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Review

Antibiotic prescription and resistance: A contemporary literature review

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Worldwide, antibiotics are among the most commonly used and misused drugs because of the perception in some practitioners and patients that antibiotic resistance is theoretical or only a minor risk. This review therefore aims to update knowledge and promote proper antibiotic prescription with the goal of optimizing use and halting the trend of rising resistance. A literature and internet (Medline, embase, HINARI and Cochrane data bases) search showed that prescription of antibiotics only when indicated following standard guidelines minimizes the incidence and spread of resistance. Mechanisms of resistance development include bacterial mutation or horizontal transfer from plasmids, transposons, integrons and gene cassettes between commensal organisms and potential pathogens by transduction, translocation, transposition, transformation or conjugation. Resistance may emerge following indiscriminate use of antibiotics, unhygienic conditions, poor drug handling and non-adherence. To halt resistance, priority areas include prudent use of antibiotics; development of antimicrobials with novel mechanisms of action; use of bioinformatics and genomic techniques to identify and study new targets of attack; use of alternatives to antibiotics such as bacteriophage-derived therapy or chemical agents that can block or reverse resistance pathways; use of agents in natural products, vaccines and pro-biotics as well as implementing public health strategies and education of the populace. In response, initiatives at the local, national and international levels are now directed towards promoting good antibiotic stewardship, infection control, sanitation and hygiene practices.

Key words: Antibiotic, antimicrobials, prescription, resistance, contemporary, review.

INTRODUCTION

One of the most pressing problems faced by healthcare services today is the increasing prevalence of inappropriate antibiotic prescription and rising resistance. Available antibiotics seem to be a limited resource, and development of resistance seem to be emerging faster than the availability of new antibiotics, a phenomenon now widely recognized as a major threat to public health (Morris, 2007; Costelloe et al., 2010; Vincent, 2011). In general practice, there are concerns about some common infections which are becoming increasingly difficult to treat, and that illness due to antibiotic resistant bacteria may take longer to resolve (Butler et al., 2006). This indicates that the inappropriate prescription by physicians for their patients may influence the effectiveness of antibiotics given to all patients. The goal is to use antibiotics prudently, reserving antibiotics which are not intended for first-line use until when the older, more commonly used medications fail (Hay et al., 2005). In addition, the adverse event profiles of various antibiotics differ, so the administration of these drugs to individual patients must be based on the risk-benefit evaluation for each patient (Walsh, 2003).

Although many countries have been successful in reducing primary care prescribing of antibiotics, primary care is still responsible for the majority of antibiotics

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prescribed (Lipsitch and Samore, 2002; Prescription Pricing Authority, 2006). Most of the antibiotic use is for the treatment of suspected respiratory infection (NICE, 2008), and the levels of prescribing vary widely within and between countries suggesting that further reductions are possible (Brooks et al., 2008; Clifton et al., 2009). However, there are many barriers to reducing the inappropriate use of antibiotics. These include unfavorable health climate (Okeke and Sosa, 2003); the expectations of patients and practitioners (Macfarlane et al., 1997); lack of patients' awareness of problems caused by antibiotic resistance (Brooks et al., 2008); and a false perception in primary care clinicians and patients that antimicrobial resistance is only a theoretical problem or that it carries minimal risk (Kumar et al., 2003; Butler et al., 2006; Simpson et al., 2007). Although the reason for holding such view is unclear, it may in part be due to inadequate information on appropriate antibiotic prescription and resistance. In response to the antimicrobial resistance resulting from either inappropriate or inadequate use of antibiotics, there are various initiatives now being put in place to reverse the trend (Goossen, 2011). However, such initiatives rely for success on the continuing education of prescribers and patients. This review, therefore, aims to promote current knowledge of good antibiotic stewardship with the goal of improving the appropriate use and halting the rise of resistance, particularly in Nigeria.

ANTIBIOTIC PRESCRIPTION

Antibiotics

These are molecules used to treat or prevent disease in humans and animals. Their mechanism of action is to kill microbes (bactericidal) or at least stop their growth (bacteriostatic). Strictly speaking, the term *antibiotics* refers to naturally occurring molecules, and the term *antimicrobials* encompasses both naturally occurring and synthetically derived molecules (Walsh, 2003). However, since the term *antibiotic* is so widely used, this review refers to all antimicrobials as "antibiotics". The review concerns agents used to treat or prevent bacterial infections rather than fungal or viral infections.

