DECEMBER 2015 SCOR inFORM

ANTIMICROBIAL RESISTANCE

GABRIELA BUFFET
Medical Director

SCOR Global Life

Antimicrobial therapy has significantly contributed to improving health care by the treatment of infectious diseases. Complex medical procedures such as cardiac surgery, organ transplantation, aggressive therapy of autoimmune diseases and malignancies would not be possible without effective antibiotics. Unfortunately, an increase in antimicrobial resistant microorganisms threatens the effectiveness of antimicrobial therapy and the benefits of these drugs.

In this paper we will focus on antibiotic resistance, explaining the influence of medical and non-medical use of antibiotics on the development of resistance. The paper will conclude with a view on the spread of resistant bacteria and the related health, economic and insurance industry consequences. We will discuss several microbiological pathways and mechanisms that lead to resistance in bacteria and we will provide descriptions of the main types of resistant bacteria.

KEY POINTS

- Antibiotic resistance raises the risk of treatment failure mainly for common infections, increasing morbidity and mortality.
- The future mortality, directly or indirectly, associated to antimicrobial resistance is estimated, for 2050, at 10 million deaths, mainly in Africa and Asia.
- New antibiotics and new antibiotic classes are highly necessary.
- So far, the increase in the pandemic risk has not been reported.
- Control of antibiotic resistance is an initiative that requires cooperation amongst countries around the globe.

BACKGROUND

In April 2014, the World Health Organisation released a special report on antimicrobial resistance (AMR). It states "*Antimicrobial resistance (AMR) is an increasingly serious threat to global public health. AMR develops when a microorganism (bacteria, fungus, virus or parasite) no longer responds to a drug to which it was originally sensitive. This means that standard treatments no longer work; infections are harder or impossible to control; the risk of the spread of infection to others is increased; illness and hospital stays are prolonged, with added economic and social costs; and the risk of death is greater—in some cases, twice that of patients who have infections caused by non-resistant bacteria.*

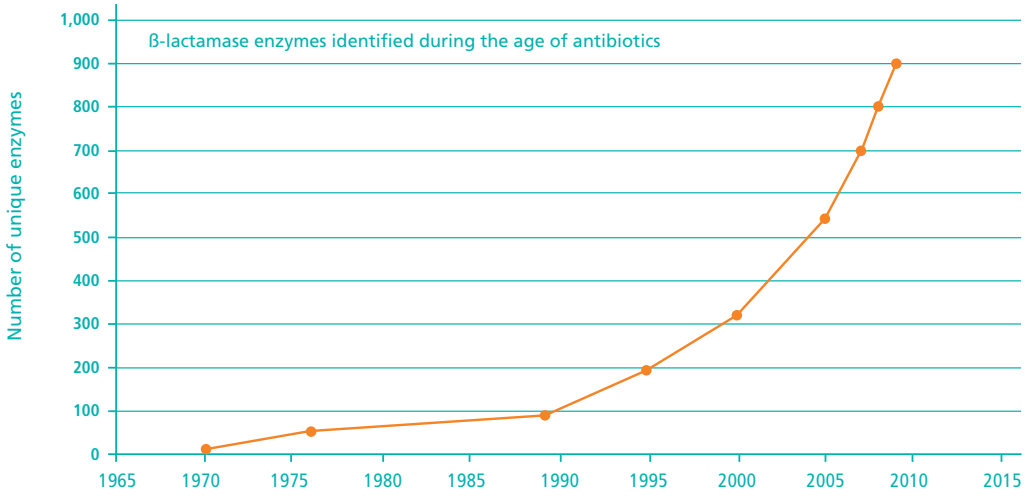
The problem is so serious that it threatens the achievements of modern medicine. ***A post-antibiotic*** *era— in which common infections and minor injuries can kill—****is a very real possibility for the 21st century.***"

Antibiotic resistance does not give advantages to bacteria in terms of transmission, fitness or pathogenicity, it only provides an increased possibility of survival when exposed to antibiotics. From a public health point of view, antibiotic resistance increases the risk of treatment failure for common infections, increasing morbidity and mortality.

