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Review

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Antimicrobial resistance (AMR) is one of the most serious global public health threats in this century. The first World Health Organization (WHO) Global report on surveillance of AMR, published in April 2014, collected for the first time data from national and international surveillance networks, showing the extent of this phenomenon in many parts of the world and also the presence of large gaps in the existing surveillance. In this review, we focus on antibacterial resistance (ABR), which represents at the moment the major problem, both for the high rates of resistance observed in bacteria that cause common infections and for the complexity of the consequences of ABR. We describe the health and economic impact of ABR, the principal risk factors for its emergence and, in particular, we illustrate the highlights of four antibiotic-resistant pathogens of global concern – *Staphylococcus aureus, Klebsiella pneumoniae,* non-typhoidal *Salmonella and Mycobacterium tuberculosis* – for whom we report resistance data worldwide. Measures to control the emergence and the spread of ABR are presented.

Keywords: Antimicrobial resistance, Global surveillance, Antibiotic use, Veterinary medicine, MRSA, *Klebsiella pneumoniae*, Non-typhoidal *Salmonella*, *Mycobaterium tuberculosis*

Introduction

Antimicrobial resistance (AMR) has emerged as one of the principal public health problems of the 21st century that threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi no longer susceptible to the common medicines used to treat them. The problem of AMR is especially urgent regarding antibiotic resistance in bacteria. Over several decades, to varying degrees, bacteria causing common or severe infections have developed resistance to each new antibiotic coming to market. Faced with this reality, the need for action to avert a developing global crisis in health care is imperative.

The World Health Organization (WHO) has long recognised the need for an improved and coordinated global effort to contain AMR. In 2001, the WHO Global Strategy for Containment of Antimicrobial Resistance has provided a framework of interventions to slow the emergence and reduce the spread of antimicrobial-resistant microorganisms;[1] In 2012, WHO published The Evolving Threat of Antimicrobial Resistance – Options for Action[2] proposing a combination of interventions that include strengthening health systems and surveillance; improving use of antimicrobials in hospitals and in community; infection prevention and control; encouraging the development of appropriate new drugs and vaccines; and political commitment.

Following the indication of a primary role for surveillance, in April 2014, WHO published the first global report on surveillance of AMR collecting experiences from national and international surveillance networks.[3] This report shows that surveillance data, where available, can be very useful for orienting treatment choices, understanding AMR trends, identifying priority areas for interventions, and monitoring the impact of interventions to contain resistance. The lack of adequate surveillance in many parts of the world leaves large gaps in existing knowledge of the distribution and extent of this phenomenon.

Our review examines the main factors contributing to the development of antibiotic resistance and the consequences for human health focussing on the impact of resistance in species commonly associated with infection (i.e. *Staphylococcus aureus, Klebsiella pneumoniae,* non-typhoidal *Salmonella*) in different settings and in the treatment of tuberculosis.

Impact of Antibiotic Resistance

The impact of antibiotic resistance in terms of mortality and of the public health cost is quite difficult to estimate, and there are few studies addressing this issue. The US Center for Disease Control and

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Prevention (CDC) conservatively estimated that, in the US, more than two million people every year are affected with antibiotic-resistant infections, with at least 23 000 dying as a result of the infection.[4]

In Europe each year, the number of infections and deaths due to the most frequent multidrug-resistant bacteria (*S. aureus*, *Escherichia coli*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) was estimated at ~400 000 and 25 000, respectively, in 2007.[5]

Several fields of modern medicine depend on the availability of effective antibiotic drugs; chemotherapy for cancer treatment, organ transplantation, hip replacement surgery, intensive care for pre-term newborns and many other activities could not be performed without effective antibiotics. In fact, infections caused by multidrug-resistant bacterial strains are among the main factors influencing morbidity and mortality in patients undergoing these procedures. A report from the University of Texas, published in 2014, showed high antibiotic resistance rates in infections in cancer patients with chemotherapy-related neutropenia.[6] A recent study from the Medical University of Warsaw, on infections after orthotopic liver transplantation, showed a high proportion of isolates of antibiotic-resistant bacteria.[7]

