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Initiatives across countries to reduce antibiotic utilization and resistance patterns; impact and implications

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Abstract

Introduction: Greater accessibility to antibiotics has resulted in their excessive use, leading to increasing antimicrobial resistance (AMR) and strains on healthcare systems,

with only a limited number of patients in ambulatory care treated according to guidelines. High rates of AMR are now seen across countries and continents, resulting in AMR becoming one of the most critical issues facing healthcare systems. It is estimated that AMR could potentially cause over 10 million deaths per year by 2050 unless addressed, resulting in appreciable economic consequences. There are also concerns with under-treatment especially if patients are forced to fund more expensive antibiotics as a result of AMR to first line antibiotics and do not have available funds. Over-prescribing of antibiotics is not helped by patient pressure even when physicians are aware of the issues. There is also extensive dispensing of antibiotics without a prescription; although this is now being addressed in some countries. Aim: Review interventions that have been instigated across continents and countries to reduce inappropriate antibiotic prescribing and dispensing, and associated AMR, to provide future guidance. Method: Narrative case history approach. Findings: A number of successful activities have been instigated to reduce inappropriate prescribing and dispensing of antibiotics across sectors. These include the instigation of quality indicators, suggested activities of pharmacists as well as single and multiple interventions among all key stakeholder groups. Conclusion: Multiple inter-linking strategies are typically needed to enhance appropriate antibiotic prescribing and dispensing. The impact of ongoing activities need to be continually analysed to provide future direction if AMR rates, and their impact on subsequent morbidity, mortality and costs, are to be reduced.

1. Introduction

1.1 Extent and threat of antimicrobial resistance and its impact on future healthcare and costs

Before the discovery of antibiotics, infectious diseases were the principal cause of morbidity and mortality (Md Rezal et al., 2015). This changed with their advent (Bosch et al., 2008; Alharbi et al., 2014; HMG, 2014). Antibiotics have now become the cornerstone of treatment for bacterial infections across healthcare sectors(van de Sande-Bruinsma et al., 2008; Holloway et al., 2011; WHO Europe, 2014; Laxminarayan et al., 2015), and are seen as an essential part of modern medical practice(Hwang et al., 2015). As a result, they are now amongst the most prescribed and dispensed medicines across health care settings (Larsson et al., 2000; Jande et al., 2012; Kho et al, 2013; Almeman et al., 2014; Md Rezal et al., 2015; Podolsky et al, 2015; Truter, 2015). Antibiotic utilisation increased 36% globally between 2000 and 2010, with Brazil, China, India, South Africa and Russia accounting for 76% of this increase (Van Boeckel et al., 2014; Laxminarayan et al., 2015). This is set to continue unless addressed.

Greater accessibility to antibiotics has resulted in their irrational and excessive use, leading to increasing antimicrobial resistance (AMR) and a concomitant strain on healthcare systems (Goossens et al., 2005; de Jong et al., 2008; van de Sande-Bruinsma et al., 2008; Davies et al., 2010; Kesselheim et al., 2010; de Kraker et al., 2013; Barnett et al., 2014; Versporten et al., 2014; Truter, 2015). For instance in Pakistan, the average number of antibiotics prescribed per physician encounter is 1.1 in ambulatory care and 2.4 for inpatient care (Riaz et al., 2015). In Botswana, only 31% of children were correctly prescribed an antibiotic and 40.3% of children who did not require an antibiotic left the health facility with a prescription for one (IMCI, 2004). In Kenya, antibiotics were prescribed in two thirds of patients seeing a physician for diarrhoea

(Brooks et al., 2006). In Kampala, Uganda, there was also appreciable self-purchasing of antibiotics for acute respiratory tract infections (RTIs) including common colds, mainly amoxicillin and co-trimoxazole, before patients or their families sought medical help (Massele et al., 2015). Self-purchasing of antibiotics is also common in many other countries despite being illegal in most (Chatterjee and Fleck, 2011; Godman et al., 2014; WHO Europe 2014; Massele et al., 2015; WHO, 2015), and is strongly correlated with increasing AMR rates in low-income and middle-income countries (LMICs) (Alsan et al., 2015).

The consumption patterns of antibiotics among humans and its use in agriculture, especially in animal husbandry, have been found globally to correlate with the development of AMR (Oduyebo et al., 2008; Goossens, 2009; Meyer et al., 2013; Adesokan et al., 2015; Velickovic-Radovanovic et al., 2015). Resistant strains of bacteria have been isolated from food animals, plant source and dairy products in different parts of the world (Brookes et al., 2006; Goossens 2009; de Kraker et al., 2013; WHO, 2015). The HIV/AIDS epidemic, especially on the African continent, coupled with the use of co-trimoxazole prophylaxis, has also increased AMR rates (Cotton et al., 2008; Marwa et al., 2015).

In addition, only a limited number of ambulatory care patients with infections are currently treated according to guidelines. Over 40% of prescriptions for antibiotics are considered inappropriate particularly for upper respiratory tract infections (URTIs), which are typically viral in origin (Gonzales et al, 2001; Holloway et al., 2011; Little et al., 2013; Barnett et al., 2014; Hassali et al., 2015). For instance a study in the UK concluded that the complication rate after URTIs is very low and antibiotic therapy is ineffective. As a result, the authors estimated 4000 patients or more with URTIs need to be treated with antibiotics to prevent a single episode of pneumonia (Petersen et al., 2007).

Overall, it is estimated that resistance rates of ≥50% are seen worldwide to common bacteria such as *Escherichia coli, Klebsiella pneumonia and Staphylococcus aureus* (WHO, 2014). In 15 European countries, more than 10% of bloodstream *Staphylococcus aureus* infections are due to *methicillin-resistant Staphylococcus aureus* (MRSA), with seven of these countries having resistance rates above 25% (ECDPC, 2015; HMG, 2014). High rates of antibiotic resistance are seen across Africa, the Middle East and Asia (Table 1), with 5 out of 6 WHO regions reporting high resistance rates leading to increased prescribing of second line antibiotics (WHO, 2014).

For instance in Tanzania in children aged between 0–7 years with septicaemia, AMR was a major risk factor for a poor outcome (Blomberg et al., 2007). In Uganda in patients with surgical site infections, extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* and MRSA organisms were also major risk factors for a poor outcome (Seni et al., 2013). AMR is of particular concern in community settings where infections are common and can easily be transmitted among the population (NCCID, 2010; WHO, 2014). However, the true burden of bacterial infections in many African countries, including South Africa, remains unknown (Laxminarayan et al., 2015; Mendelson et al., 2015).