The level of antimicrobial resistance displays large variations depending on the bacterium type, antimicrobial group and geographical region.

Recurrently new resistance mechanisms and new outbreaks of multidrug resistant bacteria are reported in the world (i.e. E. coli, Acinetobacter, Klebsiella). Recently a new plasmid mediated colistin resistance in Gram-negative bacteria was reported in China, where colistin is heavily used for veterinary use. Colistin is also used in human medicine to treat severe infections produced by multidrug resistant pathogens. The emergence of plasmid mediated resistance to colistin could have serious consequences in morbidity and mortality if new classes of antibiotics or new antibiotics are not developed in the medium time.

RESISTANCE RISING



Source: Davies J, Davies D. Origins and Evolution of Antibiotic Resistance. Microbiology And Molecular Biology Reviews, Sept. 2010, p. 417–433

ANTIBIOTIC DEVELOPMENTS

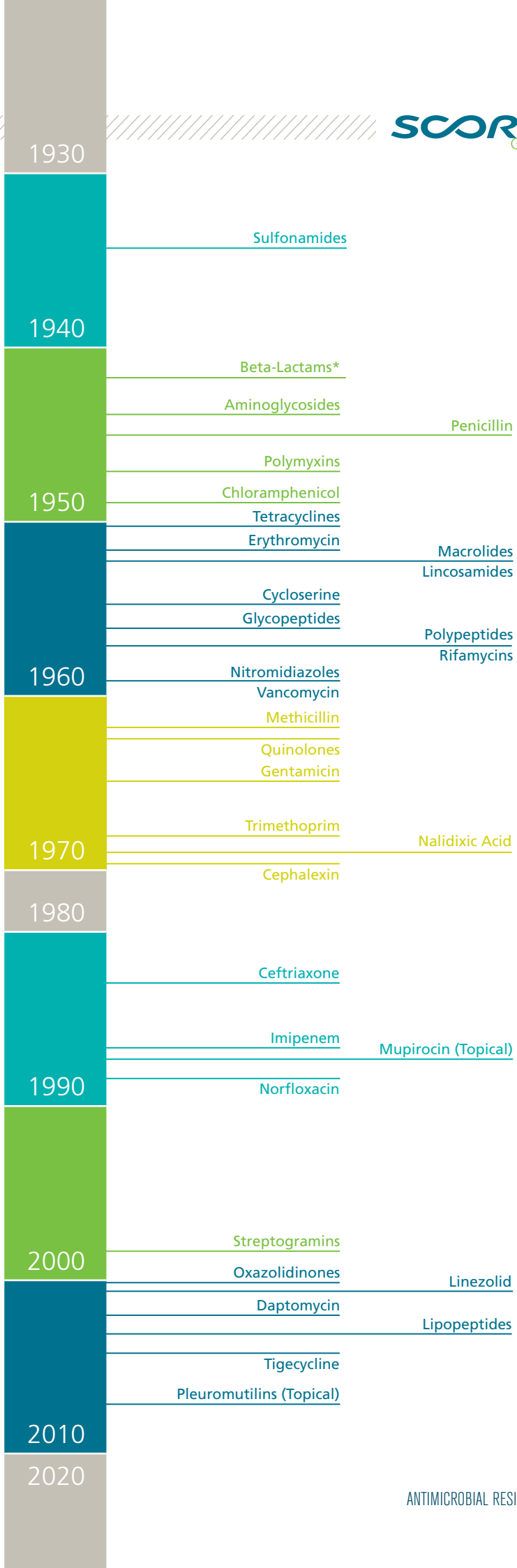
The occurrence of resistance is a natural and inevitable phenomenon. Antibiotic resistance was observed rapidly after the introduction of penicillin, the first class of antibiotics to be discovered in 1928. In the last 50 years, we have been witness to an evolutionary arms race between the development of new antibiotics and the emergence of resistance. However, the speed of this race has been accelerated by local as well as global trends such as urbanisation, global trade, travel, higher proportions of elderly people requiring hospital-based care, pollution and changing weather patterns. Aggravating this is the misuse of antibiotics in livestock farming, where they are used not for medical purposes but for improving quality and yield.

