Strategies to improve the management of upper respiratory tract infections and reduce inappropriate antibiotic use particularly among lower and middle-income countries; findings and implications

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ABSTRACT

Introduction: Antibiotics are indispensable to maintaining human health; however, their overuse has resulted in resistant organisms increasing morbidity, mortality and costs. Increasing antimicrobial resistance (AMR) is a major public health threat resulting in multiple campaigns across countries to improve appropriate antimicrobial use. This includes addressing the over use of antimicrobials for self-limiting infections such as upper respiratory tract infections (URTIs), particularly in lower- and middle-income countries (LMICs) where this is greatest inappropriate use and where antibiotic utilisation has increased the most in recent years. Consequently, there is a need to document current practices and successful initiatives in LMICs to improve future antimicrobial use.

Methodology: Documentation of current epidemiology and management of URTIs particularly in LMICs as well as campaigns to improve future antimicrobial use. **Results**: There is still considerable concern regarding the prescribing and dispensing of antibiotics for URTIs among LMICs. This includes considerable self-purchasing, up to 100% of pharmacies in some LMICs. However, multiple activities are now ongoing to improve future use. These incorporate educational initiatives among all key stakeholder groups as well as legislation and other activities to reduce self-purchasing as part of National Action Plans (NAPs). Further activities are still needed though. These include increased

physician and pharmacist education starting in medical and pharmacy schools, greater monitoring of prescribing and dispensing practices including the development of pertinent quality indicators as well as targeted patient information and health education campaigns. It is recognised that such activities are more challenging in LMICs given more limited resources and a lack of healthcare professionals. **Conclusion**: Initiatives will grow across LMICs to reduce inappropriate prescribing and dispensing of antimicrobials for URTIs as part of NAPs and other activities, and these will be monitored

1. INTRODUCTION

The development of antimicrobial resistance (AMR) is a major issue world-wide, associated with increasing morbidity, mortality and health care costs (1-16). Globally, the irrational, indiscriminate, and excessive use of antibiotics, including for self-limiting infections, is a key driver of increasing AMR rates and a considerable public health concern (4, 9, 17-30). Such concerns are exacerbated by the spread of AMR from one geographic locality to others resulting in resistance to reserve antibiotics including colistin together with a number of organisms including *Klebsiella pneumoniae, Escherichia coli*, *Salmonella typhi* and *Neisseria gonorrhoeae* growing (18, 31-36). As a result, bacteria causing severe health problems have become resistant to multiple antibiotics during the past 20-30 years (18, 37, 38). This overuse urgently needs addressing alongside the development and implementation of guidelines to restrict the use of key antibiotics as well as reduce their inappropriate use (39-41).

High AMR rates are a particular issue in LMICs, exacerbated by poor hygiene, malnutrition and overcrowded living conditions, lack of adequate infrastructures and pressure by patients and carers on physicians to prescribe antibiotics and on pharmacists to dispense them without a prescription (13, 14, 19, 21, 42-55). Unfortunately, antibiotics can achieve good health outcomes even in patients with viral infections, which runs counter to changing public perceptions of their efficacy (56-59). Concerns with rising rates of AMR, coupled with the continued irrational use of antibiotics to treat self-limiting infections such as upper respiratory tract infections (URTIs), have resulted in multiple initiatives internationally, regionally, and nationally aimed at reversing current trends (6, 8, 21, 36, 40, 60-74).

URTIs, which include infections of the nose, nasal cavity, pharynx, and larynx with the subglottic area of the trachea, are the most common infections seen in ambulatory care (17, 28, 75-83). The majority of these infections are viral in origin, involving any part [more or less] of the upper respiratory tract (80, 83-88), and will typically resolve without the use of antibiotics (21, 83, 85, 89-95). Consequently, the inappropriate use of antibiotics in respiratory tract infections (RTIs) will appreciably enhance AMR rates with antimicrobial use in RTIs seen as the greatest misuse of antimicrobials worldwide (88, 96).

Sub-optimal management of URTIs in LMICs including the overuse of antibiotics is promoted by misconceptions, social-cultural issues, diagnostic uncertainty, and clinical competency as well as commercial, patient and time pressures (21, 29, 50, 52, 57, 92, 96-109). Inappropriate management is also a concern in countries with high rates of infectious diseases such as HIV, malaria and tuberculosis (TB), which is the case in sub-Saharan Africa, as this may complicate treatment (110-112). Certain antibiotics temporarily suppress symptoms of TB, leading to delays in diagnosis and patients potentially receiving several antibiotics due to the wrong clinical diagnosis (113). Ideally, patients with TB should be referred by pharmacists to specialists if patients first visit them. However, such activities can be very variable and may depend on whether patients have suspected or confirmed TB (113, 114). Development of AMR in patients with RTIs and other underlying infectious diseases can increase morbidity and mortality; consequently, antibiotic use in such patients needs to be carefully managed (115).

In view of growing AMR rates and the implications of this, there is an urgent need to review key issues relating to the use of antibiotics for patients with URTIs as well as potential strategies to reduce irrational use to guide future activities. This is because a considerable proportion of antibiotics prescribed and dispensed worldwide are in ambulatory care, and, as mentioned, predominantly for URTIs (21, 82, 85, 88, 90, 116-118). There is also a need to focus on LMICs, including sub-Saharan Africa, because infectious disease rates are higher in LMICs than in developed countries, there is extensive self-purchasing of antibiotics in LMICs because of their relatively easy availability, and issues surrounding their inappropriate use have been less well researched and understood in LMICs compared with higher income countries (43, 45, 49, 100, 104, 119-124). In addition, a considerably higher percentage of patients with URTIs are inappropriately treated in LMICs compared with high income countries (88). In addition, much of the increase in antibiotic consumption in recent years has been in LMICs including Brazil, China, India and South Africa (11, 125-127). Overall between 2000 and 2015, worldwide consumption of antibiotics increased by 65%, driven principally by increased rates in LMICs (11, 12).

Self-purchasing of antibiotics, sometimes referred to as 'non-prescription sales', can be a particular concern in terms of the accuracy of diagnosis and the over-use of antibiotics, enhanced by issues of accessibility, affordability (i.e. whether patients can afford to see both a physician and purchase their medicines) and economic benefits. In addition in some situations, pharmacists are the only healthcare professional available to patients (47, 128-141). Self-purchasing of antimicrobials is particularly problematic in LMICs compared with high income countries (49, 52, 120, 121, 123, 142, 143).

Consequently, the principal objective of this paper is to document and debate key issues surrounding antibiotic use, including misuse, in ambulatory care patients with URTIs in LMICs to provide future guidance. The includes identifying and building on suggested activities from the published literature supplemented by knowledge and experience from key senior personnel working in this area across LMICs. We did not consider the quality of available antibiotics in this paper, which have resulted in concerns with generic antibiotics and/ or counterfeit medicines, as these issues have been extensively explored elsewhere (144-148). We also did not consider antibiotic availability, which can also be a concern in LMICs (149). The key issue discussed in this paper is potential ways to reduce rising AMR rates given the high global priority via the appropriate management of URTIs in LMICs (29, 88, 125, 150).

We are aware that an appreciable number of publications and ongoing research already exist discussing potential ways to improve antibiotic utilization especially in LMICs, which includes improved surveillance (29, 45, 61, 66, 85, 100, 119, 120, 151, 152). A number of systematic reviews regarding the management of URTIs and ways to improve both the prescribing and dispensing of antibiotics for patients with URTIs have also been published (21, 43, 45, 57, 61, 74, 85, 108, 153, 154). These include systematic reviews determining possible reasons behind dispensing antibiotics without a prescription (141, 155), patient-related determinants regarding antibiotic use (156), and reviews assessing the influence of targeted communications among patients to reduce excessive antibiotic use (157). In addition, there are initiatives such as GRIP (Global Respiratory Infection Partnership Declaration) to help reduce unnecessary antibiotic utilisation through recommending non-antibiotic treatments for patients with URTIs (158, 159). However, we believe to date there have not been any publications that have comprehensively focused on all aspects of prescribing and dispensing of antibiotics for URTIs in LMICs, which can be very different to high income countries with different practices and beliefs. In addition, few reviews have contextualised the findings from multiple authors from a wide range of LMICs to provide future guidance building on WHO and other international initiatives. Consequently, we believe our findings and the implications should be of interest to all key stakeholders in LMICs seeking ways to improve antibiotic utilization among their patients with URTIs.

2. METHODOLOGY

A systematic review was not performed as there have already been an appreciable number of recent publications, including systematic reviews, discussing ongoing research in this area, which includes current self-purchasing rates as well public awareness campaigns (29, 43, 45, 49, 57, 61, 66, 74, 85, 100, 108, 119, 120, 123, 141, 151-157, 160).

Consequently, our findings and suggested activities for key stakeholder groups is based on relevant publications known to the authors, coupled with their considerable knowledge of ongoing activities in their own countries (and more broadly) to improve the prescribing and dispensing of antibiotics for patients with URTIs. This approach has been used successfully to stimulate debate in other priority healthcare areas to provide future guidance (161-171).

