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Review Article

Antibiotic Resistance in Malaysia, and its Public Health Implications

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ABSTRACT

The World Health Organization (WHO) notes high-rates of resistance among bacteria associated with common illness in all the WHO-regions - both hospital-acquired and community-acquired (WHO 2014). An estimated 2 million cases of antibiotic-resistance are reported in the US annually, causing 23,000 deaths. With reference to such, the US CDC states that about 30% of the total-annual 150 million prescriptions for antibiotics is not justified. There is a need for greater prudence in the use involving joint-efforts in surveillance, public health awareness additionally, and in formulating clear policies on procurement and prudent use.

Keywords: Antibiotic Resistance, Public Health, prescriptions

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INTRODUCTION

Antibiotics, in the practice of modern medicine, have been instrumental in reducing morbidity and mortality from infectious-diseases. But here, decades of advancements stand threatened by the emergence of antibiotic-resistance.

The cause of antibiotic-resistance is multi-factorial. But, increased consumption in the community not only produces greater resistance at the individual patient-level, also at the community, country, and regional levels - and, such could harm individual patients (Bell BG et al 2014).

The cost to the 'fitness' of an organism is its ability to replicate and survive in a competitive environment. For instance if antibiotic resistance could be acquired by bacteria without any "fitness cost" all the human bacteria (as well as all the environmental ones) would be pan-resistant already (Melyn AH et al 2015).

The World Health Organization (WHO) notes high-rates of resistance among bacteria associated with common illness in all the WHO-regions - both hospital-acquired and community-acquired (WHO 2014).

An estimated 2 million cases of antibiotic-resistance are reported in the US annually, causing 23,000 deaths. With reference to such, the US CDC states that about 30% of the total-annual 150 million prescriptions for antibiotics is not justified.

The situation is the same in Malaysia - a steady increase in antibiotic-resistance involving common organisms has been observed.

Alvarez-Uria G et al (2018) using mixed linear models and inverse probability weighting methods concluded that third-generation cephalosporins and carbapenems could be ineffective against a sizeable proportion of infections by *E. coli* and *K. pneumoniae* in most parts of the world by 2030.

There is a need for greater prudence in the use involving joint-efforts in surveillance, public health awareness additionally, and in formulating clear policies on procurement and prudent use.

PATTERNS OF ANTIBIOTIC-RESISTANCE

Escherichia coli - resistance to third-generation cephalosporins and to fluoroquinolones

E. coli in the intestine in humans and animals is part of the normal flora.

Alvarez-Uria G et al (2018) estimated the prevalence of antimicrobial resistance (AMR) in 2015 was 64.5% (95% CI 42-87%) for third-generation cephalosporin-resistant (3GCR) *Escherichia coli*, and 5.8% (95% CI 1.8-9.7%) for carbapenem-resistant (CR) *E. coli*. The projected AMR prevalence in 2030 was 77% (95% CI 55-99.1%) for 3GCR *E. coli*, and 11.8% (95% CI 3.7-19.9%) for CR *E. coli*.

It is:

- the commonest cause of community and hospital-acquired urinary tract infections (including kidney-infections);
- the commonest cause of bloodstream-infection at all ages;
- commonly the cause of intra-abdominal infections such as peritonitis, besides skin and soft tissue infections caused by multiple microorganisms;
- a cause of meningitis in neonates; and
- a leading causative-agent of foodborne-infections globally.

Infections caused by such resistant-strains of *E. coli* carry a risk of poorer clinical-outcomes in patients and increasingly use up health-care resources.

Summary: Public health implications of E coli resistance to third-generation cephalosporins

Due to high-reported proportions of resistance to third-generation cephalosporins treatment for severe infections by *E. coli* may need to be initiated with broader therapy (e.g. carbapenems) leading to higher costs and stimulus to the expansion of carbapenem-resistant strains.

Summary: Public health implications of E coli resistance to fluoro-quinolones

Quinolones are a widely-used groups of antibiotics in the treatment of urinary tract infections, of which *E. coli* is the commonest cause.

Resistance to quinolones frequently means resistance to one of the last available oral-treatment options.

Without availability of oral-treatment, treatment by injection becomes necessary – costing patients and the health-systems additionally.