This situation allowed the emergence of multi-resistant bacteria, mainly Enterobacteria (*Escherichia coli, Acinetobacter spp., Klebsiella spp.*), *Enterococci* and *Staphylococci.*

The speed of antibiotic development has experienced a severe downturn, and very few new antibiotics have been developed over the last 10 years. Pharmaceutical research and development has suffered from a deficit of new knowledge and technology available for antibacterial drug discovery. Only two new classes of systemic antibacterial antibiotics have been brought to the market in the past 30 years. The US Federal Drug Administration (FDA) approved 16 new drug applications for antibiotics from 1983 to 1987 for use in the US, compared with the approval of only 2 systemic antibacterial agents from 2008 to 2012.

However, in the last 2 years there have been 5 new antibiotic drugs which have obtained FDA approbation and as of June 2015, 31 drugs are in development process. At best, only 1 out of 5 drugs that reach the initial phase of testing in humans will receive approval from the Food and Drug Administration for use.

TIMELINE OF CLASSES OF ANTIBIOTICS



** Beta-lactams include three groups sometimes identified as separate classes: penicillins, cephalosporins, and carbapenems.*

NON-MEDICAL USE OF ANTIMICROBIALS

Over the last 50 years the increasing demand for livestock products combined with new developments in breeding, nutrition and management practices led to modifications in animal production systems. The current state of animal production systems cannot tolerate disease outbreaks in production animals. Various antimicrobial drugs are administered at sub-therapeutic levels aiming at disease prevention. Antibiotics can be found in cattle, pigs and poultry. The percentage of antibiotic consumption in farm animals in the USA has risen from 16% in 1951 to 80% in 2011. The use of antibiotics in farm animals can lead to the development of resistance in bacteria associated with the animal or with people who eat the animal.

Veterinary use of antimicrobial drugs creates a pathway for the emergence of antimicrobial-resistant bacteria, including animal pathogens, human pathogens that have animal hosts, and symbiotic bacteria that are present in animals.

Drug-resistant bacteria can spread to humans either by the food supply (e.g. meat, fish, eggs and dairy products), direct contact with animals or, more indirectly, through the environment. Antibiotics may be found in public water systems when the runoff from livestock facilities and feedlots contaminates streams and groundwater. The use of antibiotics in this way contributes to the emergence of antibiotic resistant pathogens and reduces the effectiveness of the antibiotic for human infections.