The clinical significance of bactericidal compared with bacteriostatic drugs is not clear in most infectious diseases. The human immune system is also important in curing infections. Of note, antibiotics that appear potent in the test tube are not necessarily more beneficial in people when treating or preventing disease (Pankey and Sabath, 2004). That is why data from human clinical trials are so important for understanding the benefits and risks of prescribing these powerful but often misused drugs (Malhotra-Kumor et al., 2007; Rafailidis et al., 2009; Siempos et al., 2009). If used appropriately, antibiotics can make patients feel better and live longer. However, the commonly held notion particularly by the non-health professionals that antibiotics "can't hurt" is incorrect because antibiotics may cause serious and life threatening adverse reactions such as anaphylaxis and liver toxicity. Less serious but more common adverse events include nausea, vomiting, diarrhea and skin rash (Neugut et al., 2001; Katzung, 2009).

Antibiotics have no efficacy against viral infections, such as the common cold or flu (Harvey and Champe, 2009). Therefore, prescribing for a viral infection is not warranted except occasionally for controlling secondary bacterial infection such as acute necrotizing ulcerative gingivitis secondary to herpes simplex infection (Colgan and Powers, 2001; Hay et al., 2005).

Basic principles of prescribing antibiotics

Prescribing antibiotics for conditions for which they are not needed contributes to antimicrobial resistance, thereby increasing the risk that these drugs will not be effective when they are needed. These drugs must therefore be used when the benefits clearly outweigh the risks (Hardman, 2006; Chung et al., 2007). The principles for prescribing antibiotics therefore include:

i. Correct diagnosis of a bacterial infection for which specific antibiotics are known to be effective compared with placebo (Brunton et al., 2008).
ii. Choose a drug that has the fewest adverse events for that patient so as to maximize the benefit and minimize the risk (Hardman, 2006).
iii. Choose a drug that has efficacy in treating or preventing the disease but leaves other bacteria in the body intact. This minimizes the spread of resistance and leaves intact the body's own organisms that are a natural defense against other invading organisms. Adherence to this principle minimizes the incidence of superinfection (Goosens, 2011).
iv. As much as possible choose a drug that is available, convenient and inexpensive to assure adherence and contain healthcare costs (Asworth et al., 2005).
v. The dose of an antibiotic varies according to a number of factors including age, weight, hepatic and renal functions, and severity of infection. The prescribing of the so-called "standard" dose in serious infections may result in failure of treatment or even death of the patient; therefore, it is important to prescribe a dose appropriate to the condition (Katzung, 2009).
vi. The route of administration of an antibiotic often depends on the severity of the infection. Life-threatening infections require intravenous therapy. Whenever possible, painful intravenous injections should be avoided in children (Hardman, 2006).
vii. Duration of therapy depends on the nature of the infection and the response to treatment (Rafailidis et al., 2009). Courses should not be unduly prolonged (except

in cases like tuberculosis (Katzung, 2009) or chronic osteomyelitis (Karamanis et al., 2008), because they encourage resistance, increase side effects and are costly.

viii. Use of antibiotics in combination may be justified for empirical therapy of an infection for which the cause is unknown; for treatment of polymicrobial infections; to enhance antimicrobial activity for a specific infection (i.e for synergy); or to prevent emergence of resistance as in tuberculosis treatment (Patel, 2006; Cunha, 2007; Brunton et al., 2008).

ix. Antibiotics prophylaxis may be used to protect healthy persons from acquisition of or invasion by specific micro-organisms to which they are exposed e.g. respiratory infections (Siempos et al., 2009) and bacterial endocarditis (Westphal et al., 2009).

ANTIBIOTIC RESISTANCE

Mechanism of resistance

Historically, resistance to antibiotics has been seen for all agents, soon after their discovery. Not long after Nobel Laureate Alexander Flemming discovered penicillin, he identified staphylococci that were resistant to the first "wonder drug". He correctly predicted that imprudent use of antibiotics could lead to clinical failures with these drugs in the future (Walsh, 2003). Until this time, all staphylococci were considered sensitive to penicillin and many gram negative organisms were known to be intrinsically resistant.

