led by SAASP since 2012. One study published to date has adopted two persuasive interventions to augment restrictive practices that were already in place at a central hospital in Cape Town;[32] ABS ward rounds and a dedicated antibiotic prescription chart were included in a trial in two general medical wards for a 12-month period, using the previous intervention-free year as comparator. Weekly multidisciplinary ward rounds involved the prescribing physicians, an infectious diseases specialist, microbiologist, infection control officer, and pharmacist. The charts and case

reports of each patient on a single ward, alternating weekly, were reviewed. Antibiotic use was reduced by 19.6% without an increase in inpatient mortality or 30-day readmission rate. Although not a primary objective of the study, the intervention resulted in a 35% reduction in antibiotic budget. This type of multidisciplinary team is unlikely to be reproducible across SA and most developing country settings; however, a prescriber and pharmacist can form the nucleus of any such stewardship team.

A dedicated antibiotic prescription chart in the study by Boyles *et al.*[32] was designed to focus the prescriber's attention on the indication for prescribing antibiotics, whether the infection was community or hospital acquired, and provided strong messaging to trigger appropriate sample(s) to be sent for culture (Fig. 2). Antibiotic prescribing was divided into infection episodes – if a patient developed a second or third bacterial infection in hospital, the prescriber would have to go through the same process again, and the antibiotics used to treat that infection could immediately be identified for review and audit. The use of choice architecture, which describes the way in which decisions can be influenced by how choices are presented,[46] was recently used to improve anti-infective prescribing in a comparative study from a large UK teaching hospital.[47]

Through its national strategic plan for AMR,[48] SA has national core standards for antimicrobial stewardship (and for infection prevention control) that will be monitored by the Office of Health Standards and Compliance. These standards include the requirement for stewardship committees and teams in all our hospitals and at district level. A clear roadmap for change is being implemented.

Barriers to antibiotic stewardship

Behaviour modification is a major factor in rectifying poor prescribing practice. Inappropriate prescribing is driven by a complex set of prescriber and patient behaviours. At the most basic level, community prescribing is often influenced by prescribers who perceive that their patients will be dissatisfied should they not receive an antibiotic. This is especially evident in how doctors perceive parental expectations.[49] Patient expectations of receiving an antibiotic, particularly for ARI, is often high, and these have a significant influence on prescribing, even when the prescriber believes that an antibiotic is unnecessary.[50,51]

Raising public awareness to the risks posed and drivers of ABR is an important intervention. Yet, not all campaigns have been successful;[52] national campaigns in different European countries have had mixed results, with those in Germany, Spain, Greece and the UK being unsuccessful in leading to important reductions in community antibiotic use or knowledge about appropriate use, as opposed to those in Sweden, Norway, France and Belgium. Successful national campaigns are characterised by a multifaceted nature and repetition over several years. Unfortunately, there seems to be no simple relationship between knowledge and appropriate use; in a face-to-face household survey of 10 981 randomly selected UK adults in 2003, multivariate analysis found that better knowledge in women was associated with being more likely to give an antibiotic to someone else for whom it was not prescribed.[53] This endorses the fact that behaviour change is complex and more than merely about providing information.

In terms of creating public behavioural change, despite media campaigns being more successful at disseminating information, medical professionals are more successful in changing patient behaviour.[54] Potential behavioural changes in community prescribers include improving their belief in the consequences of overprescribing and addressing their concerns around the consequences of not prescribing. Encouraging patients to adopt self-care for symptomatic relief of URTIs by consulting pharmacists instead of requesting antibiotics from doctors and greater mentoring of patients on their antibiotic use have the potential for creating change in antibiotic use at the community level.

To enable good stewardship, prescribers must have access to affordable antibiotics of assured quality. Producing a new antibiotic pipeline is not in itself the answer to the ABR problem, as resistance has developed within 16 years of every antibiotic introduced to date;[55] penicillin resistance was first identified 3 years before the antibiotic was introduced. However, lack of access to antibiotics is a major cause of mortality, mainly in children <5 years of age, of whom more currently die of pneumonia owing to a lack of available treatment than of ABR. Substandard and falsified antimicrobials have undermined prescribing in these countries, as has the lack of affordable medicines, whereas the use of generic medicines has successfully driven down cost.[56] Generics produced locally to rigorous good manufacturing practice standards may enhance access to quality-assured antibiotics and thus save lives.[57-59] A strong medicine regulatory authority is a prerequisite to ensure the success of a generic antimicrobial policy.

Conclusion

The development of ABR cannot be prevented, but the extent to which it impacts on modern medicine can be altered through access to assured-quality, affordable antibiotics used in an appropriate manner. The onus is on every prescriber to become an antibiotic steward, ensuring that an antibiotic is only prescribed for a bacterial infection that requires treatment, and that the use of that antibiotic is optimised at an individual patient level. Programmatically, ABS must be developed as part of a national plan along with enhanced surveillance, reporting and infection prevention initiatives. Behavioural change programmes aimed at supporting prescribers and changing patient expectations are critical interventions, as is the need for increased access to diagnostic services and the development of POC or near-POC rapid diagnostics that couple pathogen and resistance information.

If we are to alter the course of history, and prevent a situation where 10 million people die annually from antibiotic-resistant infections by 2050,[60] prescribers and public alike need to join the international community in change to preserve this precious resource.

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