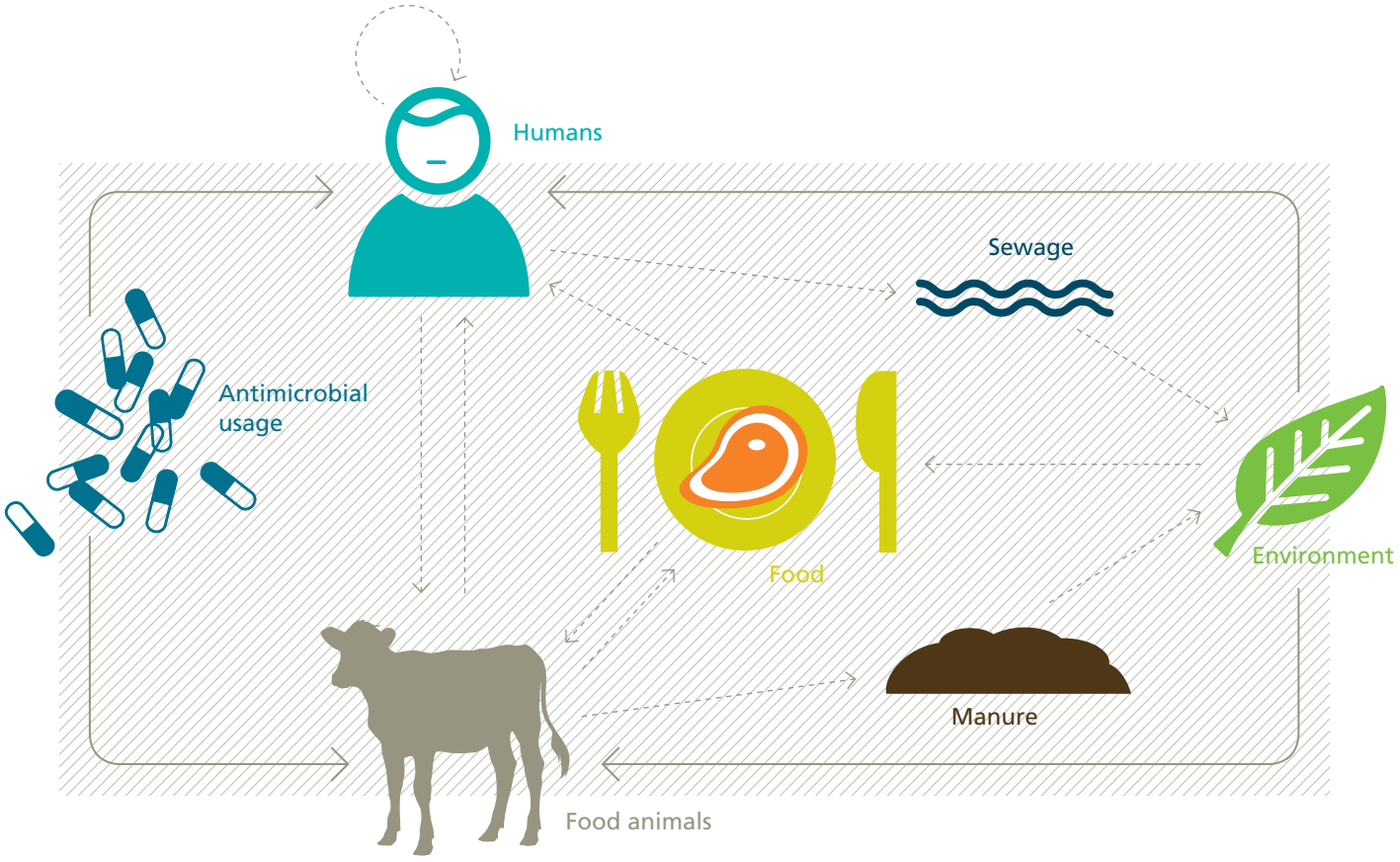
ESTIMATED ANNUAL ANTIBIOTIC USE IN THE UNITED STATES

Data are shown as approximate numbers of kilograms of antibiotics used per year.

Data from Hollis A. Ahmed Z. Preserving Antibiotics, Rationally. N Engl J Med 369;26, 2013

Antibiotics do not induce resistance but the selective pressure on the microbes allows the emergence of resistant strains. In human medicine, any antibiotic therapy facilitates the evolution of resistant strains. In livestock and agricultural use of antibiotics (treatment of bacterial diseases of plants and animals), the antibiotic residues present in the outside environment are the origin of the selection of resistant bacteria. Resistant bacteria can be found in food animals and food products destined for consumption by humans.

PATHWAYS TO ANTIMICROBIAL RESISTANCE



ECONOMIC AND INSURANCE INDUSTRY CONSEQUENCES

Drug-resistant bacteria can circulate in humans and animals through food, water and the environment, and transmission is influenced by trade, travel and both human and animal migration.

The human consequences of this increase in resistance are mainly higher mortality in patients with resistant infections, increased length of hospital stays, and higher treatment costs for resistant infections. The economic consequences include loss of productivity such as loss of individual income, diminished workforce productivity, and increased costs of diagnostics and treatment such as medical consultation, infrastructure, screening, cost of equipment, and drug costs.

An estimated 25 000 people die every year in Europe from antibiotic-resistant bacteria. In the USA in 2005, an estimated 94 000 invasive Methicillin Resistant *Staphlycoccus Aureus* (MRSA) infections required hospitalization and were associated with 19 000 deaths.

A recent report by the US Center for Disease Control and Prevention conservatively estimated that at least 2 million illnesses and 23 000 deaths a year in the USA were caused by antibiotic resistance. In addition to the cost in human lives, there are high economic costs for health care. Resistant infections are more expensive to treat and patients infected with resistant strains of bacteria are more likely to require longer hospitalization and face higher treatment costs than are patients infected with drug-susceptible strains.