The 2018 World Bank classification was used to break countries down into LMICs or upper income countries where applicable (172) (Supplement - Table A). Upper income countries are only commented on where pertinent. This is because typically there are different practices, cultural beliefs as well as a greater availability of healthcare professionals in higher income countries. In addition in LMICs, the costs of medicines can account for up to 70% of total healthcare expenditure, much of which is out of pocket (173-175). This is again very different to high income countries where typically expenditure on pharmaceuticals is 15% or less of total healthcare expenditure and there is often universal healthcare (176, 177). There can also be long waiting times to see physicians in primary healthcare centres (PHCs) in LMICs, as well as long distances to travel to PHCs, putting time pressures on physicians as well as patients to seek alternative approaches including community pharmacists and private physicians (49, 69, 98, 178-182).

We have not documented prescription rates for antibiotics to treat URTIs in LMICs in view of the difficulties with obtaining reliable data as well as high rates of self-purchasing of antimicrobials. However, this is starting to be addressed in LMICs (183). We have though documented the impact of different interventions and initiatives where published to provide future direction. We have also not divided LMICs into different continents and regions as they share many of the same characteristics.

3. Results

The aetiology of URTIs and their symptoms will first be discussed followed by known prevalence rates for URTIs and factors influencing their prescribing to provide a background before discussing the management of URTIs in LMICs including non-prescription sales. This will be followed by documenting and debating potential strategies to reduce the irrational use of antibiotics to treat URTIs in LMICs to provide future direction.

3.1 Aetiology of URTIs and Symptoms

URTIs can develop from 24-72 hours of neonatal life right up to an advanced age, with a number of viruses implicated (184-189). The principal invading viruses include the human rhinovirus/enterovirus, respiratory syncytial virus, the parainfluenza virus, adenovirus, coronavirus and the H1N1 flu virus (185-187, 190). However, there can be bacterial involvement, including *Group A beta-haemolytic Streptococcus*, *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis* and *Mycoplasma pneumoniae* (138, 185, 188, 191-193).

URTIs are often reported as a minor health problem (184). For instance, the common cold is viral in origin and generally mild and self-limiting, with patients typically improving within 7 to 10 days of onset (99, 189, 194, 195) . Children of six years or below are the most vulnerable to develop a common cold, with young children typically having six to eight cold episodes per year, whereas

adults typically have only two to three common colds a year (189). Smokers generally suffer the symptoms of URTIs for longer than non-smokers (194).

Typically, a medical consultation is not needed for URTIs if symptoms resolve within ten days since, as mentioned, URTIs are frequently viral in origin, generally self-limiting and hardly ever life-threatening (88, 196, 197). However, some children can develop pneumonia, which requires hospitalisation and specialised treatment (198). Despite URTIs generally being a minor illness, they do result in an appreciable number of medical consultations globally (87, 199-203). The number of healthcare consultations combined with parental and patient pressure enhances antibiotic use for URTIs including LMICs thereby increasing AMR rates (88, 153, 200, 204-209). Patients who are concerned about their or their child's respiratory illness are likely to seek treatment, and likely to want an antibiotic, especially if they perceive the illness as severe (21, 209, 210). As mentioned, extra care is needed for patients with underlying infectious diseases such as HIV, malaria and TB, especially in tropical countries. These infections may compound the diagnosis and treatment of URTIs particularly where no laboratory facilities for definitive diagnosis are available. For example, a study undertaken in Kenya in a malaria endemic zone at the peak malaria infection period demonstrated a high rate of viral respiratory tract infections (52%) among children suspected of having malaria using clinical symptoms only (211). These children are more likely to be treated for malaria than URTIs as it was demonstrated they had gained immunity to plasmodium parasites by being in a malaria endemic zone (211).

3.2 *Epidemiology of URTIs*

It is difficult to fully estimate the prevalence of URTIs especially in LMICs where extensive self-purchasing of antibiotics occurs (42, 43, 49, 123, 212). Overall, the incidence and prevalence of URTIs varies considerably across and within countries and across age groups, although children from newborn to four years are at the highest risk of developing a URTI (69, 188, 213-218). Females may be at more risk of developing URTIs than males; however, this is not always the case and may depend on the patient's age (189, 213, 215, 219).

Supplement Table B in the Appendix contains further details of epidemiology rates for URTIs in both high income countries as well as LMICs.

3.3 *Factors influencing antimicrobial utilization in URTIs*

Group A beta-haemolytic streptococcus (GABHS) is the most common bacterial cause of acute pharyngitis; however, culture and sensitivity testing (CST) can take up to 48 hours for the results and an appreciable number of URTIs are viral in origin anyway (220-222). However, rapid antigen detection tests (RADTs) for GABHS take only 5 to 10 minutes to perform and can reduce unnecessary antibiotic prescribing (222). Consequently, their use is likely to grow in the future (152). Alternatively, clinical scoring systems such as FeverPAIN or Centor criteria help to reduce inappropriate prescribing of antibiotics for acute sore throats, including acute pharyngitis (223, 224).

3.3 *Physician management of URTIs in LMICs*

Ideally, physicians should consider multiple issues when treating patients with URTIs including the potential use, delayed use or misuse of antibiotics (151, 192, 225-227). This is especially important as there is no perceived clinical benefit from the use of antibiotics in the treatment of URTIs in many patients, including those with a common cold or persistent acute purulent rhinitis, with evidence of significant adverse events in adults from antibiotics (21, 27, 85, 228). However, as mentioned, there is a need for care in patients with other underling infectious diseases such as HIV, malaria, and TB.

Despite this lack of benefit, considerable prescribing and dispensing of antibiotics still occurs for patients with URTIs especially in LMICs (21, 87, 88, 92, 120, 209, 227, 229, 230), although rates vary appreciably across countries. For example, Holloway et al found in their recent review that the rates of treating URTIs inappropriately in children in LMICs were high, with the use of antibiotics ranging from 42% to 72% of patients (97), and Ahiabu et al found that 86.4% of patients with URTIs attending primary healthcare facilities in Ghana were prescribed an antibiotic (231). Table 1 documents prescribing practices for patients with URTIs across a range of LMICs whilst Table C in the Supplement contains details of prevalence rates from a number of higher income countries for comparative purposes.

Table 1: Prescribing Practices for Patients with Respiratory Tract Infections among LMICs

Country	Antibiotic utilization
LMICs (8 countries)	33% of children under five in eight LMICs were reported to have either a cough or fever in the past two weeks, with 86% of young children attending health facilities being prescribed an antibiotic (amoxicillin – 38.0%, cotrimoxazole 27.8%) for their respiratory infection (183)
Botswana	72.9% of ambulatory care patients in the private sector had at least one antibiotic dispensed for a URTI (180, 232).
China	Among physicians working in rural China, the antibiotic prescription rate for children with URTIs was 84% before multiple interventions to reduce inappropriate prescribing (88)
Ghana	An audit of antibiotic prescriptions among four public and private PHCs showed that over 86% of patients diagnosed with an URTI were prescribed an antibiotic, mostly a broad-spectrum antibiotic (231).
India	• 45% of patients in the public sector and 57% of patients in the private sector with acute respiratory tract infections were prescribed at least one antibiotic (233) • In another study, 46% of patients had taken an antibiotic for a URTI, either prescribed or self-purchased (234)
Namibia	• The rate of antibiotic prescribing among patients with URTIs at a regional referral hospital was 78% (235) • This was no doubt enhanced by current antibiotic policies in Namibia promoting the over-prescribing of cotrimoxazole, amoxicillin and azithromycin in the public sector (236)
Nigeria	• 56.4 % of physicians surveyed treated children with a sore throat empirically with an antibiotic. This was despite a similar percentage of physicians believing viruses were the commonest cause of pharyngitis (237) • In a study conducted among 423 nursing mothers, the authors reported the use of unprescribed antibiotics for the treatment of URTIs in 75.9% of cases (238)
Malaysia	• Study one (2015) - In the public healthcare system, 31.8% of prescriptions for a URTI included an antibiotic, an improvement though on previous studies (over 60%) (69) • Study two (2015) - Among GPs in the private sector, 49.6% felt antibiotics were helpful in treating URTIs, with most GPs believing patients expected an antibiotic for a URTI enhancing their use (98) Study 3 (2016) (239) • Among both private and public primary care clinics, there is greater prescribing of antibiotics in private clinics

	• URTIs were the most frequent diagnosis in patients receiving an antibiotic, accounting for 49.2 % of all prescriptions • Of those diagnosed with an URTI, 46.2 % received antibiotic treatment greater in private (57.7%) versus public (16.8 %) clinics with penicillins, cephalosporins and macrolides the most commonly prescribed antibiotics
Zimbabwe	37% of nurses, who are often involved in managing patients in public health care centres in sub-Sahara Africa, believed antibiotics accelerated recovery in patients with influenza, enhancing their overuse (240)

NB: RTI = respiratory tract infection; URTI = upper respiratory tract infection

Among LMICs generally, considerable self-purchasing of antibiotics still occurs. This averages 38.8% to 58% across countries, with higher rates seen in some continents including Africa and South America (43, 49, 120, 142, 143). However, rates do vary across and within countries, as well as populations within countries. Supplement Table C gives details of a range of prevalence rates for non-prescription sales of antibiotics for common diseases, including respiratory infections incorporating URTIs, among LMICs.

Self-purchasing of antibiotics for URTIs is encouraged by misconceptions about them and their usefulness in managing this condition, which for instance was seen among more than 75% of Thai students in a study pulished in 2012 (241). Common infections for non-prescription sales of antibiotics in systematic reviews include URTIs (up to 50 – 67% of patients) or fever (47%) (43, 120). Having said this, there have been low rates of non-prescription sales of antibiotics in some LMICs in the past. For example, in a study of community pharmacists in Zimbabwe published in 2007, the authors found that the majority of pharmacists (69%) stated that they would never sell an antibiotic without a prescription and very few did despite high patient demand (115). However, in recent years this has changed with appreciably higher self-purchasing rates (242).