Klebsiella pneumoniae – resistance to third-generation cephalosporins and to carbapenems

K. pneumoniae infections in hospitals are particularly common among vulnerable individuals such as pre-term infants besides patients with impaired immune systems, diabetes or alcohol-use disorders, and those receiving advanced medical-care.

Alvarez-Uria G et al (2018) estimated the prevalence of antimicrobial resistance (AMR) in 2015 was 66.9% (95% CI 47.1–86.8%) for 3GCR *Klebsiella pneumoniae*, and 23.4% (95% CI 7.4–39.4%) for CR *K. pneumoniae*. The projected AMR prevalence in 2030 was 58.2% (95% CI 50.2–66.1%) for 3GCR *K. pneumoniae*, and 52.8% (95% CI 16.3–89.3%) for CR *K. pneumoniae*.

Urinary and respiratory tract infections are most common and bloodstream infections in neonates - a common cause of Gram-negative bloodstream infections. Globally, carbapenem-resistant *K. pneumoniae* infection is commonly seen.

Summary: Public-health implications of resistant Klebsiella

In the same manner as *E. coli* resistant to third-generation cephalosporins, the high proportions of cephalosporin-resistance mean that treatment for severe *K. pneumoniae* infections frequently must rely on carbapenems (if available).

Such frequently leads to greater costs besides a risk of added expansion of carbapenem-resistant strains - which subsequently require treatment by those not so effective and not so widely available.

Staphylococcus aureus – resistance to methicillin

S. aureus causes a variety of infections - skin, soft tissue, bone and bloodstream infections. As a cause of postoperative wound infections it is the commonest.

Some strains of *S. aureus* produce toxins which could cause toxic shock syndrome and food poisoning.

Summary: Public health implications of methicillin-resistant staph aureus (MRSA)

There is high-reported proportions of MRSA treatment for suspected or verified *S. aureus* infections in many countries. The implication of this is it could require additionally expensive second-line anti-bacterials. Such also includes prophylaxis in orthopaedic and many different surgical procedures.

Koeck M et al (2019) found that the incidence of invasive MSSA (methicillin-sensitive) was more than twice that of invasive MRSA in two counties in Minnesota, USA. Invasive *S. aureus* infections were associated with a high case-fatality rate. Infection-types were similar except septic arthritis of bigger frequency noted among invasive MSSA cases and bacteremia and pneumonia of bigger frequency noted among invasive MRSA cases; these findings were consistent with those of various studies, although some previous studies found a bigger case-fatality rate for MRSA than MSSA infections, possibly attributable to the older age and co-morbidities among invasive MRSA case-patients. Although here case-patients with invasive MSSA had fewer co-morbidities and were less likely to have pneumonia (a syndrome associated with poor outcomes) than case-patients with invasive MRSA, case-fatality rates were similar.

Invasive MSSA-isolates were susceptible to bigger number of antimicrobial drugs and were genetically diverse than invasive MRSA isolates, consistent with results of previous reports. Penicillin-susceptibility was observed in 33% of invasive MSSA-isolates, which is considerably bigger than for previous studies of invasive and noninvasive MSSA isolates, and was seen for multiple strain types.

The authors state that infection-control interventions have effectively decreased healthcare-associated invasive MRSA incidence. But, invasive *S. aureus* burden and mortality-rates remain a concern. Most invasive *S. aureus* disease was HACO (Health-care Associated; Community Onset) or Community Associated (CA), highlighting the need for preventing these community-onset infections through new approaches and infection prevention in settings outside acute care. Additionally, present-surveillance data could notify planning for future interventions, such as improved wound-care, enhanced infection prevention in nursing-homes and dialysis-centers, and added attention to chronic conditions and development of effective vaccines.

Streptococcus pneumoniae – resistance (non-susceptibility) to penicillin

Globally, *S. pneumoniae* is the prime cause of community-acquired pneumonia. Such pneumonia is among the main killers of children under 5 years of age.

Besides mild infections, *S. pneumoniae* also causes invasive disease with high mortality such as meningitis. Among the bacterial causes of meningitis, *S. pneumoniae* carries the highest case-fatality rate. It is the most likely to leave survivors with permanent residual-symptoms.

According to one estimate globally, *S. pneumoniae* caused about 826 000 deaths in children aged 1 - 59 months.