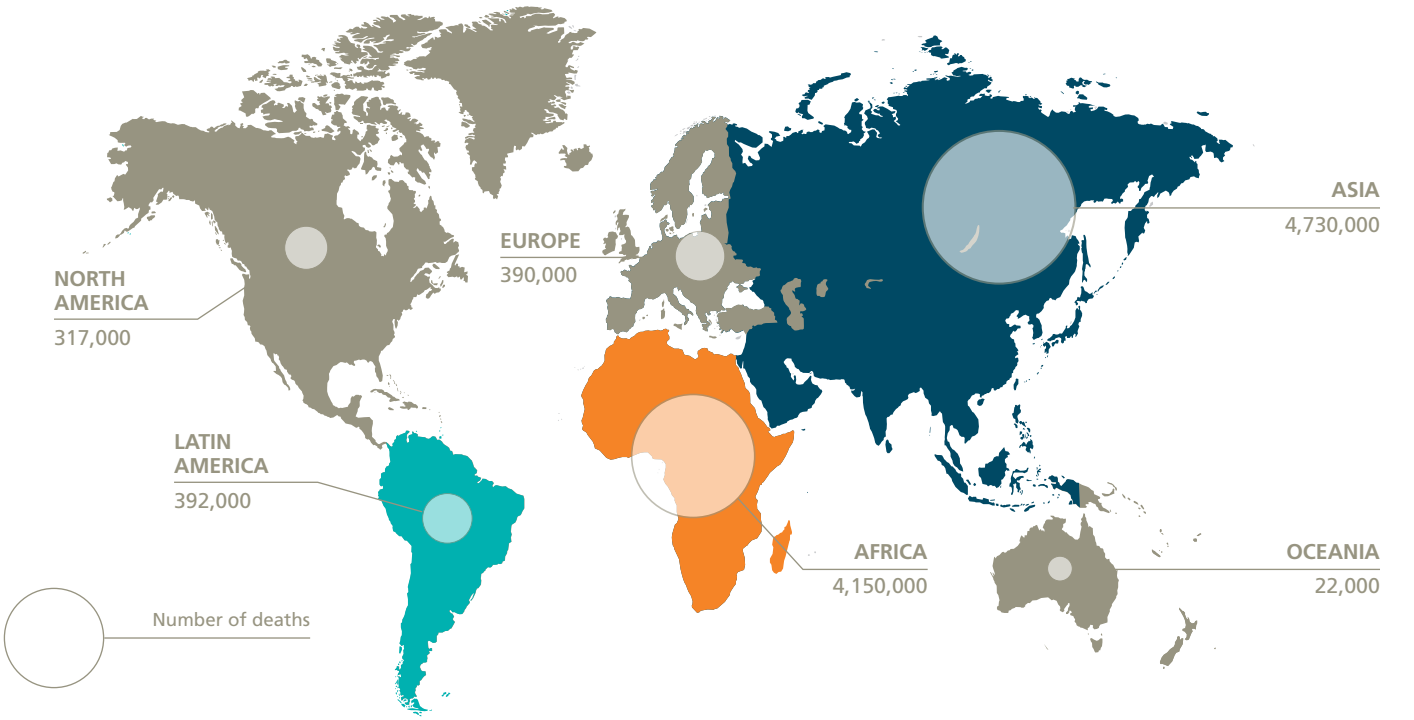
The annual impact of resistant infections is estimated to be $20 billion in additional health care costs and 8 million additional hospital days in the United States, and over €1.6 billion in costs and €2.5 million additional hospital days in the European Union. Antimicrobials currently account for over 30% of hospital pharmacy budgets in the US.

According to a report commissioned by UK Prime Minister, in 2050, the deaths attributable to AMR will be approximately 10 million/ year. The regions most affected will be Africa and Asia with more than 4 million deaths/ year per continent. In Europe and US the number of deaths is estimated at 707.000/ year.

