INTERVENTIONS TO REDUCE ANTIBIOTIC PRESCRIBING FOR UPPER RESPIRATORY TRACT INFECTIONS IN PRIMARY CARE SETTINGS, A MAJOR DRIVER FOR ANTIMICROBIAL RESISTANCE

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We conducted a systematic review of interventions to reduce antibiotic prescribing for upper respiratory infections in primary care. We searched PubMed, Cochrane, Embase, and Google Scholar from 1 January 1980 to 28 February 2018 for published studies, using the following keywords: "antibiotics", "antibiotic prescribing", "primary care", "respiratory infectious", "respiratory diseases", "education", "training", "RCT" and "randomized control trial". Out of 133 studies, we identified 16 trials reporting results relating to interventions for reducing antibiotic prescription rates (APR) in primary care settings. Of these, 12 were conducted in high-income countries (five in the United States, five in Europe, one in Canada and one in Israel), and four in low- and middle-income countries (LMICs) (two in China, one in Vietnam and one in Iran, but only two were properly designed and implemented). Interventions ranged from 14 days to 18 months, targeting either clinicians (11), patients/caregivers (one) or both (four). We reported the intervention strategies, their effects and the gaps in these studies. We called for more studies in developing countries, and studies examining the long-term effects of interventions, to guide international AMR strategies in primary care settings.

Antimicrobial resistance has become one of the most important global health threats with adverse effects on patient health outcomes and health expenditure. The attributable costs per patient with infections of antimicrobial-resistant organisms were US$ 6,000 to US$ 30,000 more than patients with antimicrobial-susceptible organisms *(1)*. Taking societal cost into consideration, a reduction of 0.4% to 1.6% of gross domestic product (GDP) due to antimicrobial resistance was projected in 2004, which is equivalent to many billions of today's dollars globally *(2)*.

Upper respiratory tract infections (URIs) are the most common reasons for children to come to primary care facilities and they are mostly viral infections and self-limiting, and thus don't require antibiotics. However, URIs are frequently associated with high numbers of antibiotic use, ranging from 20% to 90%, with the highest rates being reported in Africa and Asia *(3)*. This is problematic because misuse of antibiotics contributes to the global issue of antimicrobial resistance. Given that primary care settings are usually associated with poor diagnostic tools and less-qualified doctors in developing countries, URIs could be a good starting point to reduce antibiotics use, as they are easier to be diagnosed and treated without antibiotics compared to other diseases, such as pneumonia, which are relatively more complicated.

There have been a number of randomized, controlled trials investigating the impact of interventions to reduce antibiotic prescription rates in clinical cases of URIs. Interventions can be categorized based on whom the intervention was targeted towards: clinicians, patients or both. Including trials that investigated URI patients of all ages, ten interventions targeted clinicians only *(4-14)*, one intervention targeted patients only *(15)*, and three interventions targeted both

patients and clinicians *(16,17,18)*. Intervention strategies on clinicians included clinical guidelines, peer leader training and regular feedback on antibiotic prescription rate. Intervention strategies on patients was focused on patient education with brochures, videos and posters. Ten out of 15 of the included studies were successful in creating a drop of antibiotic prescription rate in the intervention group compared to control group. The relative reduction ranged from 3% to 29% in terms of absolute antibiotic prescribing rate reduction. A study investigating a clinician-only intervention *(12)* and a study investigating a patient-only intervention *(15)* saw no impact. This indicates that the interventions targeting both patients and clinicians are more effective.

A meta-analysis of studies investigating interventions specifically towards antibiotic prescription rates in patients aged 18 and under presenting with URI showed a similar trend *(19)*. The papers selected for analysis included seven cluster RCTs, two individual RCTs, and three non-RCTs. While in general, interventions in these papers were associated with lower antibiotic prescription rates, it was specifically interventions that targeted clinicians and parents that showed a significant effect.