Table 1 – Antibiotic resistance rates among African, Middle East and Asia countries

Country	Antibiotic resistance patterns
Asia	• High prevalence of AMR across Asian countries (Jean et al., 2011; Kim et al, 2012; Kang et al., 2013; Lai et al., 2014) • The prevalence of *Streptococcus pneumonia* resistant to erythromycin is 80.7% in Vietnam, 84.9% in Taiwan and 96.4% in China (Song et al., 2004; Kim et al., 2012; Kang et al., 2013; Lai et al., 2014)
Botswana	• MRSA in 22.6% of isolates from skin and soft tissue infections from hospitalized children and adults (Wood et al., 2009) • Hospital antibiograms in 2013 and 2014 in a tertiary care hospital in northern Botswana showed *Klebsiella pneumonia* is resistant to most beta-lactam antibiotics with less than 50% sensitivities (Massele et al., 2015)
India and Pakistan	• Up to 95% of adults have bacteria that are resistant to β-lactam antibiotics. This includes the carbapenems (Reardon, 2014)
Kenya	• Multi-drug resistant (MDR) *Non-typhi Salmonella* was 42% in 2003 (Kariuki et al., 2005), and the estimated incidence of community-acquired *Non-typhi Salmonella* was 166/ 100,000 people/ year for children <5 years (Berkley et al., 2005a). 35% of all *Non-typhi Salmonella* cases in newborns resulted in death in a National referral hospital (Kariuki et al., 2006) • MDR *S. typhi* was over 75% of all *S. typhi* among private clinics and the main referral hospital in Nairobi (Kariuki et al., 2010), with 43% of *S. Pneumonia* isolates in Nairobi resistant to penicillin (Kariuki et al., 2003). The prevalence of MRSA was 33% of *S. aureus* isolates at a National referral hospital (Ngumi, 2006) • *E. coli* isolated from among hospital patients were highly resistant to commonly used antibiotics including ampicillin, amoxycillin/clavulanic acid, and trimethoprim/ sulphamethoxazole, with less resistance to ciprofloxacin and third-generation cephalosporins (Kiiru et al., 2012). In one region, resistance to *E.coli* was 85% tocotrimoxazole, 78% to amoxicillin and 42% to chloramphenicol (Bejon et al., 2005) • 50% of isolates of *Haemophilus influenzae type B* from children with severe pneumonia were resistant to penicillin (Berkley et al., 2005b) • 65% of the *N. gonorrhoeae* isolates were resistant to penicillin and plasmid-mediated tetracycline resistance was 97%. In 2007, quinolone-resistant *N. gonorrhoeae* first appeared, increasing to 50% in 2009 (Mehta et al., 2011)
Malaysia	• The National Surveillance on Antibiotic Resistance in 2014 reported an increase in antibiotic resistance rates among common strains of bacteria such as *Streptococcus pneumonia*, *Enterobacter cloacae* and *Salmonella spp* (Ahmad, 2014) • Hospital acquired pneumonia associated with *Acinetobacter spp.* showed a very high rate of resistance to imipenem (86.7%) (Kang et al., 2013) • In a multicentre surveillance study, 60.6% of *Streptococcus pneumococcus* isolates were resistant to erythromycin (Kim et al., 2012)
Nigeria	• The susceptibility of antibiotics commonly used as empirical treatment for many infections in hospitals - especially those of the urinary tract, ear infections and post-operative wound infections - has declined considerably, e.g. as many as 88% of *Staphylococcus aureus* infections are resistant to methicillin (Reardon, 2014)

	• Studies have reported susceptibility rates to empiric antibiotics below 60% in urinary tract isolates and over 98% resistance to β-lactam antibiotics in post-operative wound infections(Okesola et al., 2011; Muoneke et al., 2012; Dibua et al., 2014) • Studies have also reported susceptibility rates below 50% for antibiotics used for empirical treatment of patients with community acquired pneumonia (Iroezindu et al., 2014)
South Africa (Mendelson et al., 2015)	• 50% of all hospital-acquired *S. aureus* in public hospitals in 2010 were MRSA, with MRSA accounting for 75% of all hospital-acquired *S. aureus* infections in a large tertiary level paediatric hospital. • *Enterococcus faecium* bloodstream isolates from the private sector showed variable sensitivity to vancomycin, ranging between 33-100% depending on the geographical location • Up to 75% of *K. pneumonia* isolated from hospitalised patients were ESBL producing bacteria • 16% of carbapenem–susceptible *Enterobacteriaceae* in the private sector contained acarpapenemase producing gene, and Carpapenemase-producing *Enterobacteriaceae* are widespread among public hospitals in South Africa
Vietnam (Hoa et al., 2011; Van Nguyen et al., 2013; Van et al., 2014)	• Pneumococcal penicillin-resistance rates are typically the highest in Asia, with carbapenem-resistant bacteria (notably NDM-1) recently emerging • *Streptococcus pneumoniae* penicillin-resistance rates increased from 8% to 75% from 1999 to 2007 in Ba Vi, not helped by high rates of self-purchasing of antibiotics (Table 3) • More than 90% of isolates from principally patients in an intensive care unit in Hanoi tested for resistance to *A. baumannii* were resistant to tested b-lactamase inhibitors/ b-lactamase, carbapenems,cephalosporins, fluoroquinolones and trimethoprim/sulfamethoxazole. Overall, 25.4% of isolates were resistant to all tested aminoglycosides, b-lactams and quinolones • There has been a significant increase in resistance of *Streptococcus suis* to tetracycline and chloramphenicol in isolates between 1997and 2008, concurrent with an increase in multi-drug resistance organisms

MRSA is also a common problem worldwide. New community-acquired strains of MRSA (CA-MRSA) are also now emerging causing concern (FIP, 2008).

Increasing AMR rates is now seen as one of the most critical problems facing healthcare systems (WHO, 2001; Sumpradit et al., 2012; Barlam et al., 2015; Hoffman et al., 2015a). It is estimated that AMR infections currently cause approximately 50,000 deaths a year in Europe and the US alone (HMG,2014). This increases to several hundred thousand deaths each year when other countries are included (HMG,2014). The continual rise in AMR could result in it becoming a leading cause of death worldwide by 2050 with over 10 million deaths per year, potentially reducing GDP by 2% to 3.5% and costing up to US$100 trillion (HMG, 2014; Md Rezal et al., 2015). Other authors have suggested lower costs; however, their estimates typically fail to consider the costs for patients or health authorities after patients are discharged from hospitals (Gandra et al., 2014).

As a result of increasing AMR rates, common infections are becoming more difficult to treat, causing life-threatening illnesses and potentially death (Costelloe et al., 2010).

This combination of overuse of antibiotics, misuse, stopping treatment before courses are finished, cultural differences, and under use due to a lack of access and financial support, are seen as key drivers of AMR (WHO Europe, 2014; Klein et al., 2015; Laxminarayan et al., 2015; Md Rezal et al., 2015). These factors lead to the phenomenon which has been termed selective pressure (WHO, 2001).As mentioned, increasing antibiotic resistance poses a threat to health and healthcare systems across countries as it can lead to high associated costs (Van Nguyen et al., 2013), for example forcing a shift to more expensive and more broad spectrum antibiotics (Laxminarayan et al., 2012; Md Rezal et al., 2015).