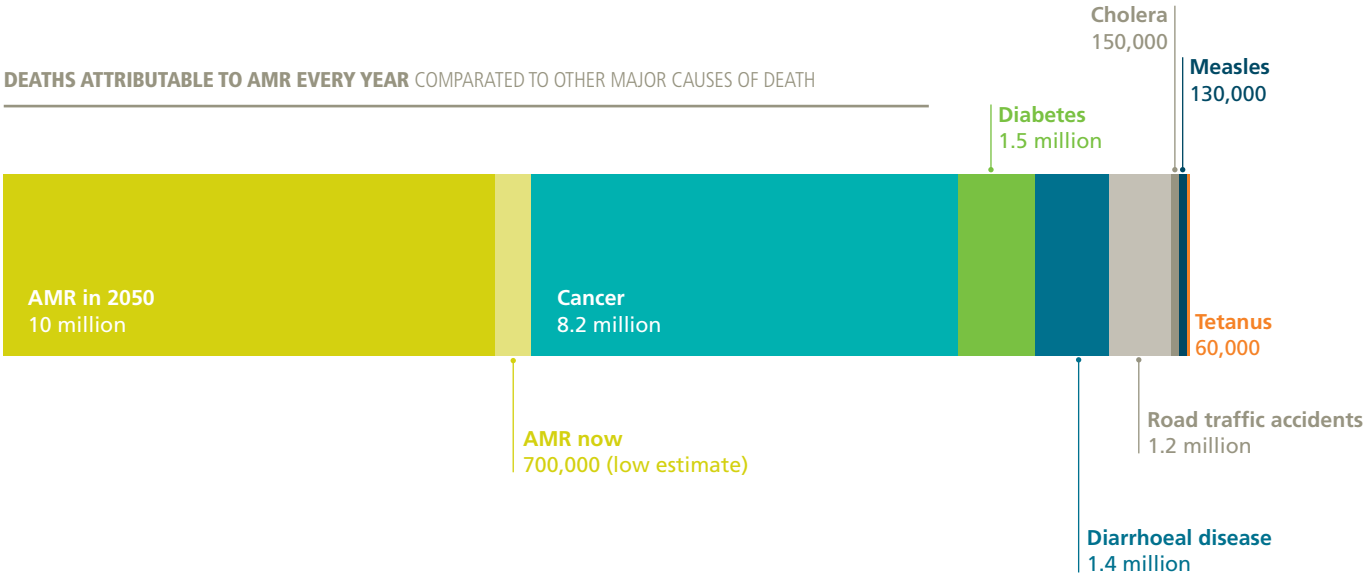
DEATHS ATTRIBUTABLE TO AMR EVERY YEAR BY 2050

MORTALITY PER 10,000 POPULATION

5 6 7 8 9 10 >



DEATHS ATTRIBUTABLE TO AMR EVERY YEAR COMPARATED TO OTHER MAJOR CAUSES OF DEATH



Source from the above charts: Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. The Review on Antimicrobial Resistance. Jim O'Neill. December 2014

FIGHT AGAINST ANTIMICROBIAL RESISTANCE

Prudent antimicrobial use along with comprehensive infection prevention and control strategies that target all healthcare sectors are the cornerstones of effective interventions aiming to prevent selection and transmission of bacteria resistant to antimicrobial agents.

The fight against antimicrobial resistance in the long term requires conservation of existing antibiotics and innovation to develop new antibiotics and new antibiotic classes.

Conservation policy includes several components:

- Reducing antibiotic overuse in medical and non-medical settings
- Reducing incorrect antibiotic use (improving diagnosis, reviewing antimicrobial indication, choice, dose and treatment duration)
- Reducing need for antibiotic use by lowering infection exposure (improving public sanitation, increasing vaccinations and improving hospital infection control).

Health International entities (WHO, CDC, ECDC) and Governments have recently reported on the subject and stricter measures will be proposed, mainly in USA and Europe.

INNOVATION POLICY

New antibiotics and new antibiotic classes are highly necessary. Investments in research and development are required not only in antibiotic research but in new treatment strategies including methods to stop plasmid replication and resistance mechanisms, bacteriophage treatments and antimicrobials developed by nanotechnology.