Kim L et al (2016) state that β -Lactam resistance is the hallmark of pneumococcal adaptability, requiring multiple independent recombination events that are traceable to non-pneumococcal origins and stably perpetuated in multi-resistant clonal-complexes. Pneumococcal-strains with elevated minimal inhibitory concentrations (MICs) of β -lactams are most frequently resistant to additional antibiotics. Basic underlying mechanisms of most pneumococcal resistances have been identified, although new insights that increase understanding are continually provided. Although here all pneumococcal infections can be successfully treated with antibiotics, the existing choices are limited for some strains. Invasive pneumococcal disease data compiled during 1998 to 2013 through the population-based Active Bacterial Core surveillance program (U.S. population base of 30,600,000) demonstrated that targeting common capsular-serotypes with conjugate-vaccines (7-valent and 13-valent vaccines implemented in 2000 and 2010, respectively) is extremely effective in reducing resistant-infections. Nevertheless, resistant non-vaccine-serotype clones continue to emerge and expand.

Summary: Public health implications of S. pneumoniae resistance (non-susceptibility) to penicillin

When penicillin was first introduced, it very much changed the outcome for patients with pneumococcal pneumonia and accompanying bloodstream infection (which is common) from a case-fatality rate of about 90% to a survival-rate of about 90%. Resistance could reduce this advantage accorded.

Besides, resistance-data also influences laboratory-diagnosis and treatment-guidelines for bloodstream-infections.

Nontyphoidal Salmonella – resistance to fluoroquinolones

Globally, bacteria of the genus Salmonella are a main cause of foodborne-illness.

Salmonella is a zoonotic-pathogen, and the bacteria can be found in the intestines of numerous food-animals such as poultry and pigs. Infection is most frequently caused by consuming contaminated-water or food of animal-origin.

Most Salmonella strains cause gastroenteritis. Certain strains are more invasive and typically cause Enteric fever - a largely serious-infection that brings about problems in treatment in numerous parts of the world due to antibiotic-resistance (ABR).

Nontyphoidal Salmonella (NTS) comprise the bigger proportion of diarrhoeal-pathogens transmitted through the food-chain. One estimate indicates that there is found around 94 million cases, resulting in 155 000 deaths, of NTS gastroenteritis each year globally.

Kariuki S et al (2015) state that data from regions where enteric fever and iNTS (invasive) disease are endemic clearly show that ABR is a major public health problem, with MDR the norm and evidence of emerging resistance to cephalosporins and the fluoroquinolones that make these conditions untreatable in resource-limited settings. In addition to advocating for prudent use of existing antimicrobials where such are still effective, improved sanitation to reduce burden of illness and the wider introduction of WHO recommended typhoid vaccines and the acceleration of trials for novel typhoid, paratyphoid and iNTS vaccines are additional very useful steps that play a major role in management and control of these infections.

Summary: Public health implications of Salmonella resistance to fluoroquinolones

Infections caused by NTS are frequent but are usually self-limiting. In severe cases, antibacterial-treatment may be required.

In multidrug-resistant Salmonella enterica serotype Typhimurium there is found a bigger risk of invasive-infection, frequent hospitalization with bigger time-length of stay, prolonged-illness, and increased-risk of death in comparison with infections caused by susceptible strains.

Shigella species – resistance to fluoroquinolones

Shigella species are a main cause of diarrhoea and dysentery throughout the world. These bacteria are transmitted by fecal-oral route through contaminated food or water, or through person-to-person contact.

Patients usually recover without complications within seven days, but shigellosis could become a life-threatening or fatal disease, particularly in children. Globally, the annual number of Shigella-episodes is estimated around 165 million (of which more than 100 million is found in the developing world) causing in excess of one million deaths.

Gebrekanan A et al (2015) in a study in Northern Ethiopia found that isolates of Shigella showed 100, 86.7 and 66.7 % resistance to ampicillin, amoxicillin and cotrimoxazole respectively. Low levels of resistance were observed for norfloxacin and ciprofloxacin (6.7 % each). Overall, 80 % of the isolates showed multidrug resistance. The researchers suggest that antibiotic-surveillance is needed to prevent added emergence of drug-resistant Shigella-strains. Provision of latrine, and supply of safe drinking-water to the community needed to be improved to reduce the disease-burden.

Summary: Public health implications of Shigella resistance to fluoroquinolones

Antibacterial drugs have a proven outcome in the treatment of Shigella-infections, and frequently lifesaving. Emerging-resistance has been reported as a concern in some countries.