Improving the rational use of antibiotics is one of the best ways to slow down the development and spread of AMR (van de Sande-Bruinsma et al, 2008; Sumpradit et al., 2012; Earnshaw et al., 2013). This means addressing issues such as physicians' lack of adherence to treatment guidelines and their lack of knowledge and training regarding antibiotics, the lack of diagnostic facilities as well as uncertainty over the diagnosis, pressures from patients and the pharmaceutical industry, and finally fear of clinical failure (Little et al., 2013; Van Nguyen et al., 2013; Hassali et al., 2015; Md Rezal et al., 2015; Riaz et al., 2015). In LMIC countries and others, this also includes implementing regulations surrounding the dispensing of antibiotics including self-purchasing where this is a concern (Radyowijati et al., 2003; Kotwani et al., 2010; Li et al., 2012; Van Nguyen et al., 2013; Holloway et al., 2014; Holloway et al., 2015).

Adoption of antimicrobial resistance strategies in countries including South Africa and Vietnam as well as the WHO Europe strategic action plan on AMR, the recent WHO global report on antimicrobial resistance documenting alarming levels of AMR in many countries and the endorsement of the Global Action Plan for Antimicrobial Resistance in May 2015 are seen as important steps to help reduce AMR (WHO Europe, 2011; Department of Health RSA, 2014; WHO, 2014; Abdula et al., 2015; Cluzeau et al., 2015; Mendelson et al., 2015).

1.2   Physician attitudes towards antibiotics

A recent systematic review showed that physicians still have limited knowledge and misconceptions about antibiotics and their prescribing (Md Rezal et al., 2015). In addition, some physicians still prescribed antibiotics despite knowing they are generally of limited benefit in a number of situations (Md Rezal et al., 2015). For instance in Brazil, 38.2% of interviewed patients declared that they had taken antibiotics in the previous 6 months. For patients who had received an antibiotic prescription for oral/dental infections, only 9.3% presented with a fever, indicating over prescribing of antibiotics by physicians (Del Fiol et al., 2010).

Several factors influence physician prescribing of antibiotics. These include the severity and duration of infections, expectations of patients, uncertainty over diagnosis, the risk of losing patients, and pharmaceutical company influence (Md Rezal et al., 2015). Inadequate knowledge regarding the prescribing of antibiotics appears prevalent among physicians across countries. However, many physicians are interested in addressing this to help reduce AMR rates (Md Rezal et al., 2015). Qualitative research undertaken by Thatoyaone Kenaope and colleagues also found that among pharmacists in South Africa, the socio-economic status of patients, patient satisfaction, their knowledge of

antibiotic indications and the professional relationships between healthcare professionals also influenced physician prescribing behaviour (Massele et al., 2015).

To be able to successfully reduce AMR rates, physicians need to be knowledgeable about the prevailing epidemiology of infections and current antimicrobial sensitivity status in their location as well as strictly comply with evidence based treatment guidelines. However, across-national study conducted among physicians in England and France found only 31% and 26% of physicians respectively knew the correct prevalence of antibiotic misuse and of MRSA in their hospitals (Pulcini et al., 2011). Among medical doctors and students in the Congo Democratic Republic, there was very limited knowledge of local antimicrobial resistance patterns (Thriemer et al., 2013). These and other studies demonstrate the need to tackle all key stakeholder groups to enhance appropriate prescribing and dispensing of antibiotics.

1.3   Antibiotic prescribing and dispensing in pharmacies

There is a large body of literature discussing pharmacists' antibiotic dispensing practices across countries, e.g. in Kenya 25% of the population go to retail pharmacies first before seeking out-patient care (Sharma et al, 2008; Thoithi et al, 2009). This is illustrated by 24% of patients with symptoms of acute RTIs in rural Kenya already purchasing an antibiotic from pharmacies before seeing a physician (Bigogo et al., 2010).

As mentioned, dispensing of antibiotics without a prescription, albeit unlawful, is common. Countries where this happens include Albania (Hoxha et al., 2015), Brazil (Rauber et al., 2009), Egypt (Dooling et al., 2014; Sabry et al, 2014), Greece (Contopoulos-Ioannidis et al., 2001; Plachouras et al, 2010), India (Kotwani et al., 2012; Salunkhe et al., 2013), Iraq (Mikhael, 2014), Jordan (Almaaytah et al., 2015), Lebanon (Farah et al, 2015), Portugal (Roque et al., 2014; Roque et al., 2013), Saudi Arabia (Abdulhak et al., 2011; Emeka et al., 2012; Al-Mohamadi et al., 2013), Serbia (Godman et al., 2014), Spain (Zapata-Cachafeiro et al., 2014), Syria (Bahnassi, 2015) and the United Arab Emirates (Abasaeed et al., 2013). Table 2 illustrates the extent of self-purchasing across countries.

Table 2. Examples of the extent of dispensing antibiotics without a prescription

Authors	Country	Extent of dispensing antibiotics without a prescription (%)
Hoxha et al.,2015	Albania	80.0
Farah et al., 2015	Beirut, Lebanon	32.0
Volpato et al, 2005*	Brazil	74.0
Almaaytah et a.l, 2015	Jordan	74.3
Salunkhe et al., 2013	Pune, India	94.7
Abdulhak et al., 2011	Riyadh, Saudi Arabia	77.6

*NB Studies conducted before prescription requirements in November 2010 among private pharmacies.

However in some countries such as Thailand, pharmacists are allowed to dispense antibiotics without a prescription (Saengcharoen et al., 2008). Among the wider European countries including former Soviet Union countries, it is also currently possible and legal to purchase antibiotics over-the-counter (OTC) without a prescription in 19 out of the 44 countries (WHO Europe, 2014), and this is also possible outside of pharmacies (12 out of 44 countries). In 5 out of the 44 countries surveyed, it is also

possible to purchase antibiotics over the internet without a prescription (WHO Europe, 2014). The situation is different in many high-income countries where regulations are typically strictly implemented, e.g. New Zealand (Dameh et al., 2012).

Among many Latin American countries, including Brazil and Mexico, restrictions on OTC sales of antibiotics were implemented in 2010 (Santa-Ana-Tellez et al., 2015). This included the requirement for a prescription for antibiotics to be dispensed even in private pharmacies. A prescription for antibiotics was always a requirement among public pharmacies in Brazil. A recent study showed a reduction in inappropriate penicillin use (as proxy for antibiotics use) among private pharmacies in Mexico after this government initiative (Santa-Ana-Tellez et al., 2015); although, a limited reduction in Brazil. However, another study showed a significant decrease in antimicrobial sales among private pharmacies in Brazil following the restrictions in November 2010 (Moura et al., 2015). The impact of the restrictions was greater in regions with overall higher socio-economic status (Moura et al., 2015).

In a systematic review of published work on antibiotic self-medication in developing countries, the overall prevalence of antimicrobial self-medication was 38.8%. Identified determinants of self-medication were citizens' age, level of education, sex, income, severity of their disease condition and history of previous successful use of antibiotics (Ocan et al., 2015). Table 3 contains additional data on the extent of self purchasing.