CONCLUSIONS

Antimicrobial resistance has developed into a serious threat for human health. Few public health problems are of greater global importance today than antimicrobial resistance.

Focusing on bacteria, the role of the exposure to antibiotics in the emergence of multidrug resistance is widely accepted by scientific community. If during the second half of the twentieth century, the discovery and use of antibiotics have been the source of some of the greatest successes of medicine, today the emergence and spread of bacterial resistance in human populations has become a pressing public health problem. Therefore, control of bacterial resistance to antibiotics is a major health issue.

Control of antibiotic resistance on international scale is an imperative that will require cooperation amongst countries around the globe to apply concerted policies and efforts to fight against drug resistance and improper use of antibiotics. The consequences of the accelerated antimicrobial evolution could be a threat to public health with an impact also on the health of the insured population, leading to shifting claims patterns in insurance and reinsurance. The main areas concerned will be increased mortality and morbidity, higher medical costs and medical malpractice.

MICROBIOLOGICAL ASPECTS

Bacterial resistance is the ability of bacteria to prevent the action of one or more antibiotics. The first cases of bacterial resistance were reported in 1940's very shortly after the start of antibiotic use.

Resistance arises as a consequence of selection pressure from antibiotic use. The decreasing effectiveness of antibiotics in treating common infections has accelerated in recent years and has spread worldwide.

Two different resistances can be observed: Natural and acquired resistance.

The natural or intrinsic resistance is a species character. It is stable, transmitted to descendants, however it is not or rarely transmitted to other bacteria of the same species or between different species.

Examples of natural resistance:

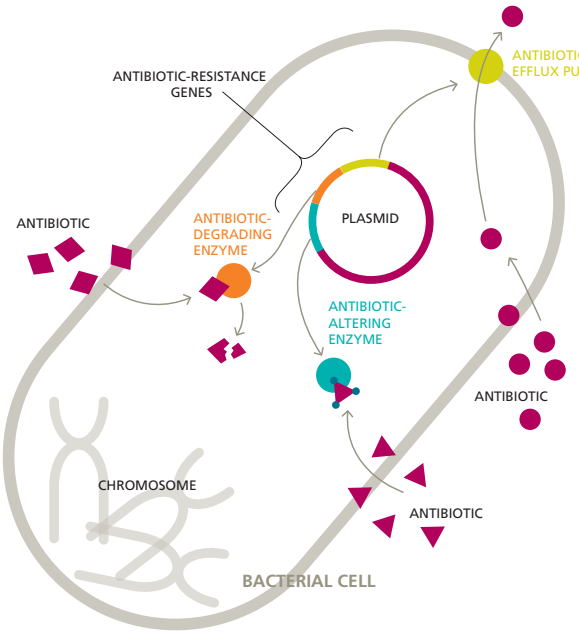
- *Klebsiella spp.* naturally produces beta-lactamases. This enzyme is then present in the periplasmic space of the bacteria and leads to the destruction of antibiotics such as penicillins, before the antibiotic arrives to their bacterial target;
- Anaerobic bacteria are naturally resistant to aminoglycosides. The passage of aminoglycosides through the cytoplasmic membrane requires an active transport system absent in anaerobic bacteria.

Acquired resistance results a change in the genetic characteristic of the bacteria, allowing it to tolerate a concentration of antibiotic higher than that of the susceptible strains of the same species. The widespread use of antibiotics has led to a selection of resistant strains. Acquired resistance is less stable but it often spreads significantly in the bacterial world.

The genetic mechanisms of acquired resistance

Mechanisms of resistance may be acquired by mutation or by transfer of genetic material between related or unrelated bacterial species. The resistance genes can be encoded in the chromosomal genetic material or extra chromosomal (plasmid) material.

THE BIOCHEMICAL MECHANISMS OF ACQUIRED RESISTANCE



Chromosomal resistance

This results from a mutation. It is a rare phenomenon, happening at random. It is not caused by the presence of an antibiotic. It is an independent event: the emergence of a mutation does not favor the appearance of other resistance mutations to different antibiotics. The probability of two simultaneous mutations is very low. The resistance mutation is permanent and it is hereditary (vertical transmission: transmission to descendants).