Intrinsic resistance poses few problems for clinicians. It is the traditionally unexpected acquired resistance - resistance in a species originally considered sensitive - that can result in dreaded chemotherapeutic failure. Bacteria strains that are resistant to an antibiotic can produce enzymes that inactivate the drug (Davies, 1994); become impermeable to it (Lim and Stynadka, 2002); actively export it from cell via an efflux pump (Li and Nikaido, 2004) or bypass the cellular target with which the agent interfers (Riska and Jacobs, 2000). Bacteria acquire the ability to do this by mutation which may lead to micro-evolutionary or macro-evolutionary changes (Chopra et al., 2003). More commonly, it is through horizontal transfer from plasmids, transposons, integrons and gene cassettes between commensal organisms and potential pathogens by transduction, translocation, transposition, transformation or conjugation (Katayama et al., 2000; Beaber and Hochhut, 2004; Fluit and Schmitz, 2004). Recently, Kumarasamy et al. (2010) reported the emergence of a new antibiotic resistance mechanism in Indian, Pakistan and UK.

Association between antibiotic use and resistance

Resistance is not only a characteristic of the infecting organism but also related to the individual's bacterial gene pool, since resistance carried on plasmids and integrons can be transferred between commensal organisms and potential pathogens. Transmission of commensal organisms between individuals and antibiotic prescribing in the community remain frequent events, therefore, even a transient effect of antibiotic use on the carriage of resistant organisms by an individual may have a major impact on the endemic level of resistance in the population (Hay et al., 2005; Chung et al., 2007).

Some studies that reported resistance in urinary and respiratory tract bacteria showed substantial increases in resistance within days of prescribing and subsequent decay in effects over three months in Chung et al. (2007) study, and six months in the Malhotra-Kumar et al. (2007) study. These draw attention to the increased risk of resistance to commonly used first-line antibiotics: if a patient has received one or more courses of such antibiotics in the previous 12 months and further antibiotic treatment is necessary, for a subsequent respiratory or urinary tract infection, the choice of a different antibiotic should be considered. This serves to highlight that the only way to avoid the vicious cycle of resistance leading to the use of more powerful broad spectrum antibiotics is to avoid their initial use whenever possible (Salmond and Welch, 2008; Cotelloe et al., 2010). This observation justifies the recommendation that, if indicated at all, the fewest number of antibiotic courses should be prescribed for the shortest period as possible (Priest et al., 2001; Hay et al. 2005; NICE, 2008, Goossens, 2011).

Factors that engender antibiotic resistance

The use of antibiotics at recommended dosage levels to treat confirmed bacterial infections is a type of exposure for which the benefit far outweighs the risk of selecting resistant strains (Rafaillidis et al., 2009). This type of acceptable selection pressure is high in many African countries like Nigeria, where there is a heavy burden of community-acquired bacterial infections that dictate a heavy requirement for curative therapy. Unfortunately, much of the antibiotic therapy is not laboratory individualized or even laboratory extrapolated. This coupled with the high proportion of life-threatening infections that require immediate treatment, means that antibiotic prescription, usually with first-line drugs such as ampicillin, ampiclox, cotramoxazole, chloramphenicol, erythromycin, gentamicin, penicillin, tetracycline and metronidazole, is largely empirical and that resistance will often only be detected by therapeutic failure (Gordon and Banda, 2002; Iwe, 2006). The treatment of infected people in many parts of Africa is further challenged by the fact that prohibitive cost of newer second-line antimicro-bials like amoxicillin-clavulanate, cefuroxime, ceftriaxone, ofloxacin, ciprofloxacin, azithromycin, amikacin etc, when available, places them out of the reach of the majority of patients. Since there is no broad enough selection

profile of the second-line drugs, there is usually no cost-effective customization of empiric antibiotic therapy (Okeke and Sosa, 2003).