Table 3 – Extent of self purchasing of antibiotics across continents and countries (building on Table 2)

Countries	Extent of self purchasing
Brazil*	• In a study conducted in Tubarão, 85.0% of pharmacists dispensed an antibiotic without a prescription, mainly for the treatment of respiratory (62.8%) and urinary (12.0%) tract disorders. In most cases, this was for adults (64.0%), but also children (27.8%), the elderly (3.3%) and for pregnant women (1.6%) (Rauber et al., 2009) • In Jataí, antibiotic self-medication was seen in 9.1% of participants; however, 9.1% used antibiotics as recommended by pharmacists in the last month. 20.5% of responders also traditionally recommend the use of antimicrobials to family and friends (Braoios et al., 2013) • In a population-based study inBambuí, self-medication in the last 90 days was reported for 28% of the 1,221 resident and antibiotics and chemotherapeutics accounted for 6.2% of non-prescribed drugs (Loyola Filho et al., 2002)
Ethiopia (Gebeyehu et al., 2015)	• Antibiotic self-medication was common among community dwellers with RTIs, diarrhoea and physical injury
Greece (Mitsi et al., 2005)	• 74.6% of the general public reported taking non-prescribed antibiotics
Northern Israel (Raz et al., 2005)	• 18.7% of the general public reported taking antibiotics without seeking medical advice
Kenya (Karambu, 2011)	• 70% of sampled pharmacies did not ask patients for a prescription before dispensing antibiotics as required by the law • In addition, only 9% of pharmacies asked for a prescription and 18% declined to sell the antibiotics after a prescription was presented
Malaysia (Islahudin et al., 2014)	• 45.1% of patients did not consult a physician before taking antibiotics
Middle East/ Jordan	• Specifically in Jordan among Middle-East countries, self-medication with antibiotics is high (39.5%). This is significantly associated with age, education and income(Al-Azzam et al., 2007) • A high level of self-medication (40.7%) was also reported in another Jordanian study (Sawair et al., 2009).
Nigeria (Enato et al., 2011).	• In a community based study conducted in the southern part of Nigeria, over 93.6% of community dwellers who reported they were ill self-medicated with antibiotics
Serbia	• Illegal self-purchasing of antibiotics increased their utilisation by 115% to 128% in recent years compared with reimbursed utilisation (Godman et al., 2014) • This resulted in Serbia having the 3rdhighest utilization for cephalosporins in 2007 among European countries, highest for penicillins, 2ndhighest for macrolides and 3rdhighest for quinolones (Bajcetic et al., 2012) • Following this, there has been tightening of the regulations regarding self -purchasing in pharmacies, leading to a decrease in overall utilization in recent years (Godman et al., 2014)
Vietnam (Van Nguyen et al., 2013; Cluzeau et al., 2015)	• The Pharmaceutical Law (2005) made antibiotics prescription-only medicines; however, there are currently no sanctions. In addition, no pharmacist has been penalized for dispensing antibiotics without a prescription (as of March 2013)

	• Self-medication persists as it avoids lengthy and costly consultations with physicians and others in the formal healthcare systems • 91% of children in Ba Viin Vietnam in 1991 with symptoms of acute RTIs were treated with broad-spectrum penicillins, with 78% self-medicating. This corresponded to 75% of all children in this particular community • This is likely to change with the implementation of the National Plan to reduce antimicrobial resistance rates in Vietnam

* NB: All studies conducted before the changes in the law in Brazil

Several studies have reported that pharmacists have dispensed antibiotics for inappropriate conditions (Kotwani et al., 2012; Salunkhe et al., 2013; Dooling et al., 2014; Mikhael, 2014; Sabry et al., 2014), e.g. in Iraq, 45% of community pharmacists dispensed antibiotics for a common cold. Community pharmacists also dispensed several types of antibiotics including amoxicillin, amoxicillin/clavulanate, azithromycin and ciprofloxacin (Mikhael, 2014). In India, azithromycin was commonly dispensed for a sore throat in 51.2% of cases. Furthermore, antibiotics for a sore throat were only dispensed in correct doses and durations in 64.2% of cases (Salunkhe et al., 2013).

Consequently, pharmacists in many countries play a key role with enhancing the appropriate use of antibiotics given the extent of self-purchasing (WHO Europe, 2014) (Tables 2 and 3). This, coupled with concerns with appropriate prescribing and rising AMR rates, led FIP (International Pharmaceutical Federation) to urge pharmacists to undertake a number of activities to reduce this, supported by suggested activities among health authorities and governments (Box 1).

Box 1 – Suggested activities of pharmacists to reduce AMR [Adapted from (FIP, 2008)]

A) *FIP urges pharmacists to:* • Patients given proper counselling as well as provided with written information that is appropriate when dispensing antibiotics. In addition, encourage patients to comply with the full prescribed regimen. If not possible, ask them to dispose of any unused antibiotics appropriately • Work with physicians to ensure patients complete their course and correct antibiotics and doses are prescribed by providing up-to-date information. Similarly for other healthcare professionals influencing or administering antibiotics • Monitor the supply of antibiotics • Recommend treatments other than antibiotics for minor conditions such as a common cold • Become actively involved regarding hygiene and infection control across health care settings B) ***FIP urges governments and health authorities to***: • Implement antimicrobial surveillance plans nationally including monitoring of antibiotic utilisation in agriculture, humans, and veterinary medicine • Implement measures to enhance the appropriate use of antibiotics as well as stop their sale/ dispensing without a prescription or order from a qualified healthcare professional. This includes measures to strengthen regulatory and legislative controls regarding the supply antibiotics including the enforcement of any statutes and regulations to improve the rational use and dispensing of antibiotics • Impose restrictions on the prescribing of selected antibiotics; the objective being to limit development of AMR • Conduct education campaigns among all key groups to help promote the appropriate use of antibiotics. In addition, collaborate with all health professional societies to develop and help implement educational and behavioural interventions to improve appropriate antibiotic prescribing • Help with establishing infection control programs to reduce AMR • Instigate methods to dispose of antibiotics where necessary that are environmentally sound

The WHO in Europe has also produced guidance encouraging the prudent use of antibiotics including the role of pharmacists (WHO Europe, 2014). This is alongside documenting 7 key areas on potential ways to reduce AMR rates across Europe (Box 2).

Box 2 – 7 key action areas identified by WHO Europe to address AMR [Adapted from (WHO Europe, 2014)]

- To strengthen co-ordination across healthcare sectors and personnel
- To strengthen the surveillance of AMR rates as well as antibiotic utilisation patterns among the countries in WHO Europe
- Instigate measures to enhance the rational use of antibiotics (building on existing programmes)
- Strengthen infection control across all health-care settings
- Instigate measures to help prevent emerging antibiotic resistance strains in food and veterinary sectors
- Help instigate appropriate measures that help promote research into new antibiotics given their current scarcity
- Improve awareness including partnerships to promote patient safety and reduce AMR rates across Europe

Other authors and organisations have also endorsed the need for greater education of pharmacists regarding antibiotics during their training (Ahmad et al., 2015).