Neisseria gonorrhoeae – decreased susceptibility to third-generation cephalosporins

Gonorrhoea is a sexually transmitted. An acute infection of the reproductive tract may be symptomatic or asymptomatic. If untreated, or inappropriately treated, the infection may result in severe complications, including genital and reproductive tract inflammation and damage, and infertility. Infection in pregnant women may lead to infections in the new-born, including eye infections which could cause blindness.

In 2008, the WHO estimated there were 106 million new cases of gonorrhoea in adults aged 15–49 years globally.

Tapsall JW et al (2009) state that globally, antimicrobial resistance (AMR) in Neisseria gonorrhoeae is increasing in prevalence, both within and across antibiotic classes, including extended-spectrum cephalosporins, raising concerns that gonorrhea may become untreatable in certain circumstances. The AMR-surveillance that is essential in optimizing standard treatments is frequently lacking or of poor quality in countries with high disease-rates although there is recent initiatives by the WHO to enhance global AMR-surveillance that focus on multidrug- and extensively drug-resistant N. gonorrhoeae through newer surveillance-standards. Keys to meeting these new problems caused by gonococcal AMR are the reduction in global-burden of gonorrhea combined with implementation of wider-strategies for general AMR-control, and better

understanding of mechanisms in emergence and spread of AMR.

Ohnishi M et al (2011) reported when the first *Neisseria gonorrhoeae* strain (H041), that is highly resistant to the extended-spectrum cephalosporin (ESC) ceftriaxone the last remaining option for empirical first-line treatment, was isolated. Detailed characterization of H041 was performed, phenotypically and genetically, to confirm the finding, examine its antimicrobial resistance (AMR), and elucidate the resistance mechanisms. H041 proved very resistant to ceftriaxone (2 to 4 µg/ml, which is 4- to 8-fold higher than any previously described isolate) and every remaining cephalosporins, besides most different antimicrobials tested. A new *penA* mosaic-allele was found to cause the ceftriaxone-resistance. Ohnishi et al conclude that *N. gonorrhoeae* has now shown its ability to also develop ceftriaxone resistance. The researchers belief *N. gonorrhoeae* may soon become a true superbug, causing untreatable gonorrhea – that which is required is a reduction in the global gonorrhea burden by enhanced disease control activities, combined with wider strategies for general AMR-control and enhanced-understanding of the mechanisms of emergence and spread of AMR which need to be monitored globally, and public health response plans for global (and national) situations, besides the development of new drugs for efficacious gonorrhea-treatment.

Lahra MM et al (2013) report on the Western Pacific region, which is densely populated with many living in poverty and

with high-rates of infectious-diseases, a disproportionate-burden of gonococcal disease and uncontrolled antimicrobial-use, which are recognized as ideal conditions for the emergence of AMR. The authors report that there is widespread, high-level resistance to penicillin and ciprofloxacin. Decreased susceptibility to ceftriaxone (MIC ≥ 0.06 mg/L) is reported in high-levels from some countries in the region. Low numbers of isolates tested in some countries reflect capacity for testing which are suboptimal for surveillance. The emergence and spread of ceftriaxone-resistant strains regionally is found alarming. Sustaining and enhancing surveillance is felt critical but obtaining an adequate sample-size was found a long-standing problem. The implementation of molecular-surveillance strategies is felt to possibly provide broader data on the spread and threat of AMR.

Summary: Public health implications of N. gonorrhoeae resistance to third generation cephalosporins

Emerging resistance has created obstacles in the treatment and control of gonorrhoea, in both resource-constrained and good-income countries.

Due to widespread resistance, older and cheaper antibacterial drugs can no longer be used in treatment regimens. Treatment-failures with a third-generation cephalosporin (cefoxime) have been noted in many parts of the world. Yet, data from most countries around the world on the resistance is still lacking.

Figure 1: Sources of data on *Neisseria gonorrhoea*: decreased susceptibility to third-generation cephalosporins

It is predicted that gonococci will become fully-resistant to the third-generation cephalosporins globally – and consequently, could result in becoming untreatable. Neonatal-infections and disseminated gonococcal-infections could be expected to become much more common, as in the era prior to antibacterial-treatment becoming existent.