Other challenges include the use of sub-therapeutic doses (occasioned by improper prescription or patient non-compliance) which creates a situation whereby highly resistant strains are selected sequentially; and the supply of poor quality (substandard) drugs (of which neither the prescriber nor the patient is aware) that provides sub-inhibitory selective pressure to kill bacteria. Other problems include man-made conditions (warm, moist and unhygienic environments) which are not only conducive to the spread of pathogens but also good for the resistant organisms that carry resistant genes e.g. resistance in clinical *Escherichia coli*, *salmonella* or *shigella enteritis* (Okeke and Sosa, 2003; Barlow and Nthwani, 2005; Moran et al., 2005; Spellbery, 2008). Also problematic is the poor storage leading to drug degradation by heat and/or humidity during the course of distribution and display as well as overcrowding and lack of resources for effective infection control in many healthcare facilities fuelling hospital epidemics of resistant organisms such as methicillin-resistant staphylococci, multiple resistant rods, vancomycin resistant strains etc (Smith et al., 1999; Haddadin et al., 2002; Chikere et al., 2008; Kieninger and Lipsett, 2009; Ksycki and Namias, 2009).

New initiatives to halt antibiotic resistance

Several new initiatives are being put in place to halt the alarming trend of resistance to antibiotics and to deal with the ever-increasing number of infections caused by multiple resistant organisms. These include development of antimicrobials with novel mechanisms of action. This is greatly aided by the rapidly accumulating bank of microbial genome sequences that permits the use of bioinformatics and genomic techniques to identify and study new targets of antibiotic attack. Other development priorities are alternatives to antibiotics such as bacteriophage-derived therapy or chemical agents that can block or reverse resistance pathways; new agents in natural products, an age-old source of antimicrobials; reducing the need for antibiotics by developing vaccines and pro-biotics, early involvement of infectious disease experts as well as implementing public health strategies such as the ones outlined by the Centers for Disease Control and Prevention (CDC) (Okeke and Sosa, 2003; Spellbery, 2008; Dehnel, 2010; Goosens, 2011; Vincent, 2011).

CONCLUSION

The emergence of antibiotic resistance in bacterial pathogens is a serious development that threatens the end of the antibiotic era. Clearly, there is a dire need for rational prescription and prudent use of antibiotics. Prescribers must resist the pressure from patients to proffer antibiotics unless a diagnosis of bacterial infection is established. In Africa nay Nigeria, urgent measures must be taken to sanction drug vendors who are often not trained to diagnose infections or prescribe antibiotics correctly and who also serve as unofficial outlets for many antibiotics to people with limited access to orthodox healthcare. Furthermore, proper drug custody and storage, sanitation, strict hygiene and infection control are steps that will prevent the spread of resistant agents, reducing the need for antibiotics in the first place. It is imperative to educate the public about the consequences of irrational antibiotic prescription and use. Where possible, patients must be advised of the wisdom of obtaining medicines at reputable outlets, where they have been properly stored and where expiration and lot information is available.

Heartily, the above initiatives are all focus areas of local, national and international (e.g. WHO, 2001; Alliance for Prudent Use of Antibiotics [APUA]) strategy for containment of antimicrobial resistance. In countries all over the world, many are organizing chapters of APUA to identify and address the priority areas in their own countries. In particular, adopting prudent practices will conserve the efficacy of the available antibiotics. Responsibility for intensifying programs that will optimize antimicrobial therapy lies with healthcare professionals who are in a better position to understand the devastating consequences of acting otherwise.

REFERENCES

Alliance for Prudent Use of Antibiotics. www.apua.org

Asworth M, Charton J, Ballard K, Latinovic R, Gulliford M (2005). Variations in antibiotic prescribing and consultation rates for acute respiratory infection in UK practices 1995-2000. Br. J. Gen. Pract., 55: 603-608

Barlow G, Nthwani D (2005). Is antibiotic resistance a problem? A practical guide for hospital clinicians. Postgrad. Med. J., 8: 68-692

Beaber JN, Hochhut B (2004). SOS response promotes horizontal dissemination of antibiotic response genes. Nature, 427: 72-74

Brooks L, Shaw A, Sharp D, Hay AD (2008). Towards a better understanding of patients' perspectives of antibiotic resistance and MRSA: a qualitative study. Fam. Pract., 25: 341-348

Brunton L, Parker K, Blumenthal D, Buxton I (2008). Goodman & Gilman's Manual of Pharmacology and Therapeutics. International Edition, McGraw-Hill, New York, pp. 707-797