1.4 Public knowledge and attitudes towards antibiotics

Published studies have shown that there is a general lack of knowledge about antibiotics among the general public (Eng et al., 2003; McNulty et al., 2007a; Grigoryan et al., 2008; You et al., 2008; André et al., 2010; Oh et al., 2011; Al-Haddad., 2012; Chan et al., 2012; Lim &The., 2012; Napolitano et al., 2013; Van Nguyen et al., 2013; Fatokun, 2014; Islahudin et al., 2014; Gualano et al., 2015; WHO, 2015). Even in some countries in which public awareness campaigns on antibiotics had been conducted, there was still widespread belief that antibiotics are effective against viral infections (WHO, 2014). Further inappropriate antibiotic prescribing, including unnecessary prescribing of antibiotics, has heightened public perceptions that these medicines are first-line treatment for common infections such as URTIs. These perceptions do lead patients to pressurize physicians to prescribe antibiotics regardless of the indication (Hassali et al., 2015; Md Rezal et al., 2015). These pressures are enhanced by patients' perception of antibiotics as powerful therapies, with the ability to quickly stop symptoms (Sharma et al., 2008).

Gualano et al (Gualano et al., 2015) recently conducted a systematic review regarding public knowledge and attitudes towards antibiotics. The authors demonstrated that 53.9% of the general public believed antibiotics can be used to treat viral infections, with 50.9% perceiving antibiotics can be used to reduce inflammation with 33.7% unaware that antibiotics should only be used to treat bacterial infections.

There are also concerns that the public do not take their antibiotics according to the instructions on the label, take incomplete courses, take leftover antibiotics from previous treatments and share their antibiotics with others, particularly in LMICs (Zarb et al., 2012). For instance in Bangladesh, 51.4% of the general public did not take their antibiotics according to the label instructions (Sutradhar et al., 2014), and in Brazil, 30% of those interviewed could have had their antibiotic treatment compromised by ignoring their current diagnosis (the indication for which an antibiotic was prescribed);

for not understanding the dosage and administration schedule; or both (Nicolini et al., 2008).

In Asia, Europe, North America and Oceania, 47.1% of patients stopped taking antibiotics when their symptoms disappeared (Gualano et al. , 2015). In Tetovo in the Republic of Macedonia, 60.8% of parents kept leftover antibiotics at home for future use (Alili-Idrizi et al., 2014), whilst 25% of the general population in Belgium, Colombia, France, Italy, Morocco, Spain, Thailand, Turkey and the United Kingdom also saved leftover antibiotics for future use (Pechere, 2001). In Taiwan, 13% of the general public shared their antibiotics with their family and friends (Chen et al, 2005). This compares to 8% in similar studies in Hong Kong and Malaysia (You et al., 2008; Al-Haddad, 2012).

Several studies have shown a strong association between patient expectations and demands with excessive prescribing of antibiotics (Hamm et al, 1996; Macfarlane et al, 1997; Mangione-Smith et al, 1999; Gonzales, 2005; Mustafa et al, 2014). In Malaysia, 73.8% of the general population expect physicians to prescribe antibiotics for a common cold (Lim & Teh, 2012); whilst in Oklahoma, USA, approximately 65% of patients with respiratory infections expected to be prescribed antibiotics (Hamm et al., 1996). This may be because public awareness of antibiotic resistance is low across countries (Hawkings et al., 2007; Brooks et al., 2008; Brookes-Howell et al., 2012; Wun et al., 2013; Gualano et al., 2015; WHO, 2015).

Several studies have also explored public knowledge and perceptions of antibiotic resistance in Europe (Brookes-Howell et al., 2012), South India (Chandy et al., 2013) and the United Kingdom (Hawkings et al, 2007; Brooks et al, 2008). Most of the public had heard of antibiotic resistance but only a minority had the correct understanding of this term. The public often understood the term 'antibiotic resistance' as the body getting used to or becoming immune to antibiotics. Other members perceived antibiotic resistance as the body becoming incompatible with antibiotics, the illness becoming too strong for antibiotics to manage, and it is a hereditary illness (Brookes-Howell et al., 2012).

Most of the general public are also unaware of the causes and consequences of antibiotic resistance. In addition, they attributed antibiotic resistance to external factors such as overprescribing of antibiotics by physicians as opposed to internal factors, e.g. non-adherence to antibiotic therapy. As a result, they typically do not perceive themselves as being responsible for preventing the misuse of antibiotics (Hawkings et al., 2007; Brooks et al., 2008).

1.5   The need for public engagement to combat antibiotic resistance

In view of these misconceptions, public campaigns and engagement are needed to increase patients' knowledge about antibiotics and antibiotic resistance. Public engagement has been broadly defined as "involving the general public in decision-making and in the planning, design, governance and delivery of initiatives" (O'Mara-Eves et al., 2013).

In this context, the School of Pharmaceutical Sciences of Universiti Sains Malaysia, in collaboration with Action on Antibiotic Resistance (ReAct), has taken the initiative to

engage Yayasan Bina Ilmu (YBI) in addressing antibiotic resistance at the community level in Jelutong District, Penang, Malaysia. The School offers support and materials to the organization to undertake relevant work on antibiotic resistance, in line with their focus areas. Coordination, communication and commitment among all stakeholders play a key role in making this approach a success, with the findings used to support the development and implementation of a national policy to manage antibiotic resistance at the community level in Malaysia (Irawati et al., 2015).

2. Aims

Given the global importance of AMR, there is a need to review potential interventions and measures that have been instigated across continents, countries and regions to improve antibiotic utilization. Consequently, the aim of this chapter is to review interventions that have been introduced to reduce inappropriate prescribing and dispensing of antibiotics, and associated reduction in AMR, and their effectiveness to provide future guidance. This is seen as a conservatism strategy (Hoffman et al., 2015a).

It is recognized that alongside this, strategies must be instigated to enhance the development of new antibiotics to address current unmet need as well as limit their utilization to very targeted populations once launched (Hoffman et al., 2015a; Hoffman et al., 2015b; Outterson et al., 2015). This will potentially involve new methods of funding research (Brogan et al., 2013; Balasegaram et al., 2015; Hwang et al., 2015; Outterson et al., 2015). There is also a need for restrictions on the use of antibiotics in animals with for instance the utilization of antibiotics in animals in the US at least three times greater than the overall use in humans (So et al., 2015). However, new funding models for financing antibiotic research as well as programmes to reduce antibiotic use in animals are outside the scope of this chapter.

3. Methods

A narrative review of publications, including case histories, known to the co-authors to provide future guidance. This is because systematic reviews of potential approaches to improve the utilisation of antibiotics have already been undertaken by the co-authors and others (Huttner et al., 2010; Dar et al., 2015; Md Rezal et al., 2015).

We have undertaken similar approaches when reviewing measures to enhance the prescribing and dispensing of generics as well as initiatives to optimise the use of new medicines (Godman et al., 2012; Dylst et al., 2013; Godman et al., 2013; Godman et al., 2014; Godman et al., 2015).