In aiming to facilitate effective-actions against the spread of multidrug-resistant *N. gonorrhoeae*, the WHO launched the Global Action Plan to Control the Spread and Impact of Antimicrobial Resistance in *Neisseria gonorrhoeae* in 2012.

ANTIBIOTIC-RESISTANCE IN DISEASE-SPECIFIC PROGRAMMES

Tuberculosis

Globally, 3.6% of new TB cases and 20.2% of previously-treated cases are estimated to be multidrug-resistant TB (MDR-TB), with much bigger-rates in Eastern Europe and Central Asia.

Despite recent advancements in the diagnosis and treatment of MDR-TB, under-reporting of MDR-TB is extensive.

Treatment-success in MDR-TB is low, and is lower still in Extensively Drug-resistant (XDR-TB) cases.

Gangneux S et al (2000) in using mathematical models predict that the future of the multidrug-resistant tuberculosis epidemic will depend on the fitness cost of drug resistance. The researchers showed that in laboratory-derived mutants of *Mycobacterium tuberculosis*, rifampin resistance is universally associated with a competitive fitness-cost and that this cost is determined by the specific-resistance mutation and strain genetic-background. In contrast, prolonged patient-treatment resulted in multi-drug resistant-strains with no fitness defect and that strains with low- or no-cost resistance mutations are also the most frequent among clinical isolates.

Gillespie SH (2002) states that treatment with globally-approved regimens results in a very high cure-rate with few relapses and without the emergence of resistance. These regimens are effective in preventing the emergence of resistance because combination-chemotherapy makes it highly unlikely that there will be a spontaneous-mutant resistant to all of the components of chemotherapy. Patients with uncomplicated-tuberculosis who receive inadequate treatment provide a selection-advantage for resistant-mutants since bacteria may be exposed to monotherapy, permitting the emergence of resistance to single-agents and then to multiple-agents as the protection of combination-chemotherapy becomes eroded. Clinical-complications such as empyema and extensive-cavitation permit a big population to develop in a compartment to which drugs may not penetrate. This large bacterial-pool increases the population for mutation, and with poor-penetration there is an increased-likelihood of resistance emerging. A similar situation may develop in patients with extensive disease or poor immunity.

Gillespie states that resistant organisms over time will be fully virulent and that where an epidemic of multiple-drug-resistant tuberculosis is to be prevented, every step must be taken to ensure that all patients are diagnosed and effectively treated such that resistant-strains are not created and transmitted in the community.

Malaria

Surveillance of antimalarial drug-efficacy is very necessary in the early-detection of antimalarial-drug resistance since resistance cannot be detected with routine laboratory-procedures.

Areas of suspected or confirmed artemisinin-resistance have been identified. Spread of such could jeopardize precious recent-gains in malaria-control.

White NJ (2004) had stated that resistance has emerged to all classes of antimalarial drugs except the artemisinins and such was responsible for a recent increase in malaria-related mortality, particularly in Africa. The de novo emergence of resistance can be prevented by the use of antimalarial drug-combinations. Artemisinin-derivative combinations are particularly effective, since they act rapidly and are better-tolerated and very effective.

HIV

HIV drug-resistance is a clear cause of failure to achieve suppression of viral-replication, and thus causing increased-risk for disease-progression.

Data collected between 2004 and 2010 in low- and middle-income countries shows increasing levels of transmitted anti-HIV drug-resistance in patients being started with antiretroviral treatment (ART).

Tang MW and Shafer RW (2012) state that the efficacy of an antiretroviral (ARV) treatment regimen depends on the activity of the regimen's individual ARV-drugs and the number of HIV-1 mutations required for the development of resistance to each ARV — the genetic-barrier to resistance. ARV-resistance impairs the response to therapy in patients with transmitted-resistance, unsuccessful initial ARV-therapy and multiple virological-failures. In patients with transmitted drug-resistance, the virological-response to a regimen selected on the basis of standard genotypic-testing, approaches the responses observed in patients with wild-type viruses. But, since such patients are at a bigger risk of harbouring minority drug-resistant variants, initial ARV therapy in this population should contain a boosted protease inhibitor (PI) — the drug class with the highest genetic barrier to resistance.