3.4 Ongoing and potential strategies to reduce inappropriate prescribing and dispensing of antibiotics for patients with URTIs

Multiple strategies are typically needed to reduce unnecessary prescribing and dispensing of antibiotics in ambulatory care among all key stakeholder groups including patients, parents, community pharmacists and physicians (29, 40, 52, 60, 70, 71, 74, 97, 154, 243). This reflects the complexity of the situation, the different beliefs of key stakeholder groups and often multiple organizations and personnel within a country involved with improving antibiotic utilization and reducing AMR rates (244). Additional strategies include influenza and conjugated pneumococcal vaccine policies, which can help reduce the risk of acute respiratory infections and any associated irrational use of antibiotics (87, 245-247).

The public, patients and children's parents are a particularly important group to improve appropriate antibiotic use in patients with URTIs given for instance the extent of self-purchasing in LMICs (Supplement Table D) as well as patient pressure on physicians to prescribe antibiotics. Studies have highlighted that patients can have an incomplete understanding of antibiotics and AMR, misconceptions about the causes of AMR, and an inappropriate belief that the overuse of antibiotics does not contribute to the development of AMR adding to physician and pharmacist pressures (56, 59, 98, 248).

Different strategies and approaches have had varying success across countries to improve the utilisation of antibiotics in ambulatory care. Successful initiatives typically target all key stakeholder groups, are usually country specific, take into account issues of culture as well as the availability, access and affordability to physicians and medicines, and are evidence based (29, 52, 243). Given continuing concerns with AMR rates, activities and strategies to improve future prescribing and

dispensing of antibiotics for URTIs will grow in all countries, including LMICs, as they develop and monitor their antibiotic prescribing as part of their national action plans (NAPs) (66, 180, 240, 242, 249-252), with 'essential medicine' policies typically associated with lower antibiotic prescribing in LMICs (119).

Various activities by key stakeholder groups, including health authorities, physicians, nurse practitioners, pharmacists and the public, and their influence are described below to inform future activities to reduce irrational antibiotic use.

3.4.1. *Health Authorities and Governments*

Health authority and government activities are particularly important to enhance rational antibiotic use. These include addressing issues of self-purchasing and pharmaceutical company promotional activities as these can have a profound impact on subsequent antibiotic utilisation (102, 119, 253).

However, despite this importance, to date some countries have only introduced limited activities to reduce the inappropriate use of antibiotics. In Europe, this includes Poland, which resulted in Poland currently having one of the highest rates of antibiotic consumption across Europe, with utilization growing by 8.3% from 2007 to 2016 (38). In addition, some LMICs have only just published their NAPs to improve future antibiotic prescribing, including patients with URTIs, as part of agreed objectives to reduce AMR rates. Typical activities include documenting current antibiotic utilisation and resistance rates alongside planning educational, monitoring and other activities among all key stakeholder groups. Such LMICs include Botswana, Ghana (Table 2), Kenya, Kosovo, Malaysia, Nigeria, Pakistan, Swaziland, Vietnam and Zimbabwe (72, 180, 251, 252, 254-257).

Kosovo has recently launched its NAP to reduce AMR. Activities include increasing education of all key stakeholder groups, improving the monitoring and use of antibiotics as well as promoting research to improve the future use of antibiotics (72).

Malaysia has also recently implemented the Protocol of Antimicrobial Stewardship (AMS) Program in Healthcare Facilities, together with National Antibiotic Guidelines, to improve antibiotic utilisation particularly in ambulatory care (236-238). These guidance documents should benefit clinicians and pharmacists in advocating and implementing good prescribing and dispensing practices surrounding antimicrobial use to help curb rising AMR rates and reduce healthcare costs (258-260).

In 2018, the Pakistan Global Antibiotic Resistance Partnership published a situational analysis to improve future antibiotic utilisation in Pakistan, with identified challenges including addressing current irrational prescribing and dispensing of antibiotics (254). As a result, we should see improved utilisation of antibiotics in Pakistan in the future, which is encouraging given the size of the population.

National activities have also recently started in Vietnam to improve antibiotic utilisation across sectors to reverse increasing AMR rates (261). These activities especially target current high rates of self-purchasing of antibiotics in both rural and urban communities (Supplement Table C) (46, 261) building on successful targeted campaigns including greater regulatory enforcement, education and peer influence among selected private pharmacies nearly 20 years ago (262). Targeted activities include raising awareness among the public regarding AMR and the need for antibiotics especially for URTIs, as well as education of physicians through guidelines and other activities (261). The Vietnamese Ministry of Health has also recently instigated activities to improve control over the prescribing and selling of prescription medicines. This applies especially to antibiotics to reduce their irrational use given current high rates of self-purchasing in the country despite legislation. There are ongoing plans in Vietnam to instigate information technology systems across the country to connect

online suppliers and pharmacists nationwide to track antibiotic use (263, 264). This builds on activities among a number of countries (Table 2).

In sub-Saharan Africa, The National Action Plan on AMR for Nigeria (2017-22) was launched in 2017 based on the "One Health" approach. The country has further committed itself to reducing AMR rates including enrolling in the Global Antimicrobial Resistance Surveillance System (GLASS) (265). Similarly, Swaziland (now the Kingdom of Eswatini) has recently launched its strategy to improve antibiotic utilisation and reduce AMR rates (256). Encouragingly, recent studies have shown that antimicrobial stewardship programmes (ASPs) have helped improve the appropriate use of antibiotics in the Kingdom, providing direction for the future (266). National activities are also just starting in Zambia to reduce AMR rates following concerns with the extent of self-purchasing of antibiotics in ambulatory care (Supplement Table C) as well as concerns with the lack of ASPs in key sectors with suggested programmes to address this (91, 267-269).

There are also planned activities in Botswana and Namibia to develop pertinent quality indicators for assessing the quality of prescribing of antibiotics in ambulatory care given concerns with the WHO/ INRUD (International Network for the Rational Use of Drugs) indicators as well as concerns with the extent of prescribing of antibiotics for URTIs among private general practitioners in Botswana (180, 232, 270, 271). This builds on discussions of possible quality indicators to influence future prescribing of antibiotics in other LMICs (272). Adherence to current guidelines is seen as a better predictor of the quality of prescribing of antibiotics than current WHO/ INRUD criteria (271). Encouragingly in Namibia, whilst patients and parents regularly self-medicate for acute respiratory infections including the common cold and influenza for themselves and their children, this was typically with cold/ flu medication, paracetamol and decongestants, rather than antibiotics. This is helped by regulations banning the self-purchasing of antibiotics among community pharmacies in Namibia and the regular monitoring of community pharmacies (Table 4) (182, 273).

In LMICs where there are high rates of self-purchasing (Supplement Table C), the overuse of antibiotics also needs to be addressed through government and other activities. This includes a combination of increased public awareness, improved healthcare professional training, legislation and enforcement, as well as greater monitoring of antimicrobial use and resistance patterns (45, 274, 275). Board certified courses could also be instigated to adequately train pharmacists (and where relevant other health professionals such as Physician Associates or Advanced Practice nurses) to prescribe antibiotics where appropriate, especially in very rural outlying areas.

Several countries have introduced multiple initiatives over many years to improve the use of antibiotics especially for URTIs providing guidance to others. This includes instigating ASPs in ambulatory care (276, 277). A number of Governments and health authorities, including European Health Authorities, have been particularly active over a number of years (Table 2), with recent research contrasting different approaches and activities between countries to provide future guidance (244). There are also examples of government activities among LMICs outside of Europe to reduce the irrational use of antibiotics especially for URTIs, again providing guidance to others (Table 2).

Table 2: Activities among European countries and LMICs outside of Europe to improve the utilisation of antibiotics in ambulatory care especially for respiratory tract infections and outcomes where known

Country	Activities
High income European countries	
Germany	• Germany has undertaken a number of activities in recent years to improve the utilisation of antibiotics in both hospitals and ambulatory care, including patients with respiratory tract infections. • This includes developing antimicrobial stewardship programmes and raising public awareness, as well as investing in research to develop new antibiotics (244, 278, 279) • These activities are ongoing
Slovenia	• Multiple activities among all key stakeholder groups, including regular educational activities among physicians, quality targets, prescribing restrictions for amoxicillin/ clavulanic acid, cephalosporins, macrolides and the fluoroquinolones, as well as patient education activities aimed at re-enforcing that most infections in ambulatory care such as URTIs are viral in origin, appreciably reduced antibiotic utilisation in recent years in Slovenia (40) • Overall, antibiotic utilisation decreased by 31% between 1999 and 2012 through these multiple initiatives
Sweden	• Sweden has been particularly active over a number of years to improve antibiotic prescribing and reduce AMR (280) • The multiple initiatives, which included educational initiatives among physicians, academic detailing, guidelines including diagnostic criteria for each condition and an analysis of the risk and benefits of antibiotics, instigating local multidisciplinary groups discussing antibiotic prescribing, monitoring antibiotic prescribing and resistance rates including quality targets, patient education, and susceptibility testing, reduced antibiotic prescribing in ambulatory care, including primary care, by 43% between 1992 and 2016, whilst among children 4 years or under the prescribing of antibiotics including those for URTIs decreased by 73% (280) • Overall, the prescribing of antibiotics for patients with URTIs in ambulatory care in Sweden decreased from 40.5% in 2008 to 24.9% in 2013, and continues to fall further (79) • As a result of these multiple initiatives, Sweden has one of the lowest rates of antibiotic utilisation in Europe (281)
United Kingdom including England and Scotland	• Scotland has introduced a number of national and regional initiatives in recent years to improve antibiotic utilisation in ambulatory care including patients with URTIs. These centre on the instigation of the Scottish Antimicrobial Prescribing Group (SAPG) in 2008 to help implement the recommendations of the Scottish Management of Antimicrobial Resistance Action Plan (ScotMARAP) (282) • Activities included the development of quality indicators and prescribing guidelines incorporating measures to reduce the prescribing of quinolones (282) • Prescribing guidance based on a template from Public Health England is currently being used in all Scottish Health Boards (Regions) to improve antibiotic prescribing including URTIs (283-285) • In Scotland, the number of prescriptions for antibiotics (items/ 1000 patients/ day) decreased by 7.8% between 2013 and 2017 following multiple activities (286) • Multiple strategies generally throughout the UK resulted in 6.5% fewer prescriptions for systemic antibiotics in ambulatory care in 2014/ 2015 versus