4. Findings

The case histories will be divided into hospitals and ambulatory care. This will include the findings of meta-analyses as well as country and regional studies. There will also be a review of the impact of educational interventions on public knowledge and attitudes towards antibiotics and resistance.

4.1 Hospitals

- *Meta-analysis (Cochrane review) (Davey et al., 2013)*

This meta-analysis included 95 interventions principally targeting antibiotic prescribing. This included antibiotic choices as well as the timing of first dose and the route of administration. There was reliable data from 76 interventions including persuasive (majority), restrictive and structural interventions. Interventions that were restrictive in nature had a significantly greater impact on subsequent outcomes at one month and 6 months. However, there were no significant differences between the different interventions on outcomes at 12 or 24 months.

There was a reduction in *Clostridium difficile* infections as well as a reduction in the colonization or infections with resistant bacteria, including cephalosporin-resistant and aminoglycoside-resistant gram-negative bacteria, vancomycin-resistant *Enterococcus faecalis* and MRSA, with interventions that sought to reduce excessive antibiotic prescribing. There was also a significant reduction in mortality in interventions instigated to improve antibiotic prescribing in patients with pneumonia.

- *China (Zou et al., 2014)*

There have been considerable concerns regarding the over-use of antibiotics in China, driven by incentive systems for hospitals and physicians encouraging the use of IV versus oral antibiotics as well as their overuse (Reynolds et al., 2009; 2011). However, antibiotic prescribing is changing following a nationwide campaign instigating antibiotic stewardship programmes (ASPs) to address their over-use and AMR rates. A recent study assessing the impact of this nationwide campaign showed the following between 2011 and 2012:
- Decreasing antibiotic use (26.54 instead of 39.37 DDDs/100 inpatient days)
- Decreasing % of antibiotics among outpatient prescriptions and their use in hospital inpatients over the two years
- Correlation between subsequent antibiotic utilisation and the type and size of specialized hospitals; however not with the region

- *Scotland*

SAPG (Scottish Antimicrobial Prescribing Group) was established in Scotland in 2008 to coordinate a national antimicrobial stewardship programme (Nathwani et al., 2011). The collection of prevalence data in 2009 led to the development of two quality prescribing indicators: (i) the extent of compliance with antibiotic policies among acute admission units and (ii) surgical prophylaxis duration (Malcolm et al., 2013). Studies showed compliance with current antibiotic policies (81.0%) were similar to other European countries; however, the duration of surgical prophylaxis <24hr (68.6%) was higher than generally seen across Europe.

Following the implementation of prescribing indicators, there was an improvement in the indication noted in the patient records of ≥90%. Compliance with antibiotic prescribing policies also increased to 90% (Malcolm et al., 2013), with the mean proportion of patients receiving single dose prophylaxis following colorectal surgery exceeding95% (the target). Overall, SAPG has shown that the implementation of

national prescribing indicators, which are acceptable to clinicians and regularly audited, can improve subsequent antibiotic utilisation (Malcolm et al., 2013).

- *Zambia (Mubita et al, 2013; Massele et al., 2015)*

Mubita et al conducted a prospective quasi-experimental clinical audit project among Internal Medicine wards at a University Teaching Hospital in Zambia. The findings showed that the implementation of an antimicrobial prescribing care bundle was associated with an improvement in the quality of antibiotic prescribing in terms of compliance with its care elements.

A pilot study was undertaken to assess the implementation of an adapted antimicrobial prescribing care bundle. Subsequently, compare compliance of antimicrobial prescribing with the care elements (standards) of the antimicrobial prescribing care bundle before and after implementation. Implementation of the bundle involved educational programmes on antimicrobial stewardship. Topics covered included the antimicrobial prescribing care bundle, standard treatment guidelines on infections and the hospital antibiogram. Feedback on the control phase results was communicated to the prescribers. Posters of the Antimicrobial Stewardship-treatment algorithm were displayed within the medical wards. Pocket-sized cards of the Prescribers' Checklist as an aide – memoire were distributed to all prescribers in Internal Medicine.

Outcome measures were compliance with the care bundle's care elements as audit standards as well as:
- Presence of clinical evidence of bacterial infection
- Documentation of the clinical indication for antibiotics, the duration or review date as well as the route and dose of antibiotics prescribed
- Collection of appropriate culture specimens
- Appropriate empirical selection of antibiotics
- Documentation of appropriate prescribing decision option by 48 hours of antimicrobial therapy.

Table 4 shows a summary of the findings of the clinical audit project.

Table 4: Findings of the clinical audit project conducted in a teaching hospital in Zambia

Care element (audit standard)	Compliance level n (%)		p
	Control Phase (n = 128)	Intervention Phase (n = 128)	
Clinical evidence of bacterial infection	112(87.5)	116(90.6)	0.022
Documentation of the clinical indication, the duration or review date as well as the route and dose of antibiotics	9(7)	58(45.3)	0.522
Culture specimens collected according to standard treatment guidelines	84(65.6)	92(71.9)	<0.001
Appropriate empirical selection of antibiotics, i.e. prescribing according to standard treatment guidelines at initiation of antibiotics	73(57)	80(62.5)	0.333
Documentation of appropriate prescribing decision option by 48 hours of antimicrobial therapy.	64(50)	83(64.8)	<0.001
Overall compliance	7(5.5)	46(35.9)	0.044

This study recommended implementation of a formal antimicrobial stewardship programme among Internal Medicine Wards in Zambia. This would involve establishing multidisciplinary antimicrobial stewardship teams in hospitals with core membership comprising the following: an infectious diseases physician, a clinical microbiologist and a clinical pharmacist with expertise in infectious diseases.

4.2 Ambulatory care (settings, regions and countries)

4.2.1 Pharmacy dispensing

Chapter 1.3 together with Boxes 1 and 2 describe potential ways forward for pharmacists and others to reduce inappropriate dispensing and use of antibiotics. We are already seeing a number of countries tighten illegal self-purchasing of antibiotics, e.g. Brazil (private sector), Mexico and Serbia, and this will grow (Godman et al., 2014; Moura et al., 2015, Santa-Ana-Tellez et al., 2015).