Common infections in neonatal intensive care are increasingly becoming extremely difficult, and sometimes impossible, to treat.[8] *Staphylococcal* species, most notably *S. epidermidis* and *S. aureus*, cause ~60%–70% of infections, and numerous outbreaks of methicillin-resistant *S. aureus* (MRSA) have been reported in these units.[9]

Also the economic impact of antibiotic resistance is difficult to quantify, as several types of consequences must be taken into account. Increased resistance leads to elevated costs associated with more expensive antibiotics (when infections become resistant to first-line antimicrobials, treatment has to be switched to second- or third-line drugs, which are nearly always more expensive), specialised equipment, longer hospital stay and isolation procedures for the patients. Societal costs include death and loss of productivity. In Europe, the overall crude economic burden of antibiotic resistance was estimated to be at least 1.5 billion euros with more than 900 million euros corresponding to hospital costs. Productivity loss due to absence from work or death from infection accounted for 40% of the total estimated cost.[5] However, the estimate was based on antibiotic resistance surveillance data collected in 2007 and may underestimate the present burden of antibiotic resistance, which is a constantly evolving phenomenon.

In the US, the CDC estimated the cost of AMR as $55 billion per year overall: $20 billion in excess for direct healthcare costs, with additional society costs for lost productivity as high as $35 billion a year.[4]

Factors contributing to the emergence of antibiotic resistance

Antibiotic resistance is a natural phenomenon that occurs when microorganisms are exposed to antibiotic drugs. Under the selective pressure of antibiotics, susceptible bacteria are killed or inhibited, while bacteria that are naturally (or intrinsically) resistant or that have acquired antibiotic-resistant traits have a greater chance to survive and multiply. Not only the overuse of antibiotics but also the inappropriate use (inappropriate choices, inadequate dosing, poor adherence to treatment guidelines) contribute to the increase of antibiotic resistance.

Figure 1 shows a schematic representation of factors involved in the emergence and spread of antibiotic resistance. We identified four main sectors involved in the development of antibiotic resistance: human medicine in community and in hospital, animal production and agriculture, and the environmental compartment.

Antibiotic resistance in human medicine

In the community of affluent countries, the excessive prescription by general practitioners, even in the absence of appropriate indications, plays an important role in the inappropriate use of antibiotics. Diagnostic uncertainty often fosters over-prescription especially when the clinical picture of viral or bacterial aetiology is similar. Self-medication (see below) also plays an important part.

In many developing countries, excessive use is due to the easy availability of antimicrobial drugs that can be purchased without prescription of a physician or other qualified health professional. In both situations, there is the perception that antibiotics are the "wonder drugs" that can rapidly cure any kind of ailments.

In the hospital setting, the intensive and prolonged use of antimicrobial drugs is probably the main contributor to the emergence and spread of highly antibiotic-resistant nosocomial infections; but other factors can play an important role: presence of highly susceptible immunosuppressed patients (e.g. AIDS patients, cancer patients, or transplant recipients) and fragile elderly patients, invasive surgical procedures and intensity of clinical therapy, lengthy of stay in hospital,[10] failure to control infections spread from patient to patient.

- Antibiotic consumption in the community and in hospital settings

The annual report of the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) reported that in Europe during 2012 the