In patients receiving an initial ARV-regimen with a high genetic-barrier to resistance, the most common reasons for virological-failure are non-adherence and, potentially, pharmacokinetic-factors or minority-transmitted drug-resistant variants. Among patients in whom first-line ARVs have failed, the patterns of drug-resistance mutations and cross-resistance are often predictable, but the extent of drug-resistance correlates with the duration of uncontrolled virological-replication.

Second-line therapy should include the continued use of a dual nucleoside/nucleotide reverse-transcriptase inhibitor (NRTI)-containing backbone, together with a change in the non-NRTI component, best to an ARV belonging to a new drug-class.

A thorough examination of the patient's ARV-history and prior resistance-tests should be performed since genotypic and/or phenotypic susceptibility-testing is frequently not sufficient to identify drug-resistant variants that emerged during past therapies and may still pose a threat to a new regimen. Phenotypic testing is also frequently helpful in this subset of patients. Understanding the basic principles of HIV drug-resistance is helpful in guiding individual clinical-decisions and the development of ARV treatment-guidelines.

Influenza

There is very much resistance to adamantanes in circulating A (H1N1) and A (H3N2) viruses presently.

In 2007/2008, there was emergence and rapid global-spread of oseltamivir-resistance in the former seasonal A (H1N1) viruses needing global antiviral-resistance surveillance.

Van der Vries E et al (2013) identify antiviral drugs for influenza therapy and prophylaxis as either of the adamantane or neuraminidase inhibitor (NAI) class – but, the NAIs are mainly prescribed presently, due to widespread adamantane resistance involving influenza A viruses and ineffectiveness of adamantanes against influenza B. Emergence and spread of NAI resistance would further limit our therapeutic options. The authors postulate that taking into account the previous spread of oseltamivir-resistant viruses during the 2007/2008 season preceding the last pandemic, emergence of yet another naturally NAI-resistant influenza-virus may not be an unlikely event. The previous incident also underlines the importance of resistance-surveillance and searches for a better-understanding of the mechanisms underlying primary-resistance development. A better-understanding of the effect of virus-mutations upon antiviral-treatment is called for along with a tailored antiviral-approach to severe influenza-virus infections.

Resistance in systemic candidiasis

Systemic candidiasis is a common fungal-infection globally causing high rates of morbidity and mortality in certain groups of patients.

The global burden of antifungal-resistant *Candida* is unknown. Resistance to Fluconazole, and even the newest echinocandins, varies widely by country and species.

Within the limited antifungal armamentarium, the azole-antifungals are the most frequent class used to treat *Candida* infections. Azole antifungals such as fluconazole are frequently preferred treatment for many *Candida* infections and as such are inexpensive, exhibit limited toxicity, and are obtainable for oral administration. But, there is extensive documentation of intrinsic and developed resistance to azole-antifungals among several *Candida* species. As the frequency of azole-resistant *Candida*-isolates in the clinical-setting increases, it is essential to elucidate the mechanisms of such resistance with the aim to both preserve and improve upon the azole-class of antifungals for the treatment of *Candida* infections, caused by *C. albicans* besides the emerging non-*albicans* *Candida* species *C. parapsilosis*, *C. tropicalis*, *C. krusei*, and *C. glabrata*. (Whaley SG et al 2016).

Antibacterial resistance (ABR) in food-producing animals and the food chain

Major needs exist still in surveillance and data-sharing related to the emergence of ABR in foodborne bacteria, and the potential impact of such on both animal and human health.

A multi-sectoral approach is needed to contain ABR, and this has to include improved integrated-surveillance of ABR in food-producing animals and in the food chain.

ANTIBIOTIC PRESCRIBING IN PUBLIC AND PRIVATE PRIMARY CARE CLINICS IN MALAYSIA

Norazida AR et al (2016) in a study using nationwide data from 129 public clinics and 416 private clinics, showed that 5810 encounters were prescribed antibiotics.

Overall antibiotic-prescribing rate was 21.1 % - public clinics 6.8 %, private clinics 30.8 %.

Upper respiratory tract infection (URTI), which is primarily of viral-cause, was the most frequent diagnosis in patients receiving antibiotic therapy (49.2 % of prescriptions). Of the patients diagnosed with URTI, 46.2 % received antibiotic treatment (public 16.8 %, private 57.7 %), although they were mostly not indicated clinically.

More recently available broad-spectrum antibiotics such as azithromycin and quinolones were more frequently prescribed in private clinics.