4.2.2 European Surveillance of Antimicrobial Consumption (ESAC)

ESAC have suggested a number of aggregated and patient level quality indicators to improve future use of antibiotics. These include:

Aggregated indexes (in defined daily doses/ 1000 inhabitants/ day – DIDs) (Coenen et al., 2007):
- % combination pencillins including ß-lactamase-sensitive penicillins vs. All antibiotics
- % of 3rd and 4th generation cephalosporins vs. 1st and 2nd generation cephalosporins (and all antibiotics)
- % fluroquinolones vs. All antibiotics

- % Broad vs. Narrow penicillins, cephalosporins and macrolides

Quality indicators where patient level data is available include (Adriaenssens et al., 2011):
- % of patients between 18 and 75 years with acute bronchitis prescribed antibiotics (acceptable range 0 – 30%); within this % those receiving recommended antibiotics (acceptable range 80 – 100%) or fluoroquinolones (acceptable range 0 – 5%)
- % of patients older than one year with upper respiratory tract infections (URTIs) prescribed antibiotics for systemic use (acceptable range 0 – 20%); within this % receiving recommended antibiotics (acceptable range 80 – 100%) or fluoroquinolones (acceptable range 0 – 5%)

4.2.3 Internet-based training on antibiotic prescribing rates for patients with acute RTIs (Little et al., 2013)

Primary-care practices among six European countries were randomised to (i) usual care, (ii) training in the use of a C-reactive protein (CRP) tests at the point of care, (iii) training in enhanced communication skills, or (iv) in both training in CRP and enhanced communication via the internet.

The study showed that antibiotic prescribing rates were lower with training in CRP tests and lower in practices with enhanced-communication training than without such. The greatest reduction in subsequent antibiotic prescribing was seen when the interventions were combined.

The authors concluded that Internet training did achieve important reductions in antibiotic prescribing for RTIs across languages and cultures. Consequently, a potential way forward to enhance appropriate antibiotic prescribing across countries where resources are limited.

4.2.4 Belgium (WHO Europe, 2011)

Since 2000, national campaigns among GPs and communities on the prudent use of antibiotics have been organized by the Belgian Antibiotic Policy Coordination Committee. Alongside this, establishing surveillance systems across healthcare sectors, improving legislation on hospital hygiene, and disseminating guidelines on the prevention and treatment of bacterial infections.

These multifaceted campaigns resulted in a steady decrease (6.2%/ year) in the use of antibiotics in ambulatory care in recent years. In addition, the correct use of antibiotics is also increasing across sectors and resistance to streptococcal infections steadily declining.

Similar successful campaigns have been initiated in other countries including France, Spain, Poland and the UK.

4.2.5 France (Sabuncu et al., 2009)

Among European countries, France typically has the highest rate of antibiotic consumption and beta-lactam resistance in *Streptococcus spp*. This resulted in the

French government instigating in 2001 a programme entitled ''Keep Antibiotics Working''; the main component being ''Les antibiotiquesc'est pas automatique'' (''Antibiotics are not automatic'').

Compared to the pre-intervention period (2000–2002):
- Decrease by 226.5% over 5 years in the number of antibiotic prescriptions, adjusted for flu-like syndrome frequency during the winter season
- This decline in antibiotic utilisation occurred throughout France, which affected all antibiotic classes except quinolones
- The greatest decrease in antibiotic utilisation was seen among young children (6 to 15 years of age)

The authors concluded that this multifaceted campaign was associated with an appreciable reduction in unnecessary antibiotic prescribing. This was particularly in children.

4.2.6 Italy (Formoso et al, 2013)

Interventions to try and reduce antibiotic prescribing among the public included posters, brochures and adverts in the local media. There was also a newsletter on local antibiotic resistance targeting physicians and pharmacists. The design of the materials and messages was facilitated by GPs and paediatricians working in the intervention locality.

Antibiotic prescribing was significantly reduced in the intervention locality compared with controls outside the locality. There was a greater decrease for penicillins resistant to beta lactamase, as well as a decrease in the prescribing of penicillins susceptible to beta lactamase, consistent with the content of the newsletter. However, there was no difference with respect to knowledge and attitudes regarding the correct use of antibiotics among the public in the two groups.

4.2.7 Slovenia (Furst et al., 2015)

Multifaceted interventions among all key stakeholder groups in Slovenia decreased antibiotic utilisation by 2% to 9% per year from 1999 to 2012, overall by 31%. This followed a 24% increase in antibiotic utilisation at the end of the 1990s in Slovenia. There were also appreciable changes in the prescribing of different antibiotics.

Table 5 contains some of the multiple initiatives and policies undertaken in Slovenia in recent years to reduce overall antibiotic utilisation as well as significantly reduce the utilisation of 7 out of 10 antibiotics.

Table 5. Some of the activities undertaken in Slovenia to enhance the appropriate use of antibiotics (adapted from Fürst et al., 2015)

Activity	Institution (organizer)	Targeted public	Introduction / frequency
2-day symposium on antibiotics once a year	Department of Infectious Diseases of the UMC Ljubljana	GPs	1995 every year
Prescribing restrictions for amoxicillin/ clavulanic acid and the fluoroquinolones	National Health Insurance	All physicians	2000/ permanent
Workshops in Primary health centres	Primary health centres, National Health Insurance	GPs	2001/ sporadically
Informative budget targets for prescribed drugs	National Health Insurance	All physicians	2001/ permanent
Guidelines on treatment of infectious diseases	Medical professionals	GPs	2002
Audits	National Health Insurance	All physicians	2002/ regularly
Workshop on rational prescribing of antibiotics	Faculty of Medicine University of Ljubljana	Specializing GPs	2004/ every year
Prescribing restrictions for cephalosporins	National Health Insurance	All physicians	2005/ permanent
Booklet "My child has a fever"	National Health Insurance, medical professionals	Parents	2007/ always available
Workshops in regions with the highest utilisation of antibiotics	National Committee for the Rational Use of Antimicrobials	GPs	2007/ once a year
Antibiotic Awareness Day	Ministry of Health and the National Committee for the Rational Use of Antimicrobials	Lay public and GPs	2008/ every year
Prescribing restrictions for the macrolides	National Health Insurance	All physicians	2009/ permanent
Workshop on rational prescribing of antibiotics	Slovenian society of chemotherapy	Young physicians	2010/ every year
Flyer "Get well without antibiotics"	National Health Insurance, medical professionals	Lay public	2010/ always available
Quality indicators including antibiotics	National Health Insurance	GPs	2011

Streptococcus resistance to penicillin decreased, mirroring decreasing utilisation. However, *Streptococcus* resistance to macrolides increased despite their utilisation halving and *E. coli* resistance to fluoroquinolones doubled despite their utilisation decreasing by a third.

4.2.8   Thailand (Sumpradit et al., 2012; Action on Antibiotic Resistance, 2015)

The Antibiotics Smart Use programme was initiated to promote rational antibiotic use and reduce AMR rates.

Multifaceted interventions at individual and organizational levels were implemented to increase public knowledge regarding antibiotics and change antibiotic prescription practices among physicians. Interventions at the network and policy levels were used to maintain behavior change and scale up the various programmes. Key healthcare professionals, including physicians and pharmacists, as well as community leaders were trained to promote rational antibiotic use in their healthcare settings and communities. Educational materials were also provided for display or distribution to patients.

The findings showed that the combined interventions increased public knowledge regarding antibiotics and changed their attitudes towards them. Antibiotic utilization decreased by 18 to 46% after the programme, and the percentage of patients who were not prescribed antibiotics for the three targeted illnesses i.e. acute diarrhea, URTIs, and simple wounds, increased by 29.1%. Furthermore, almost all patients who were not prescribed antibiotics fully recovered within 7-10 days after the medical visits demonstrating that antibiotics were not necessary.