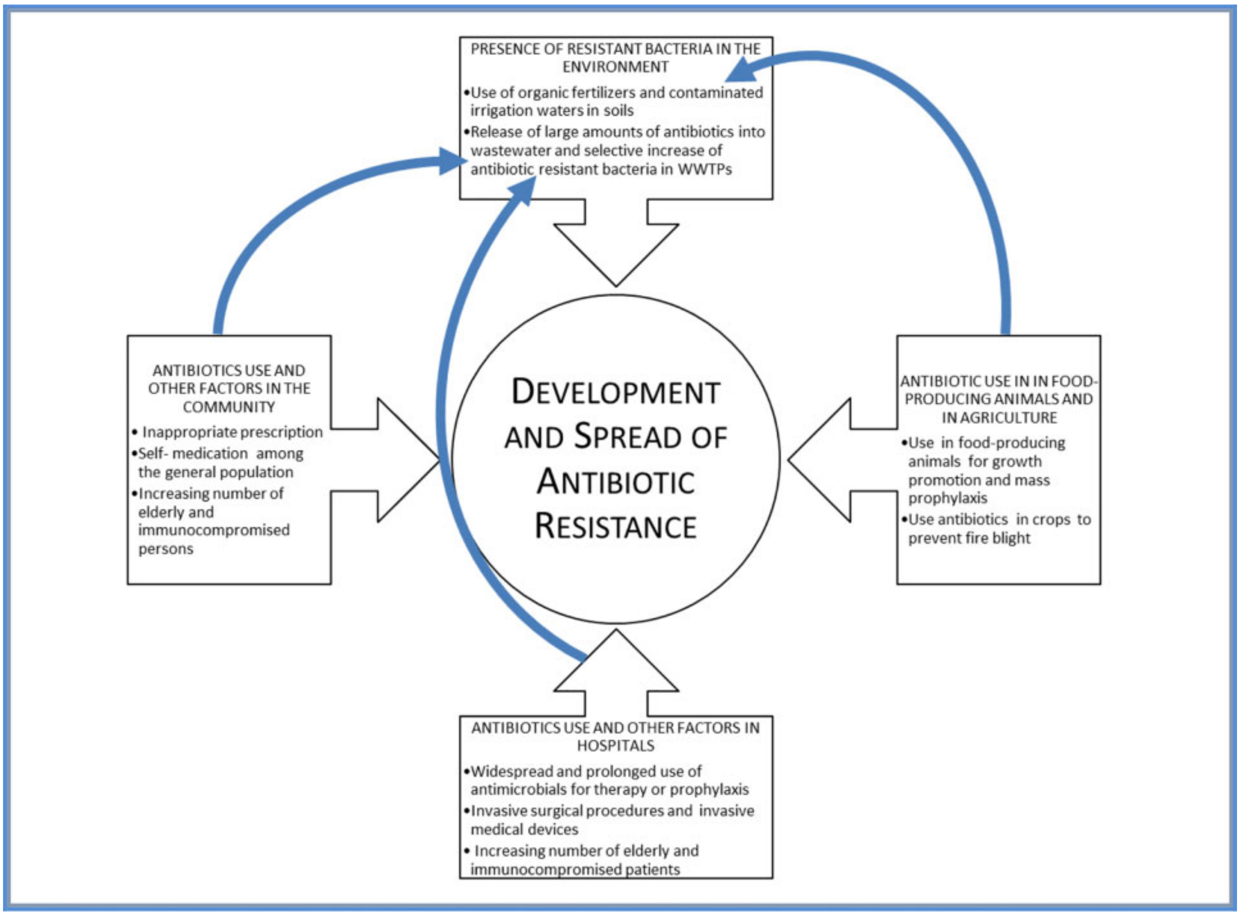

Figure 1 Factors involved in the spread of antibiotic resistance, in the sectors: human medicine in the community and in the hospital, animal production and agriculture, and the environment. These sectors are also connected among them: misuse of antibiotics in human beings, animals and agriculture is the main responsible for the presence of resistant bacteria in the environment.

consumption in the community of antibacterials for systemic use [Anatomical Therapeutic Chemical (ATC) group J01], ranged from 11.3 (the Netherlands) to 31.9 (Greece) defined daily doses (DDD) per 1000 inhabitants per day. In all ESAC-Net reports, a geographic gradient in the amount of antibiotics used can be noted, with higher DDD in the South of Europe. In 2012, the beta-lactams/penicillins group (ATC J01C) accounted for 50% of the consumption of antibacterials for systemic use and amoxicillin, alone or in combination with clavulanic acid, was the antibacterial agent most often used in almost all countries, with the exception of Norway and Sweden where the most used agent was phenoxymethylpenicillin.

In the hospital sector ESAC-Net estimated that in 2012, the population-weighted EU/EEA mean consumption for systemic use of antibacterials was 2.0 DDD per 1000 inhabitants, ranging from 1.0 DDD per 1000 inhabitants per day in the Netherlands, to 2.8 in Finland. Also in the hospital setting, the beta-lactams/penicillins group was most often used, accounting for 29.3% of all the consumption of antibacterials for systemic use.[11]

According to a recent point prevalence survey on healthcare associated infections in Europe, 35.0% of the hospitalised patients in 2011 were receiving antibiotics.[12]

In the US, healthcare providers prescribed 258.0 million courses of antibiotics (833 prescriptions per 1000 persons) in 2010. Penicillins (23%) and macrolides (22%) were the most common categories prescribed. The most frequently prescribed antibiotic agents were azithromycin and amoxicillin.[13]