	2012–2013, with 57.5% of GP practices achieving the national quality indicator of a minimum acceptable reduction in antibiotic use (287) • More recent reports showed that the prescribing of antibiotics in ambulatory care in England fell by 13.2% in the past 5 years from 2013 levels (288) • Guidance regarding the management of URTIs, as well as other strategies to improve antibiotic prescribing including patient education, has also been introduced in the UK (287, 289-292). These activities resulted in a significant reduction in the prescribing of cephalosporins and fluoroquinolones in England in 2013 versus 2005 (287) • Recent targets for GPs in the UK include reducing their rate of antibiotic prescribing by 2% per year or more through co-ordinated activities over the next five years (293). This includes patients with URTIs
LMICs including those in and outside of Europe	
Albania	• Independent studies have shown high rates of self-purchasing of antibiotics in Albania (78% - 80%) despite legislation banning this, exacerbated by one third of Albanians not covered by health insurance (294) • These concerns, coupled with variable knowledge among pharmacists regarding antibiotics and AMR (294, 295), resulted in a small pilot campaign in 2016/ 2017 targeting pharmacists and patients in community pharmacies to reduce inappropriate use of antibiotics especially for URTIs (295). Activities included a poster with advice on how to appropriately use and dispense antibiotics • Follow-up of the campaign is ongoing to assess the influence of such activities with potential roll out across Albania • More recently (2018), given concerns including the dispensing antibiotics without a prescription, the Albanian Ministry of Health established a task force to improve control over the dispensing of medicines over the counter without a prescription among community pharmacies (295-297) • Preliminary results suggest that over 20% of the pharmacies inspected to date in Albania had been fined for selling medicines without a prescription. Overall, in the first months of implementation of the new measures, 115 community pharmacies had been inspected with 20 fined for dispensing a medicine without a prescription • This MoH initiative is ongoing, with pharmacies increasingly aware of the need to only dispense medicines with a prescription else they will be fined. The impact of these additional measures is also being monitored in case further initiatives are needed to further improve the management of patients with, for instance, respiratory tract infections in community pharmacies
Azerbaijan	• Multiple activities in Azerbaijan in recent years included regular national initiatives to educate physicians not to prescribe antibiotics for likely viral infections including URTIs, and guidelines recommending penicillins first line for URTIs if an antibiotic is needed • Other activities included reinforcing in pharmacies that it is illegal to sell antibiotics without a prescription. In addition, educational campaigns in pharmacies that most infections seen such as URTIs are viral in origin and do not require an antibiotic (70) • These multiple activities resulted in a significant reduction in antibiotic utilization in Azerbaijan from 17.1 DDDs (DDDs/ 1000 inhabitants/ day) in 2011 to 8.02 DIDs in 2015, which was the lowest utilisation level compared with similar countries • In addition, an overall low utilisation of co-amoxiclav, macrolides, cephalosporins and the fluoroquinolones compared with similar countries (70)
Brazil and	• In Mexico and Brazil, national restrictions were placed on the self-purchasing of

Mexico	antibiotics in 2010, although a prescription was always a requirement for antibiotics to be dispensed among public pharmacies in Brazil (56, 74, 298) • There was a reduction in penicillin use among private pharmacies in Mexico after this initiative, with a more limited reduction in Brazil (298, 299) • Further details about the impact of these initiatives are contained in Table 4
Chile	• Chile was one of the first countries in Latin America to introduce greater enforcement of the law to reduce self purchasing of antibiotics in 1999 following concerns with increasing antimicrobial consumption and AMR, with its impact enhanced by antibiotics being removed from the list of medicines having sales incentives in pharmacies (300) • Antimicrobial consumption decreased from 12.3 DIDs before the intervention to 8.5 DID just after the enforcement (in 2000) aided also by the instigation of public information campaigns before and during greater enforcement of the regulations (298, 300) • However, there has been a slow increase in antimicrobial utilisation since 2002 suggesting that the effects of such interventions wear off unless utilization is monitored and further initiatives introduced when and where pertinent
China	• The government launched a national Action Plan in 2011 targeting antibiotic misuse in public hospitals where most antibiotics are dispensed in China (62) • The plan emphasized the key roles for DTCs and clinical pharmacists in developing formularies and monitoring prescribing against current guidance as well as developing and implementing antibiotic stewardship programmes to improve out-patient (as well as in-patient) use of antibiotics including patients with URTIs • The multiple activities reduced out-patient utilisation of antibiotics by 12.9% by the end of 2014, with a greater reduction in the in-patient use of antibiotics (62)
Ghana	• The Ministry of Health in Ghana recently launched a 5-year NAP, with assistance from the Fleming Fund in United Kingdom, to cover the period 2017 to 2021 (301, 302) • The NAP covers several areas including improving awareness and knowledge of AMR, providing evidence-based knowledge to reduce the burden of AMR to reduce inappropriate prescribing and dispensing of antibiotics, establishing a surveillance system for antimicrobial consumption, optimizing the use antimicrobials in humans and creating an enabling environment for sustainable investment in AMR reduction • As part of this, greater enforcement of software programmes in community pharmacies as a means of tracking irrational dispensing and the use of non-prescribed antibiotics (301) • The findings from these various initiatives are being followed up to see if additional activities are need to further reduce inappropriate dispensing of antibiotics in community pharmacies
Kosovo	• The Ministry of Health in December 2018 approved a new national action plan for AMR incorporating different activities for all key stakeholder groups (72) • There are also appreciable ongoing activities including workshops, social media activities, and television advertisements, to raise awareness of the consequences of inappropriate antibiotic use including antibiotics for patients with URTIs • The Ministry of Health is also currently revising the essential medicines list including available antibiotics • There is also currently an ongoing debate in the Kosovo Medicines Agency and the Ministry of Health as to whether two prescriptions should be given for antibiotics, one copy of which will be saved in the pharmacy for 5 years (comparable to narcotics) to help monitor physician prescribing practices

	• Alongside this, continual monitoring of annual antibiotic consumption as part of the WHO European Antimicrobial monitoring group (274, 303) building on activities in other disease areas (304) • These activities are being followed up to see if additional measures are needed to further reduce inappropriate antibiotic utilisation for infections including URTIs
Republic of Srpska	• In 2010, 58% of pharmacies sold an antibiotic for a self-diagnosed URTI despite legislation banning this (305) • Consequently, the Republic of Srpska has been active over a number of years to improve the prescribing and dispensing of antibiotics in ambulatory care including patients with URTIs (71) • Activities included diagnostic and prescribing advice for physicians, a limited list of reimbursed antibiotics, continual education of pharmacists and pharmacist technicians as well as published guidelines for pharmacy personnel to successfully treat URTIs patients with over-the-counter medicines or refer them to a GP (71) • In addition, continual inspections by Republic of Srpska Inspectorate personnel since by law antibiotics are restricted to prescription only medicines in the Republic • These combined activities resulted in the Republic having one of the lowest utilisations of antibiotics in recent years compared with similar countries as well as an appreciable reduction in the self-purchasing of antibiotics in recent years (71, 306)
South Africa	• South Africa has also been active with developing national action plans to combat rising AMR rates for a number of years (307, 308), providing guidance to other sub-Saharan African countries • Activities include the development of the National Department of Health Antimicrobial Resistance National Strategy Framework, 2014–2024 building on the WHO global strategy to contain and reduce rising AMR rates (250, 307). As part of this, ongoing programmes within hospitals in South Africa have instigated ASPs to reduce AMR rates, with published guidance on ASPs to help instigate such programmes (309-311) • In the community, there are also ongoing programmes to assess prescribing against agreed guidance given concerns with, for instance, the extent of antibiotic prescribing for URTIs (312). This includes promoting community pharmacists to help drive ASPs forward to improve the utilisation of antibiotics for respiratory tract infections in ambulatory care (159) • Such initiatives are likely to grow to further improve the prescribing of antibiotics in ambulatory care across all sectors, with the South African guidelines regularly updated (250, 313) • In addition, community pharmacists can also recommend alternative treatments for minor URTIs and reassure patients of the inappropriateness of antibiotics. They can also uphold the law and not permit self-purchasing of antibiotics as well as advise patients on any possible side-effects of any antibiotic prescribed to enhance adherence rates (307) • Educational activities are also being encouraged in pharmacy and medical schools and wider as part of ongoing programmes to improve their knowledge about antibiotics and AMR (50, 314, 315) • Ongoing research programmes are monitoring the impact of these multiple activities to introduce further activities and initiatives if needed
Turkey	• The Ministry of Health in Turkey recently implemented an electronic prescription system to track prescription data across the country from production to dispensing as well as provide feedback to physicians (274, 316)