They observed that excessive or suboptimal use of medicines in general, and antibiotics in particular, is a worldwide concern. A systematic review by the WHO of medicine-use in developing and transitional countries, has shown an increasing trend of antibiotics to 71% in the period 2004 – 2006, which is higher than in the Malaysian scenario.

But, when compared with more developed countries such as the Netherlands and Hong Kong, the antibiotic-prescribing rates in Malaysia are still a cause for concern.

My own observation is that many private primary care clinics prescribe antibiotics for URTI, mostly to increase their profits from a larger bill.

The newer broad-spectrum antibiotics are observed to be prescribed especially by newer clinics, and especially when insurance companies, MCO's and panel-companies allow a larger bill per patient – these newer antibiotics are costlier, and thus allow a greater profit.

It is my observation too that almost all retail-pharmacies dispense antibiotics without prescriptions – although antibiotics are classified Group-B poisons.

Norazida AR et al conclude that their findings emphasize the need for more concerted interventions targeting both prescribers and the public, reducing inappropriate prescribing.

We should all agree to that, in addition keeping dispensing by retail-pharmacists under surveillance.

In Malaysia, national antibiotic guidelines were introduced in 2008, and updated in 2014.

However, they say that the current effort to improve antibiotic stewardship in Malaysia is still in the early-stages. The right type of sustainable-intervention needs to be implemented, such as academic-detailing by senior family physicians, and feedback of prescribing data to primary care doctors – and these interventions periodically evaluated. Continuing Medical Education for practicing doctors needs to highlight the ongoing problem of antibiotic overuse and the emergence of antibiotic resistance.

Public-education of the harm of excessive antibiotic use is currently being carried out in Malaysia, but it needs to be persistent, they say.

Tan WL et al (2015), concluded that knowledge on antibiotics among our Medical Officers in public health-care facilities was only moderate.

They recommend more training and courses on appropriate antibiotic-prescribing to ensure the best-practice in antibiotic-prescription.

Muhammad Qamar et al (2014), observed that only 43% of the general public in Shah Alam had good knowledge about antibiotics.

And, 57.4% still expected antibiotic to be prescribed for common cold.

The authors concluded that although the knowledge of the public was good, the importance of correct usage of antibiotic needed to be emphasized on them, and changes in their attitude towards antibiotic usage needed to be promoted.

THE HEALTH AND ECONOMIC BURDEN DUE TO ANTIBACTERIAL RESISTANCE

Whether antibiotic resistance poses a significant Health and Economic burden for patients and healthcare systems is a key question.

To address this knowledge gap, systematic reviews were carried out for the WHO Report.

Health burden

Table 1 summarizes the Mortality, while Table 2, the Admissions

Table 1: Mortality

	All-cause mortality	Bacterium-attributable mortality	30-day mortality	ICU mortality
Third-gen cephalosprin-resistant E. coli infection	Increase	Increase	Increase	No data
Fluoroquinolone-resistant E. coli infection	Increase	No increase	Increase	No data
Third-gen cephalosporin-resistant K. pneumoniae infection	Increase	Increase	Increase	No data
Carbenepem-resistant K. pneumoniae infection	Increase	No increase	Increase	No increase
MRSA infection	Increase	Increase	No increase	Increase

Table 2: Admissions

	Length of Stay (LOS)	ICU Admissions	Incidence of Septic-shock
Third-gen cephalosprin-resistant E. coli infection	No increase	No increase	No data
Fluoroquinolone-resistant E. coli infection	No increase	Increase	Increase
Third-gen cephalosporin-resistant K. pneumoniae infection	No increase	No increase	No increase
Carbenepem-resistant K. pneumoniae infection	Increase	Increase	No data
MRSA infection	No increase	No increase	Increase

Economic burden

The cost impact of ABR has not been adequately measured.

From the few, the conclusion was that all-costs for infections caused by resistant strains were consistently greater than those for infections caused by susceptible strains, with few exceptions.

There are few studies reporting data on increased-cost associated with resistant E. coli and K. pneumoniae infections. One study from UK reported that the additional costs for urinary tract infections caused by resistant E. coli managed in general practice was £3.62. And in one remaining study from Thailand, the hospitalization costs increased to a median US\$ 528 from US\$ 108, in patients with ESBL-producing E. coli infections.