Large-scale assessments of antimicrobial use in hospitals in the USA are derived from studies conducted in groups of acute care hospitals.[14,15] According to one of these studies, a mean of 59.3% of all patients received at least one dose of an antimicrobial agent during their hospital stay.[14]

- Incorrect knowledge about antibiotics in the population and self-medication

Many studies indicate lack of knowledge about antibiotics in the general population, specifically incorrect knowledge about the activity of antibiotics on bacteria and viruses, insufficient awareness about antibiotic resistance and about the adverse effects of antibiotics.

A survey, carried out in 2009, on the use and on the knowledge of antibiotics among European citizens, revealed that 20% of the people interviewed admitted they had taken antibiotics to treat flu-like symptoms, although they knew that antibiotics do not act against viruses. In addition, 14% also said that they had taken antibiotics to treat a common cold.[16]

A survey among adults in the United Kingdom showed that 38% of respondents did not know that antibiotics do not work against most coughs or colds.[17] On the contrary, in Sweden, the knowledge about antibiotics as well as the risk of antibiotic resistance is fairly good and homogeneous. Only one-fifth of respondents was convinced that antibiotics cure common colds more quickly.[18]

The inappropriate use of antibiotics is also associated with other common behaviour patterns, such as failure to complete the recommended treatment or self-medication. Self-medication with antimicrobials almost always involves unnecessary, inadequate, and ill-timed dosing, creating an ideal environment for microbes to adapt rather than be eliminated. Self-medication with antimicrobials is common in many areas of world, particularly in developing countries with loose regulatory systems where antibiotics are sold over the counter drugs, but also in some affluent countries. A higher prevalence of self-medication with antibiotics was reported in South Europe (19%) in comparison with northern Europe (3%) and central Europe (6%). In some countries of Africa, 100% of antimicrobial use is without prescription and in Asia it reaches 58%.[19]

Use of antibiotics in food-producing animals and in agriculture

A substantial proportion of total antibiotic use occurs outside the field of human medicine. Antimicrobial use in food-producing animals and in aquaculture for growth promotion and for disease treatment or prevention is probably a major contributor to the overall problem of resistance.[20] While the use of antibiotics as growth promoters has been completely banned in Europe since 2006, this is still common practice in several countries, including the USA.[21]

The fourth report of European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) that includes data from 26 EU countries showed that sales of antibiotics for use (therapy or prophylaxis) in food-producing animals during 2012, amounted to 8000 tonnes of active ingredients, with tetracyclines, penicillins and sulphonamides being the most sold antimicrobial classes.[22] In the US, in 2012, sales of antimicrobials approved for use in food-producing animals was ~14 800 tonnes and tetracyclines represented the most sold antimicrobial class, accounting for 41% of the total.[23]

The use of antibiotics in agriculture is a controversial practice. The main use of antibiotics, specifically streptomycin, is to prevent a disease of apple and pear trees named fire blight that is caused by a bacterium named *Erwinia amylovora*. The concern that antibiotic use in agriculture might increase the frequency of antibiotic resistance genes in bacteria living on plant surfaces and that genes conferring resistance might then be transferred into clinically important bacteria has resulted in tighter restrictions on the use of antibiotics in plant agriculture in Europe and in USA.[24]

The environment and the spread of resistance

During the last years, the importance of the environment in the spread of antibiotic resistance has been widely recognised.

The soil is regarded as a reservoir of antibiotic resistance genes, since most antibiotics are derived from soil microorganisms that are intrinsically resistant to the antibiotics produced. In addition, water potentially contaminated with faecal microorganisms and organic fertilisers used on food crops may disseminate drug-resistant bacteria in the soil.