	• This was in line with the 2014 – 2017 National Action Plan to enhance the appropriate use of antibiotics in Turkey given current high utilisation rates compared with other European countries and AMR (303) • The regulations reducing future self-purchasing of antibiotics include potential fines for pharmacists following abuse aided by the "track and trace" system • It is envisaged that future studies will show an appreciable decrease in self-purchasing similar to expectations in Albania
Venezuela	• In 2006, Venezuela implemented a national policy to reduce the self-purchasing of three groups of antibiotics: namely macrolides, quinolones and third generation cephalosporins due to concerns with their over use (300) • This though was without any public awareness campaigns • Overall, there was no change in their utilisation patterns as 'enforcement' was only made via formal government publications and not followed up with any increased pharmacy supervision or any pharmacy closures/ financial sanctions for non-compliance (298, 300)

NB: AMR = Antimicrobial Resistance; ASP = antimicrobial stewardship programmes; DDD = defined daily dose; DTCs = Drug and Therapeutic Committees; MoH: Ministry of Health; URTIs = Upper Respiratory Tract Infections

3.4.2 Physicians

Many programmes have been instigated across countries to try and reduce unnecessary antibiotic prescribing among ambulatory care physicians, especially for suspected viral infections (78, 85, 88, 151, 317). However, there is no one universal programme, and programmes typically need to be tailored to the different situations with different governance structures (78, 85, 244). A team approach with consistent advice, improved communication between family doctors or general practitioners (GPs), patients and children's parents, including addressing current perceptions and de-medicalising self-limiting viral infections, is seen as critical to improve antibiotic prescribing among family doctors for respiratory tract infections (152, 156, 202, 208, 318). Seeking ways to improve guideline adherence is also seen as important (271). Education initiatives for doctors starting at medical school may be necessary in LMICs where there are concerns with current training and its impact on reducing inappropriate prescribing of antibiotics (48, 50, 315, 319-327).

Improving communication between family doctors and patients should help address concerns that physicians want to help their patients, and tend to over-estimate patients' expectations regarding their wish to be prescribed an antibiotic for their URTI (21, 153, 156). Physicians are also more likely to prescribe an antibiotic if they feel under pressure (108, 328, 329).

A number of approaches to improve the use of antibiotics in ambulatory care in high- as well as high-middle income countries have been described and reviewed by Dyar et al (85). These are of relevance to LMICs as the care of patients with URTIs increasingly moves to physicians. The approaches can be broken down into educational activities including (i) academic detailing with varying degrees of success and evidence, (ii) guidelines and clinical decision support systems, (iii) initiatives to delay the prescribing of antibiotics especially for URTIs, (iv) special prescription forms highlighting the importance of antibiotics in healthcare, (v) having posters in surgeries emphasizing the commitment of family doctors to reducing unnecessary prescribing of antibiotics, (vi) instigating point of care testing to determine the likely cause of the infection, (vii) instigating quality indicators (QIs) and monitoring performance against these, (vii) undertaking regular auditing of prescribing and feedback, (viii) restricting the number and prescribing of certain antibiotics, (ix) separating prescribing and dispensing, (x) and restricting pharmaceutical company activities (85).

Restricting or addressing inappropriate pharmaceutical company activities is particularly important in LMICs, where companies can be the principal source of physician education regarding antibiotics (330, 331). Selective point-of-care testing is seen as potentially beneficial in patients with URTIs (101, 332), and decision support systems have been shown to reduce the overuse of antibiotics in ambulatory care settings (333). Social norm feedback among physicians can also appreciably reduce antibiotic prescribing in ambulatory care (334).

Several initiatives have been introduced across countries over the years to reduce inappropriate prescribing of antibiotics among physicians especially for patients with URTIs in both high income countries as well as LMICs (29, 76, 85, 151, 335). The impact of some of these for high income countries are contained in the Supplementary material for potential reference and adaptation to LMICs (Supplement Table E).

Table 3 contains the impact of different interventions among physicians in ambulatory care in LMICs to reduce unnecessary antibiotic prescribing. These may not always be RTI or URTI specific although typically multiple interventions again appear to have the greatest impact (29). The number of published papers in LMICs is more limited compared to high income countries due to their paucity. Sun et al (2015) showed though that there can be appreciable differences in physician beliefs and actual prescribing practices. Whilst most physicians in rural areas of Shandong Province had attended further training on antibiotic use since the beginning of their medical practice as a doctor, and only 2% said they would prescribe antibiotics for patient with a common cold, the reality was very different (336). In fact, 55% of the physicians surveyed included an antibiotic prescription when treating patients with a common cold (336). In addition, Esmaily (2010) showed no significant improvements in antibiotic prescribing practices after an outcome-based educational approach among ambulatory physicians in Iran; however, overall there was an appreciable reduction in the number of medicines prescribed (337). Mobile technologies with clinical algorithms can also improve the management of childhood illness leading to an appreciable reduction in antibiotic utilisation (338). This is a potential approach for the future in LMICs given the wide use of mobile technologies across countries (339, 340).

Table 3: Initiatives to improve antibiotic utilisation among physicians in LMICs

Country	Intervention and impact
China	Study one (2014) (341) • In Ningxia Province a matched-pair cluster-randomized study was undertaken to evaluate the effects of capitation with pay-for-performance on primary care providers' antibiotic prescribing practices, health spending, outpatient visit volume, and patient satisfaction • This intervention resulted in approximately 15% reduction in antibiotic prescriptions and a small reduction in total spending per visit Study Two (2019) (88) • Cluster randomised study among 14 primary healthcare facilities in rural China • An intervention comprising clinical guidelines, monthly prescribing review meetings, doctor–patient communication skills training, and education materials for caregivers, appreciably reduced antibiotic prescription rates (ABR) in children with URTIs • There was a 49% reduction in ABR after 6 months in the intervention arm having adjusted for patient and prescribing doctor covariates • The reductions persisted after 18 months but at a lower rate (-36%) • Factors sustaining the reduction included physicians' improved knowledge and communication skills combined with focused prescription review meetings
Nepal	Study One (2006) (342) • 7 health posts and 33 subhealth posts were stratified by type with health workers from the intervention facilities receiving 5 days training on the adapted Practical Approach to Lung Health (PAL) guidelines and their use • Appropriate prescribing of antibiotics and adherence to guidelines improved; however, this was not statistically significant unlike other areas such as polypharmacy and generic prescribing rates Study Two (2009) (343) • Supervision/ monitoring involving periodic visits by district supervisors to 41 primary health care (PHC) facilities. The intervention included small-group training among prescribers followed by peer-group discussions alongside self-assessment of the data presented • In children under five, there was a significant improvement in use of antimicrobials in diarrhoea and in URTIs without pneumonia
Sudan (344)	• Twenty health centers in Khartoum Dtate were randomly assigned to receive either (a) no intervention; (b) audit and feedback; (c) audit and feedback + seminar; or (d) audit and feedback + academic detailing • The targeted interventions involving audit and feedback combined with academic detailing reduced the mean number of physician encounters with an antibiotic prescribed by 6.3 and 7.7 (p<0.001) at 1 and 3 months post-intervention, respectively. The mean number of encounters where antibiotics were inappropriatetly prescribed were also significantly reduced post intervention (p<0.001) • Reducing the number of activities reduced the overall impact

Nurse specialists can also treat patients at primary healthcare centres (PHCs) in many LMICs due to the shortage of physicians, although this is not always the case (69, 240, 313). Similar approaches to

those for physicians would be applicable in this situation to reduce inappropriate use of antibiotics in patients with URTIs (119).

3.4.2.1 *QIs to Improve Antibiotic Prescribing in Ambulatory Care*

A variety of QIs have been developed over the years to improve antibiotic prescribing in ambulatory care especially for patients with URTIs. Their development has involved a number of groups including the WHO, ECDC, and ESAC (274, 281, 345-347). QIs can range from general QIs based on the class of antibiotic prescribed (Supplement Box A) to more specific indicators based on actual prescribing. Slovenia has also instigated several QIs to enhance the prescribing of antibiotics, including those for URTIs (Supplement Box B). The general QIs (Supplement Box A) reflect the concerns of the WHO and others regarding the over use of co-amoxiclav, fluoroquinolones, third- and fourth-generation cephalosporins, macrolides and glycopeptides. Addressing the misuse of these antibiotics is seen as the highest priority to improve future prescribing and dispensing of antibiotics in ambulatory care ambulatory care (274, 347).