Investigating quasi-experimental trials targeted at both pediatric and general populations had less strong evidence, but they gave insights into effective interventions. Most studies employed a similar strategy of interventions on providers or patients. In addition, one used the tool of universal health insurance to stop reimbursement of antimicrobials for acute upper respiratory infections unless evidence of bacterial involvement was provided *(20)*; the other improved patients' access to point-of-care tests: Strep A and C-Reactive Protein *(21)*. Seven out of eight studies saw a reduction in antimicrobial use. In the four studies that antibiotics prescription rate was used as the indicator, the reduction ranged from 9%–32% *(21-24)*.

Intervention strategies

Peer leader training

Active peer leader training is the most common and effective way to reduce antibiotics use in primary care settings. The training could be conducted through online or onsite tutorial followed by interactive seminar. Training content covers a variety of issues, including principles of prescribing, diagnosis, antibiotic therapy, therapy with anti-inflammatory agents, adverse reactions to drugs, drug interactions, determinants for antibiotic prescription and clinician-patient communication skills. The main purpose of the training is to persuade doctors to reduce unnecessary antibiotic use. However, when antibiotics are indeed necessary, training needs to be moved to teaching appropriate use of antibiotic categories, such as penicillin instead of macrolides and cephalosporin that may potentially promote antibiotic resistance.

Communication skills are as important as, if not more than, other medical-related contents for the training, especially in the countries where the clinician-patient relationship is poor or patients show less trust in doctors. In some cases, it is not the medical knowledge that prevents a doctor from not prescribing antibiotics, but the doctor's concern that patients/caregivers may complain if their symptoms cannot be relieved in a short time. This usually happens when patients/caregivers actively request for antibiotics. Thus, doctors need to be trained to explore patients'/caregivers' main concerns, ask about their expectations and discuss prognosis, treatment options and reasons that should be referred to hospitals of higher level when applicable, and involve patients/caregivers in the decision-making process.

Changing doctors' behaviour is not an easy job and it is hard to sustain. When doctors really wish to improve their professional standards and provide better healthcare, it will be more likely to change their behaviours. Thus, physician engagement and commitment to the educational process is essential for successful training. This could be accomplished by guiding the physicians to play an active role in the training, e.g., role play and group discussion, with the help of a training facilitator, as well as involving local leaders in leading and supervising the training.

Operational guideline

A refined operational clinical guideline, usually less than 20 pages, is essential for primary care physicians, both in the training and the routine consultations. Unfortunately, most international and national AMR guidelines are written by specialists and are too comprehensive, often as thick as a textbook which is not very user-friendly. Clinical pathways or algorithms are effective tools that could be used in the guideline to change antibiotic-prescribing behaviour. They could be designed as a one-page decision support algorithm for each infection, assisting physicians on whether an antibiotic should be prescribed, the optimal antibiotic choice when indicated and the shortest appropriate duration of therapy. Involving patients in decision-making is also a proven way to reduce antibiotics in developed countries *(25)*. It's also important to include referral to respiratory specialists for severe conditions.

Peer reviews or feedback on antibiotics prescription rate

Conducting peer reviews regarding antibiotic prescribing has proven effective. Feedback on antibiotics prescription rate, serving as a stewardship tool, can be conducted in several ways, e.g., calculating prescribing indicators using data extracted from a hospital information system on a monthly or quarterly

basis, ranking healthcare providers at both individual and institution levels using the prescribing indicators and displaying the reports in a public space, submitting performance reports to local health authorities or mailing peer comparison to individual clinicians. Personalized and institution-based prescription audits are essential in this intervention strategy, which could easily be done where electronic prescription data are available. However, it becomes a challenge in some primary health care settings where only paper-based prescription records are used. Alternatively, they can randomly select a sample of prescriptions to review on a regular basis.

How the peer-review is conducted matters to its effectiveness. A trial in China has shown that primary care facilities having senior physicians leading the reviews, having clearly set prescription targets and sanctions for over-prescribing achieved much greater level of antibiotic reduction *(18, 26)*.