Water is a major way of dissemination of bacteria between different environmental compartments. Large amounts of antibiotics are released into municipal wastewater due to incomplete metabolism in human beings or due to disposal of unused antibiotics. Some available data show that antibiotic-resistant bacteria and antibiotic-resistant genes can be detected in wastewater samples and that the conditions in wastewater treatment plants (WWTPs) are favourable for the proliferation of resistant bacteria. In the last decade, several studies have reported high concentrations of tetracycline and sulphonamide-resistant bacteria and sulphonamide-resistant genes in WWTPs.[25,26]

The emergence of resistance in some bacterial species commonly cause of human infections

An increasing number of pathogenic organisms are resistant to one or more antimicrobial drugs. As a consequence, some common infections have become extremely difficult and in some cases nearly impossible to treat. Pneumonia, which was readily treatable after the introduction of penicillin, now more often requires second- and third-line antibiotics. Cystitis, one of the most common bacterial infections in women, which was easily treatable using oral medication, now needs quite always more complex antibiotic treatments that impose additional costs on the patients and the health system.[27,28]

We describe below three bacterial species, which exemplify antibiotic-resistant pathogens causing infections in different settings: *S. aureus*, common in hospital and in the community; non-typhoidal *Salmonella* (NTS), a major cause of foodborne diseases; and *K. pneumoniae*, causing healthcare-associated infections. In addition, a paragraph will be devoted to drug-resistant tuberculosis.

Table 1 shows the extent of resistance in *S. aureus*, NTS and *K. pneumoniae* to antibiotics commonly used to treat infections caused by these pathogens, summarised by WHO region.[3] We have considered only national data (based on at least 30 tested isolates) and not single studies, to limit the heterogeneity of the information. Unfortunately, in few countries only, national official sources are available and therefore the table provides insight into the existing surveillance gaps in ABR surveillance.

Staphylococcus aureus

S. aureus is a Gram-positive bacterium that is part of the normal flora of the anterior nares, but is one of the most commons causes of nosocomial and community-acquired bloodstream infections, skin and soft tissue infections (SSTIs) and pneumonia in almost all geographic areas.

Strains of *S. aureus* resistant to antistaphylococcal penicillins are termed MRSA. The first strains of MRSA emerged during the 1960s and spread in the subsequent years[3] in association with the increase in the number of elderly and immunocompromised patients. In the healthcare setting, MRSA can cause severe infections such as bloodstream infections, sepsis, pneumonia, and surgical site infections. Hospital-acquired MRSA (HA-MRSA) infections are associated with insertion of medical devices such as central vein catheters, with haemodialysis, or with surgical procedures such as joint replacement.[29,30] Recently, MRSA has become a common cause of infections also in the community (CA-MRSA) affecting children and young persons without underlying diseases. Community acquired-

Table 1 Resistance to key antibiotics of *S. aureus*, *K. pneumoniae* and NTS in the six World Health Organization (WHO) world regions. The data are derived from WHO[3]

WHO regions		*S. aureus* resistance to methicillin (MRSA)	*NTS* resistance to fluoroquinolones	*K. pneumoniae* resistance to third-generation cephalosporins	*K. pneumoniae* resistance to carbapenems
Africa region (47 countries)	Countries with national data	9 (19.1%)	9 (19.1%)	13 (27.6%)	4 (8.5%)
	Range (%)	0–100	0–35	8–77	0–4
	Country with lowest/highest proportion	Lesotho/Guinea-Bissau	Central African Republic/Mauritania	Namibia/South Africa	Central African Republic/South Africa
Region of the Americas (47 countries)	Countries with national data	15 (31.9%)	13 (27.6%)	17 (36%)	17 (36.2%)
	Range (%)	21–90	0–96	4–71	0–11
	Country with lowest/highest proportion	Canada/Chile	Several countries[a]/-Peru	Canada/Peru	Canada-Dominican Republic/-United States of America
Eastern Mediterranean region (23 countries)	Countries with national data	4 (17.4%)	4 (17.4%)	4 (17.4%)	4 (17.4%)
	Range (%)	10–53	2–49	22–50	0–54
	Country with lowest/highest proportion	Bahrain/Iran	Oman/Jordan	Oman/Bahrain	Oman/Iran
European region (53 countries)	Countries with national data	36 (67.9%)	29 (50.9%)	33 (62.3%)	31 (58.5%)
	Range (%)	0.3–55	0–21	2–82	0–68
	Country with lowest/highest proportion	Norway/Portugal	Several countries[a]/Finland	Sweden/Georgia	Several countries[a]/Greece
South-east Asia region (11 countries)	Countries with national data	3 (27.3%)	2 (18.1%)	4 (36.4%)	4 (36.4%)
	Range (%)	10–26	0.2–4	34–81	0–8
	Country with lowest/highest proportion	Bhutan/Myanmar	Thailand/Nepal	Bhutan/Sri Lanka	Bhutan/Myanmar
Western Pacific region (37 countries)	Countries with national data	16 (43.2%)	9 (24.3%)	12 (32.4%)	9 (24.3%)
	Range (%)	4–70	0–14	1–71	0–8
	Country with lowest/highest proportion	Micronesia/Republic of Korea	Brunei Darussalam/Philippines	Kiribati/Micronesia	New Zeland/China