Specific indicators for the prescribing of antibiotics to children for URTIs include the proportion of amoxicillin users (amoxicillin index) and the ratio of amoxicillin to broad-spectrum penicillins, cephalosporins and macrolides (*A/B* ratio) (21, 229). Such indicators are included in Slovenia's QIs (Supplement Box B). Specific QIs also include adherence to guidelines. Adherence to guidelines has been found to better represent the quality of prescribing in ambulatory care versus current WHO/ INRUD criteria (271, 313, 335, 348). However, it is important that there is only one national reference guideline since where multiple guidelines exist contradictions can occur (236). Guidelines should be readily available and combined with educational inputs and auditing of antibiotic prescribing to reduce inappropriate use (57, 250, 270, 313, 335, 349). Regular updates of antibiotic guidelines are also essential to enhance their utilisation, and updates should be rapidly disseminated to achieve agreed goals. This is being achieved in South Africa through mobile technologies (250), providing guidance to other LMICs. However as shown in New Zealand, this has to be accompanied by other interventions to enhance adherence to guidelines (340).

The HEDIS (Healthcare Effectiveness Data and Information Set) datasets in the US also include specific indicators to improve the management of patients with URTIs, again providing direction to other countries (350) (Supplement Box C).

More recently, an international multidisciplinary group consolidated potential QIs for patients in ambulatory care particularly those with respiratory tract infections. These included both structure and process measures (Box 1) (351).

Box 1: Updated Quality Indicators In Ambulatory Care Including Those For Patients With Respiratory Tract Infections (351)

- Antibiotics should be prescribed for (most) bacterial infections (e.g. acute pneumonia, urinary tract infections)
- Antibiotics should not be prescribed for viral infections or (most) self-limiting bacterial infections (e.g. acute bronchitis, influenza, acute otitis media in children > 2 years old)
- Ambulatory care patients should receive antibiotic therapy compliant with agreed guidelines; this includes, but is not limited to, indication, choice of the antibiotic, duration, dose and timing
- Some antibiotics should rarely be prescribed
- Acute upper respiratory infections and bronchitis should not be treated with antibiotics within the first 3 days, unless there is documented indication for treatment
- Ambulatory care patients with acute tonsillitis/pharyngitis should undergo a group A streptococcal diagnostic test to decide whether or not they should receive antibiotics
- Ambulatory care patients with an acute tonsillitis/pharyngitis and positive group A streptococcal diagnostic test should be treated with antibiotics
- Antibiotics for an acute tonsillitis/pharyngitis should be withheld, discontinued or not prescribed if a patient presents a diagnostic test (rapid antigen test or throat culture) negative for group A streptococci
- Prescribed antibiotics should be chosen from an essential list/agreed formulary
- Possible contraindications should be taken into account when antibiotics are prescribed
- Antibiotics from the list of essential antibiotics should be available in health facilities that dispense antibiotics
- Key antibiotics should not be out of stock in health facilities that dispense antibiotics
- Health facilities should keep adequate records of dispensed key antibiotics
- A copy of the essential antibiotics list should be available in health facilities
- Standard antibiotic treatment guidelines should be available in health facilities
- Health facilities should have access to the Summary of Product Characteristics of prescribed antibiotics, written in a local language

3.4.3 *Community Pharmacists*

Community pharmacists are often the first healthcare professional that patients consult with regarding URTIs such as a cold or cough. This is because they are typically more accessible than physicians, especially in rural communities (155). Other factors include long waiting times to see a physician or nurse in PHCs in LMICs, losing income because of loss of work, as well as possibly having to travel long distances to access healthcare professionals in PHCs along with the associated costs (69, 134, 306, 352-356).

The limited number of physicians in several LMICs, coupled with opportunities for training pharmacists, increases their role in managing most URTIs. As a result, there are increasing calls for community pharmacists to lead local ASPs in ambulatory care to reduce unnecessary prescribing and dispensing of antibiotics (159).

Consequently, pharmacists are increasingly seen as a key stakeholder group to improve antibiotic utilization in LMICs, especially when patients cannot afford to see both a physician and purchase pertinent medication (307, 353, 357-359), and given the extent of self-purchasing of antibiotics seen in a number of LMICs (Supplement Table D). The importance of pharmacists is highlighted by activities promulgated by FIP (International Federation of Pharmacists) and the WHO (360, 361) (Box 2).

Box 2: Activities of Pharmacists to Reduce AMR - Adapted from FIP And the WHO (360, 361)

- Pharmacists are an essential player in the health system and, whilst they take an increasing role in providing relevant information to patients, there is room for improvement.
- Pharmacists should encourage the prudent use of antibiotics, taking full advantage of their position as they are often the first contact patients have with the healthcare system and are increasingly seen as an effective liaison between prescribers and patients. This includes patients being appropriately counselled on the need for and use of antibiotics, particularly for URTIs to reduce adverse effects and AMR, and, for URTIs such as a common cold or a sore throat, recommending other treatments.
- When dispensing antibiotics, patients should be given proper counselling and provided with appropriate written information.
- Pharmacists should encourage patients to comply with the full prescribed or dispensed regimen when dispensed and should become actively involved in promoting hygiene and infection control across healthcare settings.

GRIP suggest similar activities including seeking to restrict non-prescription sales of antibiotics, providing data on the scale of the problem, provision of continuing professional development/training where this is currently lacking, outlining the business benefits of patient satisfaction, and the provision of guidelines and patient education material where this does not exist (158, 159).

In some LMICs, concerns have been raised regarding pharmacists', pharmacist assistant's and pharmacy students' level of knowledge on antibiotics and AMR (52, 141, 242, 295, 354, 362-368); however this is not universal (364). This may reflect a greater priority for enhancing sales in pharmacies rather than worrying about professional behaviour (128, 141, 143). As a result, there is a need to ensure good knowledge about antibiotics and AMR development in the teaching curriculum and for pharmacists and their assistants, with regular community practice follow-up post qualification (46, 362, 369). Education about ASPs is also important, building on the potential role for pharmacists in leading ASPs in the community in the future having overcome current boundaries and barriers (143, 159, 314, 370). In addition, increasing the availability of pragmatic guidelines could help pharmacists and their assistants enhance the appropriate management of patients with URTIs (306, 364).

Other potential activities include instigating and monitoring the impact of measures to restrict the sales of antibiotics without a prescription as seen in Albania, the Republic of Srpska, Ghana and Turkey (Table 2). However, these measures have had variable success (74, 134, 242, 298, 299, 369, 371), which may reflect concerns about their implementation, coupled with concerns about loss of income (128). Any measure introduced must be carefully thought through in rural LMIC communities where there is a scarcity of physicians, and community pharmacists may be the only healthcare professional that patients can readily access.

Table 4 provides a summary of some of the activities among LMICs to try and reduce the extent of self-purchasing of antibiotics especially for URTIs, and their impact, providing future direction. This builds on Table 2.

Table 4: Summary examples of initiatives to reduce self-purchasing of antibiotics in pharmacies

Country	Activity

Brazil and Mexico	A) Study One - Brazil and Mexico 2013 (298)
	• Descriptive analysis of the impact of legislation banning the sales of antibiotics to patients in private pharmacies without a prescription in Brazil and Mexico - this was always the case among public pharmacies in Brazil where patients can receive their medicines free of charge with a prescription (56, 372)
	• Variable results were seen between 2007 and 2012:
	   o Between 2007 and 2012 total antibiotic usage consumption increased in Brazil (from 5.7 to 8.5 DDD/TID, +49.3%) but decreased in Mexico (10.5 to 7.5 DDD/TID, 229.2%) during the study period
	   o Interrupted time series analysis showed a change in level of consumption of - 1.35 DDD/TID (p <0.01) for Brazil and - 1.17 DDD/TID (p <0.00) for Mexico
	• The authors concluded that whilst the effect of the restrictions on antibiotic use was similar; in Brazil, the trend of increased consumption of antibiotics was tempered after the restrictions, whilst in Mexico the trend of decreased consumption was accelerated
	• As seen in a separate study (Table 4), the authors showed an appreciable seasonal reduction in the use of penicillins in Mexico after the legislation but not Brazil (299)
	
	B) Study Two - Brazil 2015 (372)
	• Moura et al also studied the impact of the impact of the legislation in Brazil (2010) in both public and private pharmacies in a time series analysis design
	• The authors showed a decrease in antibiotic use of 1.87 DDDs/ one thousand inhabitants per day (p < 0.001) immediately after the restrictions among private pharmacies (2008 to 2012), with a greater decrease in the more developed regions as well as in the State Capitals versus other localities in the region
	• There was no difference in sales in the public pharmacies (P=0.643)
	
	C) Study Three - Brazil 2015 (373)
	• Sales data were collected from approximately 3000 private pharmacies pre and post the new legislation in Brazil
	• Amoxicillin, cephalexin, and azithromycin were the most commonly sold antibiotics before the legislation (December 2009 to November 2010) and after (December 2010 to November 2011)
	• Sales of amoxicillin fell by approximately 30% post legislation despite the general growth in the pharmaceutical market, with falls in sales for the tetracyclines (-30.5%), sulfonamides (-28.5%), and macrolides (- 25%). This showed a positive impact of the new legislation on antibiotic sales in private pharmacies in Brazil
	• Decreased amoxicillin consumption is important as amoxicillin is often associated with self-medication and self-purchasing for the treatment of URTIs
	
	The differences in the findings in Brazil between the different studies before and after the changes in legislation may well reflect differences in data sets and methodologies. Nevertheless, published studies agree that increased monitoring of antibiotic utilisation is needed to further enhance the appropriate use of antibiotics in Brazil including for URTIs, thereby helping to reduce AMR rates in the future (275)