A study in the USA in which Klebsiella spp and E. coli were included among other Gram-negative bacteria, reported that “patients infected with resistant bacteria had a median total hospital cost US\$ 38, 121 higher than that for patients infected with susceptible bacteria (US\$ 144,414 and 106,293 respectively)”.

The clinical trials for MRSA captured a few resource-use outcomes: there was a longer duration of both hospital (mean difference of 4.65 days) and ICU LOS (mean difference of 4.0 days) for patients with MRSA compared to those with MSSA. In addition, a higher proportion of patients with MRSA tended to be discharged from hospital to other care facilities (long-term care facility or other health-care facilities).

Two reviews found that because costs of resistance are mainly measured in in-patients, the overall burden may be underestimated.

Tumbarello M et al (2010) in a retrospective 1-year analysis of 134 consecutive E. coli blood-stream infections (BSIs) in a hospital, explored the clinical and economic impacts of (i) inadequate initial antimicrobial treatment (IIAT) (i.e., empirical treatment with drugs to which the isolate had displayed in vitro resistance) of these infections and (ii) ESBL-production by the bloodstream-isolate. Compared with the 107 (79.8%) adequately treated patients, the 27 (20.1%) who received IIAT had a higher proportion of ESBL BSIs (74.0% versus 15.8%), longer (+6 days) and more costly (+EUR 4,322.00) post-BSI-onset hospital stays, and increased 21-day mortality rates (40.7% versus 5.6%). Compared with the 97 non-ESBL infections, the 37 (27.6%) ESBL BSIs were also associated with longer (+7 days) and more costly (+EUR

5,026.00) post-BSI-onset hospital stays and increased 21-day mortality (29.7% versus 6.1%).

These findings confirm that the hospital costs and mortality associated with E. coli BSIs are significantly increased by ESBL production and by IIAT.

Naylor NR et al (2018) in a systematic review showed that 48% of studies estimating mortality burden found a significant impact from antibiotic-resistance - excess healthcare system costs ranged from non-significance to \$1 billion per year, whilst economic burden ranged from \$21,832 per case to over \$3 trillion in GDP loss.

Woolhouse N et al (2016) in a review state that information presently collected at global or multi-national scales is not sufficient to generate estimates of the disease burden attributable to antibiotic resistance. As a result, present knowledge of the burden of antibiotic resistance is still based largely on the collation of one-off, small-scale, individual studies that vary greatly in setting, scope, sampling frame and methodology, and often requires bold extrapolations to be made from very limited data sets. For estimation of the global burden of antibiotic resistance and, even more, for monitoring changes in burden over time more systematic approaches would be helpful. There are several possibilities the researchers state that ICD-11 replacing ICD-10 in 2017 provides an opportunity to create routinely used categories that record treatment failures, or at least linking treatments with outcomes, the most direct ways to estimate the burden of antibiotic resistance. Specific concerns, such as XDR-TB or carbapenem-resistant Enterobacteriaceae, might be prioritised for inclusion.

The researchers also state that ICD facilitates passive reporting. One version could be active reporting by recruiting sentinel sites. For example, 660 hospitals from 67 countries responded to an internet survey on antimicrobial stewardship in 2012. Monitoring treatment failures due to antibiotic resistance in these hospitals using standardised protocols would generate valuable data, it is felt. Making selected, high priority antibiotic resistant infections ‘notifiable’ at national level could further improve data capture, extending existing mandatory-reporting for specific conditions (for example in the UK for scarlet fever or invasive streptococcal group A disease). Another possibility is a more qualitative approach of recruiting a global panel of individual clinicians who are polled (proved successful

previously in different clinical-context) to determine trends in the impact of antibiotic resistance on their patients.

Besides estimating the global burden of antibiotic resistance an additional useful exercise would be to estimate the global-burden due to lack of access to suitable antibiotics. The two matters potentially overlap where there is a lack of knowledge of local resistance profiles (perhaps due to lack of testing facilities) and that alternative drugs would have been effective.

Knowledge-gap

Based on the current findings, the following gaps need to be addressed:

1. standardization and implementation of a minimum data set;
2. evaluation of both clinical outcomes and resource use in high-quality studies;
3. evaluation of health and economic burden in a broader array of settings – including low- and low-middle-income countries; and
4. The need for improved models, besides recent ones, to assess economic impact on health-care systems and society.

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