[a] We reported “several countries” when more than two countries have the same rate of resistance.

MRSA can especially infect persons in activities that cause skin damage and close contacts or crowding (athletes, military personnel, inmates, etc.). While most of the CA-MRSA infections involve the skin, some presentation (necrotising pneumonia, fasciitis) can be very serious.[31,32] Methicillin-resistant *S. aureus* infections require second-line antibacterials, such as vancomycin, that are less effective, more expensive, and need careful monitoring to avoid adverse side effects. New treatment options for MRSA, such as linezolid and daptomycin, are also expensive and not devoid of side effects.

In the United States, in 2011, MRSA were estimated to account for more than 80 000 invasive infections; of these only 14 000 occurred in the hospital.[33,34]

During the past decade in Europe, several countries implemented national action plans targetted at reducing the spread of MRSA in healthcare facilities. According to the data reported by European Antimicrobial Resistance Surveillance Network (EARS-Net), in the last years (2010–2013), six European countries (Belgium, France, Germany, Ireland, Spain and the United Kingdom), reported a significant decrease in the percentage of MRSA from invasive infections; however, the percentage of MRSA remained above 25% in seven out of 30 reporting countries, mainly in southern and eastern Europe.[35]

Globally, MRSA proportions exceed 20% in all WHO regions, and in some countries exceed 80%[3] (Table 1).

Non-typhoidal Salmonella (NTS)

Salmonellosis is one of the most common and widely distributed foodborne diseases and is caused by bacteria of the genus *Salmonella*. NTS are infections caused by all serotypes of *Salmonella enterica* except for serovars Typhi and Paratyphi, which are more invasive and are associated with enteric fever.

There are over 1500 NTS serotypes, the most common being *S.* Enteritidis, *S.* Typhimurium and *S.* Heidelberg, that can be found worldwide in domestic and wild animals (including birds and amphibians). In recent years, the incidence of NTS infection has increased considerably; A study on the global burden of NTS estimated that there are 94 million cases of NTS gastroenteritis, resulting in 155 000 deaths globally each year.[36] The majority of the disease burden is in the South-east Asian region.

As for all zoonotic pathogens, also for NTS, the widespread use of antimicrobial agents in food animal production for growth promotion, prophylaxis or treatment purposes has contributed to the spread of antibiotic resistance.[37–39] Multidrug resistance to different commonly used antimicrobial agents (ampicillin, chloramphenicol, sulphonamides and tetracycline) is frequent in NTS. Multidrug resistance has been associated with a higher risk of invasive infection, higher frequency and duration of hospitalisation and increased risk of death as compared to infections caused by susceptible strains.[40,41] In addition, from 2000, several studies have shown a decreased susceptibility to fluoroquinolones, drugs of choice for treatment of invasive gastrointestinal infections, in many parts of the world.[42–44]

According to data reported by WHO, fluoroquinolone resistance in NTS is lower in the European region, while it is much higher in some countries of Africa (30%–35%), of Eastern Mediterranean region (46%–49%) and in Peru (96%). In the South-east Asian and Western Pacific regions, where disease burden is very high, there are many information gaps[3] (Table 1).

Klebsiella pneumoniae

K. pneumoniae causes infections (bloodstream infections, urinary and respiratory tract infections) that are particularly common in hospitals among vulnerable individuals such as pre-term infants, elderly and patients with impaired immune systems.[45,46] In intensive care units and neonatal care facilities, *K. pneumoniae* can spread readily among patients, leading to nosocomial outbreaks. In recent years, the number of multidrug-resistant K. pneumoniae has risen rapidly.[47] Resistance mediated by extended-spectrum beta-lactamases (ESBLs) includes all penicillins, cephalosporins (including third-generation cephalosporins) and aztreonam. Recent studies showed a prevalence of ESBL-producing *K. pneumoniae* of 38.9% in Europe, 8.8% in the USA and 21.5% in the Asia-Pacific region.[48] WHO reported that third-generation cephalosporins resistance in *K. pneumoniae* was higher than 30% worldwide and higher than 60% in some countries[3] (Table 1). This high proportion of cephalosporin resistance means that treatment for severe *K. pneumoniae* infections have to rely on carbapenems.