Kenya – 2018 (358)	• Cross-sectional study among selected pharmacies in Nairobi • Monitoring of antibiotic dispensing among pharmacies allied to the University of Nairobi showed a low level of dispensing of antibiotics without a prescription,

	with 94.1% of antibiotics dispensed with a valid prescription
	• No antibiotics were prescribed or dispensed for patients with a common cold or influenza, with over-the-counter (OTC) medications such as cough and cold syrups and lozenges often dispensed
Namibia 2018 (182, 273)	• In a survey involving 100 households in Namibia, the authors found that patients regularly self-medicated for themselves or their children for acute respiratory infections, including for common colds and influenza • However, this was typically with cold/flu medication, paracetamol and decongestants, rather than antibiotics • This is helped by regulations banning the self-purchasing of antibiotics with community pharmacies regularly monitored
Republic of Srpska 2017 (305, 306)	• Observational, cross-sectional study involving community pharmacists across all regions to assess the influence of a series of interventions in recent years (Table 2) including guidelines for pharmacists and greater enforcement of the regulations banning self-purchasing of antibiotics • This resulted in the self-purchasing of antibiotics for self-diagnosed URTIs significantly decreasing from 58% to 18.5% among the pharmacies visited (Table 2) • The most common reason for not dispensing an antibiotic was that antibiotics cannot be dispensed without a prescription • These multiple activities are continuing to further improve the management of patients with respiratory tract infections visiting pharmacies, including further lowering the extent of dispensing an antibiotic without a prescription

NB: DDDs = defined daily dose, DD/ TID = DDDs per one thousand inhabitants per day, OTC = over-the-counter, URTI: Upper respiratory tract infection

3.4.4 Patients and the Public

Finally, it is vitally important to target patients and the public in any future initiative as they can put pressure on physicians, pharmacists and nurses to prescribe and dispense antibiotics for URTIs (98, 157, 208, 374). People vary in their knowledge about antibiotics and AMR; however, and they can have strong beliefs about the effectiveness of antibiotics even for viral infections (104, 137, 157, 248, 375-377).

Multifaceted approaches are typically needed to change behaviour and attitudes among patients (6, 292); however, there have been varying degrees of success (157, 160, 378, 379). Approaches include addressing issues of communication between healthcare professionals and patients during the consultation, which involves eliciting and addressing key issues including patients' beliefs concerning the effectiveness of antibiotics for URTIs (85, 202, 380, 381). Factors enhancing the success of any antibiotic awareness campaign include: (i) the use of carefully designed and simple key messages; (ii) targeting a wide audience including patients and their families as well as healthcare workers; (iii) designing key messages with all key stakeholder groups including healthcare professionals; and (iv) using mass media and social media to raise awareness. In addition, key messages should be continuously repeated to meet the needs of new parents and others (60, 157, 160, 382, 383).

The success of any campaign targeting patients and the public will necessarily depend on social, cultural, and geographical factors as well as existing patterns of prescribing (61). Encouragingly, two systematic reviews report significantly reduced antibiotic prescribing with patient campaigns. McDonagh et al found that parent education reduced antibiotic prescribing for acute RTIs by 21% (151) and Cross et al (principally including high income countries in Europe and the US targeting both

physicians and the general public) found that the majority of studies reported reductions of more than 14% in the prescribing of antibiotics for RTIs up to a maximum reduction of 30% (157).

Table F in the Supplementary material contains details of several patient campaigns and their influence, especially in high income countries to help inform LMICs. However, it is acknowledged that patient campaigns will be more challenging in LMICs, especially where resources and personnel are key issues (119).

Parents with lower paid employment are a particular focus for any patient campaign in LMICs as it is this population group that is most likely to seek antibiotics from pharmacists in the belief that their children will recover more quickly from their infection with an antibiotic and they will be able to have a quicker return to work (203). However, patient educational initiatives in LMICs have not yet been fully elucidated, including the costs of campaigns and their effectiveness (61). Consequently, caution is still needed.

4. DISCUSSION AND CONCLUSION

The irrational use of antibiotics, including their over-prescribing and self-purchasing, for the management of patients with URTIs continues to be an issue among LMICs. Such practices need to be urgently addressed to reduce rising AMR rates.

The major drivers of inappropriate prescribing and dispensing of antibiotics for RTIs include (i) variable knowledge among patients, prescribers and dispensing staff regarding antibiotics and AMR; (ii) limited knowledge regarding current antibiotic utilisation patterns and resistance rates, especially for patients with URTIs in a number of countries; (iii) lack of ASPs in ambulatory care; (iv) pressure from patients and caregivers to prescribe and/ or dispense antibiotics because of their beliefs surrounding antibiotics, (v) profit motive and concerns among pharmacists coupled with a lack of enforcement of legislation banning the self-purchasing of antibiotics for URTIs where this is a concern; (vi) lower socioeconomic status in LMICs with issues of overcrowding and malnutrition; and (vii) long waiting times to see health professionals in PHCs in a number of LMICs.

Multiple strategies are needed to improve the future prescribing and dispensing of antibiotics among all key stakeholder groups for patient with URTIs. These include additional education and training for physicians where pertinent incorporating enhanced communication skills with patients, closer monitoring of the prescribing of antibiotics for URTIs, and the instigation of quality indicators. Educational initiatives are also needed where pertinent for community pharmacists along with the instigation of guidelines for patients with URTIs, greater tracking of antibiotics through the supply chain and the instigation and enforcement of policies to reduce inappropriate self-purchasing of antibiotics where pertinent. As these activities progress, rising AMR rates should start to reduce. Health education activities among patients and the public are also needed to supplement activities with physicians and pharmacists. Such activities should principally centre around communicating that URTIs are predominantly viral in origin and self-limiting; consequently, antibiotics are often inappropriate. Antibiotics can also cause side-effects as well as increase AMR rates.

Suggested strategies to improve the prescribing and dispensing of antibiotics for URTIs among LMICs are based on the findings in Section 3.4 coupled with the knowledge and practice of the multiple co-authors. These have been divided into short- and long-term initiatives (Table 5).

Table 5: Suggested strategies (particularly In LMICs) to improve appropriate prescribing and dispensing of antibiotics for URTIs

Time scale	Potential strategies
Short term – including a situational analysis where appropriate	***Health authority/Government - the following (if not already done so):*** • Ensure functional supply chains to meet the needs of prescribers • Governments and health authorities must be committed to reducing inappropriate use of antibiotics especially for URTIs as part of any ongoing/planned NAP. This will involve resources being made available for implementation and monitoring activities including any ASPs associated with NAPs • Ascertain, if pertinent, current rates of prescribing and dispensing of antibiotics for patients with URTIs in ambulatory care using both qualitative and quantitative approaches to inform future activities • Ascertain current knowledge of physicians, nurses, pharmacists and patients regarding the appropriateness of antibiotics and AMR – especially for the management of URTIs - using both quantitative and qualitative approaches to guide future activities, including the need for any education and training • Building on this - contact key universities regarding current physician, nurse and pharmacy training regarding antibiotics, AMR and ASPs, and seek to address concerns where these have been identified. Subsequently, monitor the situation • Evaluate current programmes in schools and implement educational programmes to improve children's knowledge of antibiotics and AMR (159) • Assess the potential for introducing point-of-care testing in both public and private ambulatory care facilities as well as other clinical support systems – including issues of acceptance, availability and affordability, as well as developing and supporting the implementation of a national integrated AMR surveillance system where appropriate (short to medium term) • Develop or update current guidelines for the management of patients with URTIs with key stakeholder groups and make these readily accessible in electronic formats. Active communication and dissemination of guidelines is key to enhancing adherence rates (340, 384). Physician/nurse/pharmacist trust in any guideline produced is also critical to enhance their acceptance (385, 386). Consequently, any guideline produced must be evidence based, free from commercial input and include key local personnel (with declared conflicts of interest if needed) - building on the WHO EML • Subsequently, monitor prescribing against current guidelines and NAPs, enhanced by auditing, academic detailing and implementing electronic prescribing systems (384, 385) • Use the findings from any research activities to develop additional educational programmes where needed among all key stakeholder groups to further improve antibiotic utilisation as part of any NAP - recognising that multiple interventions are likely to have greater success – building on documented exemplars (Tables 2 and 3). This includes ASPs that are culture and country specific, and sustainable in the long term, as well as multidisciplinary given the concern with their

introduction in some LMICs (370)

- Pertinent programmes could include developing additional QIs for the setting (Supplement Box D) building on current QIs (Box 1 and Supplement Boxes A to C) - alongside other programmes to enhance the rational prescribing of antibiotics for URTIs among physicians (building on exemplars in Table 3). This also includes evaluating potential approaches to improve adherence to any developed QIs including benchmarking helped again by electronic prescribing systems (384, 385), being part of CPD programmes and possibly including financial incentives (small in relation to physician income)
- Relevant programmes could also include:
  - Developing and implementing communication strategies where required creating awareness and influencing behavioural changes via a multi stakeholder approach - co-ordinated by governments/ health authorities
  - Instigating country-wide vaccination programmes such as pneumococcal and influenza vaccines to reduce the prevalence of URTIs where these do not currently exist. Vaccines should be provided free-of-charge and available in both public and private sectors, which may require donor help initially
  - Developing a range of additional activities among pharmacists to reduce self-purchasing of antibiotics for URTIs where this is a concern - building on exemplars in other countries (Table 4) and ongoing research programmes. This could include remuneration schemes for pharmacists if reducing dispensing of antibiotics appreciably impacts on their profit levels
  - Enforcement of laws banning self-purchasing of antibiotics where these exist, which could include greater use of IT systems tracking the distribution of antibiotics (building on electronic prescribing systems). As part of this, also explore the current situation regarding telemedicine and other activities involving inappropriate selling of antibiotics for patients with URTIs on the internet, and seek to instigate measures to address issues where there are concerns as this is a growing area
  - Ensuring that only qualified personnel sell antibiotics to patients in pharmacies where such activities are essential – especially in rural LMICs. For example in Tanzania, different levels of pharmacies can dispense different treatments for malaria based on their knowledge level and skills (133)