The antibiotics prescription rate feedback could be used together with other antibiotics stewardship strategies to achieve better effectiveness. Firstly, it could be linked with performance evaluation for an individual physician or healthcare facility, with relevant reward or sanction. Medical insurance authorities, local health authorities and health organization managers can use the feedback data for decisions in payment or reimbursement, health planning and other performance management. Secondly, the feedback data could be transparent to their patients, displayed in the public area of a healthcare facility, together with key health education messages on how it is linked with quality of care. This effect may be limited where health literacy of local population is poor. In conclusion, antibiotics prescription feedback may impose "pressures" on health providers arising from government, managers, colleagues and patients. However, the level of pressure depends on access to feedback, how the population understand it and whether reward and sanction is involved.

New diagnostic tools

C-reactive protein (CRP) has been proved as a reliable test in primary care settings to predict pneumonia. Studies have shown that training physicians in CRP testing lowered antibiotic prescription rates by between 10–20% *(6, 14, 27)*. Training of physicians on antibiotic prescribing is normally the first step of these trials. The European trial employed internet-based training and showed a 15% reduction in antibiotic prescribing rates *(6)*. Another recent trial introduced CRP in Vietnam and achieved a 20% reduction of antibiotic prescribing in two weeks *(14)*. CRP should be used to address lower respiratory tract infections, not URIs to maximize its cost-effectiveness. CRP has two major limitations: 1) it is relatively costly for developing countries; and 2) it has a blur area in cutoff values where no indication of viral or bacterial infections can be drawn. The effect of using CRP, both for economic and clinical reasons, seems to be diminishing quickly over time. In the IMPACT study, a three and a half-year follow-up found that physician training on antibiotic use and communication skills, not the use of CPR, were likely to be the major reason to maintain the intervention effect in the long-term *(28)*.

Patient/caregiver education

Patient/caregiver education included face-to-face health education during the consultation delivered by doctors (which is more efficient), and education materials handed out, such as leaflets and posters, and videos displayed in waiting rooms. The content of health education materials should be designed to be eye-catching and acceptable by the local population. Electronic versions could be kept by healthcare facilities, so that they can print by themselves after the interventions have ended. Alternately, in the areas that mobile devices are available, health education materials could be designed into these devices and updated via a communication network.

Interventions in developing countries

Most of above evidence derives from trials conducted in developed countries. Evidence from developing countries is rare where the problems are enormous. Up until now, there have been two well-designed and conducted trials in developing countries. One was conducted in rural Guangxi China, which is a relatively poor province bordering Vietnam and has an antibiotic prescribing rate for URIs as high as 70%–90% *(29)*, while another was conducted in northern Vietnam, close to Guangxi, with a similar high antibiotic prescribing rate of 80% *(14)*. The trial in China was to investigate the impact of an antimicrobial stewardship programme *(18)* in township hospitals that targeted both healthcare providers and caregivers of patients aged two to 14 years-old with a clinical diagnosis of URIs. The intervention package included evidence-based clinical guidelines, refresher training, monthly peer review meetings and health education information on appropriate antibiotic use during consultation. In the Vietnam trial, CRP, a diagnostic tool to distinguish either viral or bacterial infection was introduced. Both trials were successful. The trial in China lasted for six months and achieved a fall of 29% in antibiotic prescription rate compared with usual care; while the trial in Vietnam, followed up after two weeks, achieved a 20% reduction in antibiotic prescribing and a 14% reduction in antibiotic use, compared with usual care. Both studies are promising to developing countries. Interventions in China were designed to be embedded within routine primary care and that could easily be scaled up at country level: e.g., to make the best use of routine refresher training and monthly meeting opportunities. The Vietnam trial showed CRP would benefit

developing country settings, if proved cost-effective. However, long-term follow-up studies are badly needed to observe if these interventions, and their effects, are sustainable in a resource-constrained settings.

Conclusion

Effective antimicrobial resistance stewardship strategies in primary care settings have targeted both clinicians and patients/caregivers, which included user-friendly guidelines, training, peer-reviews/feedback to clinicians, use of new diagnostic tools such as CRP, and education for patients/caregivers. More evidence in developing countries, and the long-term effects of these interventions, are urgently needed. ■

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