The first *K. pneumoniae* producing an enzyme (carbapenemase) capable of hydrolysing all beta-lactams, including the carbapenems, was identified in the USA in 1996. Since then, carbapenem-resistant *K. pneumoniae* rapidly emerged as a cause of multidrug-resistant infections worldwide. The WHO showed alarming rates of carbapenem resistance in *K. pneumoniae*, exceeding 50% in some countries of Eastern Mediterranean and Europe.[3] In 2013, EARS-Net reported that the most affected countries in Europe were Greece and Italy with a percentage of carbapenem resistance of 59.4% and 34.3%, respectively.[35] Very few therapeutic options remain to treat infections due to carbapenemase-resistant *K. pneumoniae*, one being an old and rather toxic antibiotic, colistin. However, a recent Italian study showed that among 178K. *pneumoniae* carbapenemase-producing *K. pneumoniae* isolates from different hospitals, 43% were also resistant to colistin.[49] Infection control and interventions targetted to prevent the dissemination of these almost untreatable pathogens are highly needed.

Development of drug resistance in tuberculosis

The emergence and spread of multidrug-resistant strains of *Mycobacterium tuberculosis* (MDR-TB) represent one of the most daunting challenges to disease control worldwide. Incorrect treatment, consisting in prescription errors, low patient compliance, or poor quality of drugs, is the main cause for the development of resistant TB.[50] The development of resistance to anti-TB drugs began shortly after the initial introduction of drugs to treat TB; MDR-TB is defined as TB caused by a multidrug-resistant strain, that is strain resistant to rifampicin and isoniazid. In MDR-TB, the number of drugs necessary for treatment is higher than in non-MDR-TB, the treatment outcome is less favourable and mortality is higher.[51]

In 2012, the estimated global burden of MDR-TB was of 450 000 cases, of whom 300 000 were incident cases. Globally, almost 4% of all new TB cases and more than 20% of those with previous history of TB treatment are estimated to be MDR-TB.[50]

Table 2 shows the number of TB and MDR-TB cases notified in the years 2011–2013 in the six WHO regions.[52,53] Europe, South-east Asian and Africa are the regions with the highest number of MDR-TB cases since over 50% of the global MDR-TB cases in 2012 occurred in the Russian Federation, India and South Africa,[3] respectively.

Extensively drug-resistant TB (XDR-TB) is defined as TB caused by an MDR strain that is also resistant to any fluoroquinolone and to any of the second-line injectable drugs (capreomycin, kanamycin, or amikacin). The first XDR-TB cases were described in 2006; in 2012, XDR-TB cases were reported from 92 countries. It is estimated that 9.6% of MDR-TB cases are indeed XDR-TB.

The only measure to reduce the burden of patients with XDR-TB is appropriate treatment of patients with MDR-TB.[54] Therefore, the identification of new and effective drugs to fight resistant strains of *M. tuberculosis* is of the outmost importance. The introduction of bedaquiline for treatment of MDR-TB is a first step towards this end.[51]

Concluding remarks

Antimicrobial resistance is now recognized by the scientific community, the society at large and most policy-makers as an important problem to confront.

Table 2 Number of notified TB and multidrug-resistant strains of *M. tuberculosis* (MDR-TB) cases and ratio between MDR-TB and TB cases in the six World Health Organization (WHO) world regions. The data are derived from WHO[52]