4.2.9   *United Kingdom – Scotland (Nathwani et al., 2011; Colligan et al., 2015)*

We have previously documented the initiation and activities of SAPG in Scotland (Section 4.1), which significantly reduced *Clostridium difficile* infection rates. An integrated approach to antimicrobial stewardship is being achieved through engagement with key stakeholder groups at all levels, aided by implementation of data management systems and training materials on antimicrobial stewardship. Improving the treatment of infections such as community-acquired pneumonia was also helped by quality improvement methodologies.

A self-reported survey in 2014 evaluating stewardship activities by the regional Antimicrobial Management Teams (AMTs) as part of the SAPG programme, demonstrated good compliance with 9 of the 10 key European indicators. 50% of the AMTs achieved all 9 indicators and 100% achieved at least 6 out of the 9 indicators (67 %). The authors concluded that collaborative working between SAPG and AMTs, together with central funding, has been key to achieving good success, providing direction to other countries and regions.

4.3 Impact of educational interventions on public knowledge and attitudes towards antibiotics and antibiotic resistance

Numerous public education campaigns have been conducted, particularly in high-income countries, to improve antibiotic utilization (Finch et al., 2004; Rodis et al., 2004; Gonzales et al., 2005; Curry et al., 2006; Huttner et al., 2010; Greene et al., 2011; Holloway, 2011; McKay et al., 2011; Fürst et al., 2015), some of which have already been described earlier. All campaigns have tried to convey that AMR is a major public health problem and, in addition, that the misuse of antibiotics contributes to this. Furthermore, most campaigns have tried to educate the public that most RTIs are viral in origin and consequently should not be treated with antibiotics (Finch et al., 2004; Huttner et al., 2010).

The campaigns have used various means of communication. The most common has been printed educational materials such as brochures, leaflets and posters. Some campaigns have used mass media such as newspapers, radio, television, billboards and public-transport advertisements, whilst others have conducted public seminars to provide opportunities for interactive education and behavioural change (Freimuth et al., 2000; Finch et al., 2004; Huttner et al., 2010; Holloway, 2011; Furst et al., 2015). Nearly all campaigns have used the internet in some way (Finch et al., 2004; Huttner et al., 2010).

Table 6 contains details of a number of the campaigns and their impact, building on the experiences of Thailand and other countries described above.

Table 6 – Influence of educational activities among patients

Country	Programmes and their influence
Belgium (Goossens et al., 2006)	• The majority of the public (79%) who recalled the national antibiotic campaign recalled information from the television rather than other means of communication • Compared with the pre-campaign, patients expectations to be prescribed an antibiotic decreased significantly for acute bronchitis, cold, flu, diarrhoea and sore throats
Israel (Hemo et al., 2009)	• Exposure to media campaigns was associated with positive attitudes by patients towards antibiotics • Parents exposed to the media campaign were more likely to agree with current standards of the appropriate prescribing of antibiotics and less likely to expect physicians to prescribe antibiotics for RTIs, otitis media and pharyngitis than parents not exposed to the campaign
USA – North Carolina (Greene et al., 2011)	• A pharmacy student-driven education programme raised public awareness of the threat of AMR and the appropriate use of antibiotics • After participating in the programme, 71% of patients stated that they would not now be requesting antibiotics from their physicians
USA – Ohio (Rodis et al., 2004)	• Patients' knowledge about the appropriate indication for prescribing antibiotics improved following a pharmacist-initiated educational intervention • The post-intervention survey demonstrated a significant increase in the % of patients agreeing that antibiotics should not be used for a cold as well as for influenza combined with cough and body aches

Shehadeh et al (Shehadeh et al., 2015) recently conducted a study to assess the impact of a pharmacist-initiated educational intervention on public knowledge of antibiotics and antibiotic resistance in Jordan. The mean knowledge score for the pre- and post-education was 59.4% and 65.9% respectively. In addition, participants within poor and adequate knowledge categories were significantly shifted to the good knowledge category after the educational intervention. However, the authors believed the improvement in participants' knowledge may not always translate into a change in subsequent antibiotic–seeking behavior.

Despite these initiatives, it appears difficult in practice to educate the public about the differences between bacterial and viral infections (Finch et al., 2004; Goossens et al., 2006; Huttner et al., 2010). Telephone surveys among the public in Canada did not show any impact of a campaign educating them of the bacterial or viral nature of certain infections. Prior to the campaign, 54% of the public agreed that antibiotics are effective for the treatment of viral infections. After the campaign, 53% still did not know that antibiotics do not work against viruses (NIPA, 2013). In New Zealand, a post-education survey demonstrated that the general public still had misconceptions that antibiotics are needed to treat viral infections (Curry et al., 2006), and in France54% of the public still remained unaware that most URTIs are caused by viruses and do not require antibiotic treatment despite successive campaigns over five years (National Health Insurance, 2008). However, this should not dissuade health authorities from instigating programmes in the future to try and educate patients regarding the appropriate use and

requests for antibiotics given the impact of inappropriate antibiotic use on increasing AMR rates.

Increasing knowledge of antibiotics among the public can result in a paradoxical effect (Huttner et al., 2010). In the UK studies have shown that public education campaigns are associated with increased knowledge of antibiotics. However, they also resulted in increased likelihood of self-medication, sharing antibiotics with someone else and keeping leftover antibiotics (McNulty et al., 2007a; McNulty et al., 2007b). This needs to be factored into any future campaign.

Care is also needed when translating programmes from one country to another where the health systems and context can be different (Holloway, 2011). Typically, educational approaches will only be effective if they are tailored to the local context and able to address local educational needs and organizational barriers (Siddiqi et al., 2005; Sumpradit et al., 2012).

5. Conclusion

The threat of AMR with its impact on morbidity, mortality and costs is growing. As a result, becoming one of the most critical problems facing healthcare systems world-wide. A number of inter-linking strategies are needed to address this. These include enhancing access where co-payments are an issue, reducing inappropriate prescribing (conservatism) where this is a problem as well as encouraging the development of new antibiotics given the current scarcity (Hoffman & Outterson, 2015; O'Neill, 2015). Knowledge regarding current utilisation and resistance patterns in a country or region is a pre-requisite to instigating future interventions to improve future rational prescribing and dispensing of antibiotics (WHO Europe, 2014).

We have shown that multiple approaches, including all key stakeholder groups such as health authorities, physicians, pharmacists and patients, are needed to reduce inappropriate antibiotic prescribing. Within this, physicians and pharmacists are particularly important with FIP urging a number of activities among pharmacists and governments (Box 1). This is endorsed by the WHO in Europe (Box 2). Activities need to be continually analysed and sustained for maximum impact given the misconceptions that can still remain coupled with people's short memories from one year to the next.

We will continue to monitor the impact of the interventions across regions and countries to reduce future inappropriate prescribing and dispensing of antibiotics to provide direction to others to address this critical area.

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