Butler CC, Hillier S, Roberts Z, Dustan F, Howard A, Palmer S (2006). Antibiotic-resistant infections in primary care symptomatic for longer and increased workload: outcomes for patients with *E. coli* UTIs. Br. J. Gen. Pract., 56: 686-692

Chikere CB, Omoni VT, Chikere BO (2008). Distribution of potential nosocomial pathogens in a hospital environment. Afr. J. Biotechnol., 7: 3535-3539

Chopra I, D Neill AJ, Miller K (2003). The role of mutators in the emergence of antibiotic-resistant bacteria. Drug Resist. Update, 6: 137-145

Chung A, Perera R, Brueggemann AB, Elamin AE, Harden A (2007). Effect of antibiotic prescribing on antibiotic resistance in individual children in primary care: prospective cohort study. B. M. J., 335: 429-434

Clifton NJ, Raghavan U, Birlon J, Stones NS (2009). Prescribing anti-biotics for sore throat: adherence to guidelines in patients admitted to hospital. Postgrad. Med. J. 85: 347-357

Colgan R, Powers JH (2001). Appropriate antimicrobial prescribing approaches that limit antibiotic resistance. Am. Fam. Physician, 64: 999-1004

Costelloe C, Metcalfe C Lovering A, Mant D, Hay AD (2010). Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. B. M. J., 340: c2096-c2107

Cunha BA (2007). Fever of unknown origin: clinical overview of classic and current concepts. Infect. Dis. Clin. North Am., 21: 867-915

Davies J (1994). Inactivation of antibiotics and the dissemination of resistance genes. Science, 264: 375-382

Dehnel T (2010). Reacting to antibiotic resistance. Lancet Infect. Dis., 10(11): 746-747

Fluit AC, Schmitz FJ (2004) Resistance integrins and super-integrons. Clin. Microbiol. Infect., 10: 272-288

Goossens H (2011). Expert-proposed European strategies to monitor and control infection, antibiotic use, and resistance in healthcare facilities. Lancet Infect. Dis., 11(5): 338-340

Gordon MA, Banda HT (2002) Non-typhoidal bacteraemia among HIV-infected Malawian adults: High mortality and frequent recrudescence. AIDS, 16: 1633-1641

Haddadin AS, Fappiano SA, Lipseell PA (2002). Methicillin-resistant *Staphylococcus aureus* in intensive care unit. Postgrad. Med. J., 78: 385-392

Hardman JG ed. (2006). Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Edition. McGraw Hill, New York, pp. 1095-1223

Harvey KA, Champe PC eds. (2009). Chemotherapeutic drugs. In: Lippincott's Illustrated Reviews; Pharmacology 4th Edition. Lippincott Williams & Wilkins, Baltimore, pp. 773-831

Hay AD, Thomas MM, Montgomery A, Wetherell M, Lovering A, McNulty C (2005). The relationship between primary care antibiotic prescribing and bacterial resistance in adults in the community: a controlled observational study using individual patient data. J. Antimicrob. Chemother., 56: 146-153

Iwe P ed. (2006). Textbook of Pharmacology. Africana First Publishers Ltd, Onitsha, Nigeria, PP: 480-495

Karamanis EM, Mathaiou DK, Moraitis LI, Falagas ME (2008). Fluoroquinolones versus beta-lactam base regimens for the treatment of osteomyelitis: a meta-analysis of randomized controlled trials. Spine, 33: E297-E304

Katayama Y, Ito T (2000). A new class of genetic element, staphylococcus cassette chromosome mec, encodes methicillin resistance in *Staphylococcus aureus.* Antimicrob. Agents Chemother., 44: 1549-1555

Katzung BG ed. (2009). Chemotherapeutic drugs. In: Basic and Clinical Pharmacology 11th Edition. McGraw Hill, Boston, PP. 773-831

Kieninger AN, Lipsett PA (2009). Hospital-acquired pneumonia: pathophysiology, diagnosis and treatment. Surg. Clin. North Am., 89: 439-461

Ksycki MF, Namias N (2009). Nosocomial urinary tract infection J. Surg. Clin. North Am., 89: 475-481

Kumar S, Little P, Britten N (2003). Why do general practitioners prescribe antibiotics for sore throat? Grounded theory interview study. B. M. J., 326: 138-141

Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R et al. (2010). Emergence of a new antibiotic resistance mechanism in India, Pakistan and the UK: a molecular, biological and epidemiological study. Lancet Infect. Dis., 9: 597-602

Li XZ, Nikaido H (2004). Efflux-mediated drug resistance in bacteria. Drugs, 64: 159-204

Lim D, Strynadka NC (2002). Structural basis for the β-lactam resistance of PBPZa from methicillin-resistant *Staphylococcus aureus*. Nat. Struct. Biol., 9: 870-876

Lipsitch M, Samore MH (2002). Antimicrobial use and antimicrobial resistance: a population perspective. Emerg. Infect. Dis., 8: 347-354

Macfarlane J, Homes W, Macfarlane R, Britten N (1997). Influence of patients' expectations on antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. B. M. J. 315: 1211-1214

Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H (2007). Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomized, double blind, placebo-controlled study. Lancet, 369: 482-490

Morris K (2007). Battle against antibiotic resistance is being lost. L. I. D., 7(8): 509

Moran GJ, Amii RN, Abrahamian FM, Talan DA (2005). Methicillin-resistant *Staphylococcus aureus* in community-acquired skin infection. Emerg. Inf. Dis.. 11: 928-930

Neugut Al, Ghatak AT, Miller Rl (2001). Anaphylaxis in the United States: an investigation into its epidemiology. Arch. Intern. Med. 161: 15-21

NICE (2008). Respiratory tract infections: prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. www.nice.org.uk/CG69

Okeke Nl, Sosa A (2003). Antibiotic resistance in Africa -discerning the enemy and plotting a defence. Afr. Health, 25(3): 10-14

Pankey GA, Sabath LD (2004). Clinical relevance of bacteriostatic versus bactericidal mechanisms of action in the treatment of Gram-positive bacterial infections. Clin. Infect. Dis., 38: 864-870

Patel SM (2006). Monotherapy versus combination therapy. Med. Clin. North Am., 90: 1183-1195

Prescription Pricing Authority (2006). Trends in antibiotic prescribing in England. www.ppa.org.uk/news/pact- 102004.htm

Priest P, Yudkin P, McNulty C, Mant D, Wise R (2001). Antibacterial prescribing and antibacterial resistance in English general practice: cross sectional study. Commentary: Antibiotic resistance is a dynamic process. B. M. J., 323: 1037-1041

Rafailidis PI, Pitsomunis, AI, Falagas ME (2009). Meta-analyses on the optimization of the duration of antimicrobial treatment for various infections. Infect. Dis. Clin. North Am., 23: 269-276

Riska PF, Jacobs WR Jr (2000). Molecular determinants of drug resistance in tuberculosis. Int. J. Tuberc. Lung Dis., 4(2 Suppl.1): S4-S10

Salmond GPC, Welch M (2008). Adaptive resistance: adaptive evolution. Lancet. Infect. Dis., 372: S97-S103

Siempos II, Dimopolous G, Falagas. ME (2009). Meta-analyses on the prevention and treatment of respiratory tract infection. Infect. Dis. Clin. North Am., 23: 331-353

Simpson SA, Wood F, Butler CC (2007). General practitioners perception of antimicrobial resistance: a qualitative study. J. Antimicrob. Chemother., 59: 292-296

Smith TL, Pearson ML, Wilcox KR for the Glycopeptide Intermediate *Staphylococcus aureus* Working Group (1999). Emergence of vancomycin resistance in *Staphylococcus aureus.* New Engl. J. Med., 340: 493-501

Spellbery B (2008). Antibiotic resistance and antibiotic development. L. I. D. 8(4): 211-212

Vincent J (2011). Antibiotic resistance: understanding and responding to an emerging crisis. Lancet Infect. Dis., 11(9): 670

Walsh C (2003). Antibiotics: Actions, Origins and Resistance. ASM Press, Washington DC, pp. 1-120.

Westphal N, Plicht B, Naber C (2009). Infective endocarditis - prophylaxis, diagnostic criteria and treatment. Dtsch. Arztebl. Int. 106: 481-490

WHO (2001). Global strategy for containment of antimicrobial resistance. www.who.int.emc.amr.html.