		2011			2012			2013		
WHO regions	Population[a]	No. of TB cases	No. of MDR-TB cases	MDR-TB/TB cases (%)	No. of TB cases	No. of MDR-TB cases	MDR-TB/TB cases (%)	No. of TB cases	No. of MDR-TB cases	MDR-TB/TB cases (%)
Africa region	755 424 976	1 468 455	12 390	0.8	1 422 655	18 156	1.3	1 387 929	13 531	1.0
Region of the Americas	884 408 678	234 488	3475	1.5	233 985	2967	1.3	233 083	2961	1.3
Eastern Mediterranean region	529 821 657	418 238	835	0.2	421 865	2246	0.5	448 633	2923	0.7
European region	885 342 838	383 577	34 184	8.9	365 282	36 877	10.1	360 783	39 540	11.1
South-East Asia region	1 696 547 103	2 358 127	6615	0.3	2 331 455	19 202	0.8	2 297 033	28 618	1.2
Western Pacific region	1 750 811 276	1 387 741	4394	0.3	1 410 835	5749	0.4	1 375 213	5908	0.4

[a] Population data refer to the year 2005.[53]

The WHO global report on surveillance of AMR, providing for the first time a global picture of the magnitude of AMR, also reveals the lack of adequate surveillance in many parts of the world and large gaps in information on microbes of major public health importance that preclude an accurate analysis of the real situation and of trends over time.

It is critical to strengthen and harmonise the AMR surveillance through the development of agreed epidemiological and microbiological methods, the adoption of common definitions to enhance the ability to share and compare resistance information, and to attain a better coordination of the surveillance networks.

With this aim, the WHO regional office for Europe (EURO) supports a new project (CAESAR-Central Asian and Eastern European Surveillance of Antimicrobial Resistance) to develop a network of national surveillance systems in the countries of the region that are not part of the EU and do not participate to EARS-Net, facilitating comparison of data throughout the entire European region.[55]

Different but coordinated strategies against AMR should be implemented, considering the type of pathogen (human or zoonotic), the setting in which it spreads (hospital or the community) and possible other specific factors contributing to the emergence of resistance. A special case is represented by the strategy against the development of MDR-TB, for which the only prevention is the improvement of treatment compliance in patients with susceptible TB.

In the hospital setting, infection control measures and antimicrobial stewardship programmes – administered by multidisciplinary teams of experts such as infectious diseases physicians, clinical pharmacists, clinical microbiologists, etc. – are very important to prevent emergence and transmission of antimicrobial-resistant microorganisms and ensuring the efficacy of available antimicrobials.[56–58]

Antimicrobial stewardship needs to be extended also to family doctors in the community, where there is a great consumption of antibiotics. The actions needed to reduce antibiotic misuse and inappropriate antibiotic prescriptions should consider: information campaigns for the consumers, information and training for the healthcare professionals, improved diagnostics for treatment decisions, treatment guidelines, and prescription audits.[59]

In veterinary medicine, the urgent need to take action for monitoring the antimicrobials use in food animals was stressed during the 2011 World Health Day. The interventions required consist in enforcing regulations governing the use of antimicrobials in food-producing animals, strengthening surveillance and monitoring, and reducing the need for antimicrobials through better animal husbandry.[2]

In January 2015, European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA) and European Medicines Agency (EMA) published for the first time a joint report on the integrated analysis of the consumption of antimicrobials and AMR in bacteria from human beings and food-producing animals. This is a very important signal for a coordinated surveillance, although several limitations in carrying out this type of analysis have been identified.[60]

In addition, innovative approaches are needed for the development of new antibiotics and other products to limit AMR. There is a shortage of new antibiotics in the pipeline and few incentives for industry to invest in research and development in this field. Only two novel classes of antibiotics have been marketed over the past 30 years (oxazolidinones and cyclic lipopeptides)[2] but both these molecules target Gram-positive pathogens. There are very few effective drugs to treat multidrug-resistant infections due to Gram-negative bacteria that represent the main threat at present. The introduction of new vaccines may reduce the prevalence of infectious diseases and thereby reduce the need for antibiotics. For example, the introduction of the pneumococcal conjugate vaccines has led to the reduction in resistant *Streptococcus pneumoniae* not only in the vaccinated population but also in the population as a whole.[61,62] The development of rapid point-of-care diagnostic tools may be of use to reduce clinical uncertainty, to save unnecessary antibiotic treatments, and to select effective antibiotics where resistance has rendered first-line treatment ineffective.[63] The recent discovery of a new antibiotic called teixobactin, with excellent activity against Gram-positive pathogens, including drug-resistant strains, represents a hope for the future and an example for new researches.[64]

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