Physicians (ambulatory care) and nurse practitioners in primary healthcare clinics (not including pharmacists)

- Ascertain current knowledge and beliefs about antibiotics and AMR especially for patients with URTIs, as well as current prescribing practices where there are gaps in knowledge
- Use this knowledge together with current QIs (Box 1 and Supplement Boxes A to C) to develop additional meaningful QIs for the specific setting (Supplement Box D) together with key stakeholder groups - including other physicians, physician societies, nurse practitioners and health authorities – to enhance the rational use of antibiotics in patients with URTIs
- Make sure current national guidelines are readily available and

accessible in their facility and regularly updated (as this is not always the case - (349)). In addition, encourage physicians through auditing and other practices to regularly consult national guidelines about optimal treatment approaches for patients with URTIs where this is a concern. Concerns with available time to consult treatment guidelines during consultations can be helped by the instigation of decision support systems (Table 3) as well as the ready availability of guidelines on smart phones and other electronic media, with social norms a powerful motivator for change

- Instigate additional educational activities where pertinent among medical and nursing students regarding antibiotics and AMR, as well as instigate/ enhance CPD activities once healthcare professionals qualify, with the help of relevant societies and the government (243). This can include communication skills with patients to help address current concerns
- Encourage physicians and nurse practitioners to become actively involved in ASPs across countries as well as push for electronic prescribing/ EHRs to improve data collection and management of URTIs with benchmarking a key motivator
- Encourage physician-pharmacist-nurse collaborative practices in the community to reduce self-purchasing of antibiotics where this a concern
- Ascertain attitudes to the instigation of point-of-care testing for potential roll out across the country, and instigate training programmes where pertinent

Pharmacists (Community)
- Ascertain current knowledge and beliefs about antibiotics and AMR especially for patients with URTIs, as well as the need to develop specific guidelines for the locality – building on, for example, initiatives in the Republic of Srpska (Table 2)
- Instigate additional educational activities among pharmacy students surrounding antibiotics and AMR where pertinent, as well as instigate/enhance CPD activities among community pharmacies with the help of relevant pharmaceutical societies and the government. This could include greater use of mobile technologies to audit and improve current practice and will help fulfil the goals laid out in Box 2 – recognising the key role pharmacists play in the management of patients with URTIs in ambulatory care especially in LMICs. This will lead to pharmacist playing a key role in driving forward ambulatory care ASPs
- Encourage pharmacists rather than technicians through CPD and other measures to be the principal personnel within community pharmacies reviewing antibiotic prescriptions and evaluating patients regarding their need for antibiotics especially for URTIs. As part of this, pharmacists should play a key role in public health promotions on enhancing appropriate antibiotics use as well as the dangers of self-purchasing of antibiotics as part of any ASP
- Pharmacists to work with health authorities to computerise and track medicine use with their patients thereby limiting self-purchasing. In addition, work with health authorities and societies to transition away from focusing on commercial retaining and business interests to professional healthcare provision where this is a concern

	• Advocate the introduction and benchmarking of national standards and guidelines for Good Pharmacy Practice (GPP) in community pharmacy settings as part of CPD (or upgrade these where such practices exist) to address inappropriate prescribing and dispensing of antibiotics for URTIs • Empower pharmacists to perform rapid diagnostic testing and assessments where appropriate and cost-effective as evidence by current high requests for antibiotics among patients with URTIs or their children in a number of LMICs, and to help review current antibiotic use among key stakeholder groups ***Patients and the public*** • Instigate health education programmes in schools if needed regarding the appropriate use of antibiotics and AMR • Ascertain the rationale for any self-purchasing of antibiotics for URTIs if needed. This is particularly important in LMICs where access, availability and affordability to see a physician are problematic. In these situations, legislation banning the self-purchasing of antibiotics may be counter-productive. This is especially important in rural areas where pharmacists may be the only healthcare professionals that patients see; alternatively, they cannot afford to see both a physician and to purchase pertinent medicines • Concurrent with this, increase advocacy for appropriate use of antibiotics, and increase access to information regarding antibiotics and AMR through advocacy programmes, patient information leaflets, social media, and other community-based activities • In addition, monitor and educate households at high risk of URTIs (e.g. those with young children) about antibiotics and AMR, again through multiple media including the internet and mobile technologies • Use educational initiatives to encourage parents/caregivers of young children to seek professional help for URTIs, including community pharmacists as the most appropriate person initially (Section 3.4.3)
Longer term potential strategies	The findings from the situational analyses and ongoing educational activities can be used together with other research findings within each LMIC to develop pertinent strategies for all key stakeholder groups. Ongoing strategies are likely to include: • Health authorities/ Governments o Regular monitoring of the prescribing and dispensing of antibiotics for patients with URTIs as part of agreed NAPs, including creating databases. This includes instigating electronic prescribing and tracking systems and addressing issues with telemedicine where concerns are raised o Instigation of additional multiple strategies where pertinent to improve antibiotic utilisation for URTIs – including potential point-of-care testing, clinical decision support systems, regular updating of guidelines including those for infection prevention and control as well as academic detailing o Regularly review ongoing vaccination programmes and update if necessary – this may mean the need for additional donor help o Increasing investment in research for new and existing antimicrobials, diagnostic tools, alternative medicines and vaccines

- Physicians and nurse practitioners prescribing antibiotics
  - Regular reviews of current educational activities in medical/nursing schools regarding students' knowledge of antibiotics, AMR and ASPs especially for patients with URTIs in ambulatory care, and adapt/update where necessary
  - Regular monitoring of prescribing activities for patients with URTIs in ambulatory care using both quantitative and qualitative research methods - helped by IT systems and mobile technologies. This can include accountability systems for prescribers where they have to justify the need for an antibiotic for patients with URTIs as well as the antibiotic selected (building on restrictions for certain antibiotics in a number of countries as well as the WHO Access, Watch, Reserve – AwaRe - antibiotic groupings (40, 71, 387, 388))
  - Seek to instigate additional measures to improve the prescribing of antibiotics in patients with URTIs where appropriate - building on systematic reviews such as Dyar *et al* and McDonagh *et al* (85, 151). This can also include refinement of any QIs produced (Supplement Box D) as these should be regularly reviewed. In addition – cognisant that physicians in different countries have different attitudes towards authorities (38)
- Pharmacists
  - Regular reviews of current educational activities in pharmacy schools regarding student knowledge of antibiotics, AMR and ASPs especially for patients with URTIs in ambulatory care, and adapt/ update where necessary
  - Act where necessary to ensure education and CPD activities fully equip pharmacists for their extended roles as custodians and managers of antibiotics in ambulatory care. This can include instigating prescribing licenses for rural pharmacies building on examples in countries where pharmacists are allowed to dispense antimicrobials under guidance (49, 123, 133)
  - Ongoing research regarding the management of patients with URTIs in community pharmacies including limiting the self-purchasing of antibiotics where this currently exists. Instigation of additional activities including updated guidelines where relevant, as well as review of initiatives including additional education and incentives
  - Development of pharmacist-led vaccination programs within the community to prevent respiratory tract infections
  - Strengthening the enforcement of pharmacy laws to curb irrational dispensing of antibiotics where pertinent. Medicine tracking systems and mobile technologies can also be effectively utilised to reduce inappropriate dispensing
- Patients and the public
  - Regular review of the influence of any educational activities for their effectiveness, cost and value in all media and sites (starting in schools)
  - It is likely that educational activities will need to be refined and regularly repeated to take account of, for example, new

		mothers who have not been exposed to previous initiatives/not aware of these and new elderly patients become more susceptible to URTIs

NB: AMR = antimicrobial resistance, ASPs = antimicrobial stewardship programmes, CPD – continuous professional development, EHRs: Electronic Health Records, NAP = national action plan, QIs = quality indicators; URTIs = upper respiratory tract infections

Supplement Box D contains key activities that must be borne in mind when developing and testing new QIs for specific situations in ambulatory care among LMICs, building on previous examples (Box 1 and Supplement Boxes A to C).

These multiple activities among all key stakeholder groups should be combined as part of ASPs in ambulatory care to improve the future use of antibiotics, and build on ongoing NAPs. Further research though is needed in LMICs to measure the impact of such initiatives especially around reducing the self-purchasing of antbiotics; tracking antibiotics through the supply chain; enforcing legislation where pertinent and developing cost-effective health educational initiatives among patients and parents of children. We will be monitoring and reporting on such activities in the future.

We are aware of a number of limitations with this research including the fact that we did not undertake a systematic review. However, the reasons for this are discussed. We have though contextualised the findings of numerous publications to provide direction of possible short, medium and long term strategies to enhance the appropriate use of antibiotics in patients with URTIs especially in LMIC. We believe these recommendations are robust based on the experience and knowledge of the multiple co-authors across LMICs, and should provide future guidance.

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