Extra-chromosomal resistance (plasmids)

Antibiotic resistance plasmids are bacterial extrachromosomal elements that carry genes conferring resistance to one or more antibiotics. Plasmids can transfer to other bacteria (horizontal transmission). These transfers are at the origin of very large spreads of resistance in bacterial populations. The resistance plasmids may change by the acquisition of extra-chromosomal genes or by transposable genetic elements. Transposable genetic elements allow spread of genes between phylogenetically distant bacteria.

- Enzyme inactivation: **The main mechanism of inactivation is hydrolysis. In the case of beta-lactam inactivation, it is a result of the action of enzymes called beta-lactamases, and it is the main mechanism of resistance to beta-lactams.**

Beta-lactamases can be grouped into 4 categories:

1. Penicillinases. These inactivate G penicillin and the A penicillins. However they don't have an effect against the M penicillin (oxacillin or methicillin) or on cephalosporins. (E.g. *Staphylococcus aureus*).
2. Expanded spectrum Beta-lactamases. These are encoded by plasmids. They cause resistance (or decreased activity) for G penicillin, M penicillin, carboxypenicillins, ureidopenicillins, 1st and 2nd generation cephalosporins (except cephamycins). The expanded spectrum Beta-lactamases are inhibited by clavulanic acid, sulbactam and tazobactam.
3. Extended-spectrum Beta-lactamases (ESBL). These Beta-lactamase enzymes are derived from previous enzymes by mutation of the genes coding for enlarged spectrum Beta-lactamase. The resistance profile is identical to that conferred by enlarged spectrum Beta-lactamase but it extends also to 3rd generation cephalosporins and aztreonam. Beta-lactamase extended spectrum remains sensitive to inhibitors.
4. Beta-lactamases resistant to inhibitors. Beta-lactamases resistant to inhibitors are derived from certain enlarged spectrum Beta-lactamase. The resistance profile is identical to Beta-lactamases enlarged spectrum however these enzymes are not inhibited by the clavulanic acid, sulbactam or tazobactam.

- Target modification: **The sites where the antibiotics bind are altered and hence less susceptible to the drug. Three mechanisms may be involved:**

1. Decrease in the affinity of the Protein Binding Penicillin (PBP) for beta-lactam antibiotics (eg. *Streptococcus pneumoniae*), beta-lactam antibiotics have difficulty binding to PBP
2. Increased synthesis of existing PBP with hyper-expression of a type of PBP that has a naturally low affinity for beta-lactam antibiotics (eg, *Enterococcus spp.*; an increase in the number of PBP available for peptidoglycan synthesis which leads to impossibility for the same dose of beta-lactam to block all target sites)
3. Synthesis of one or more new types of PBP which are unresponsive to beta-lactam antibiotics (eg. *Staphylococcus aureus* Methicillin-resistant: the acquisition and integration into the chromosome of gene (mecA) induces the synthesis of a new PBP, the PBP 2a, which alone is capable of ensuring the assembly of the peptidoglycan and it confers resistance to all beta-lactam antibiotics.

- Reduced permeability. **This results from cellular changes that reduce the penetration of the drug. Frequently the mutation affects the structure of porins or it decreases porin synthesis; porins are the proteins used by the antibiotic to penetrate into the bacteria.**
- Target protection: **Protection proteins bind to target sites and prevent drug action.**
- Efflux: **The drug is excreted by the cell, before it can have an effect, through active transport to the outside of the cell (energy system dependent)**
- Over production of the enzyme targeted by the drug
- Bypass. **Development of an alternate pathway that replaces the blocked pathway used by the antibiotic.**

The drug resistance mechanisms allow bacteria to survive, or even to actively grow, in the presence of an antimicrobial agent. Furthermore, certain bacterial variants have evolved mechanisms to resist multiple drugs, making such variants multidrug resistant to antibacterial therapy. Resistance level depends on the mechanism involved. Resistance can be high level, low level, or cross between several antibiotics.

EXAMPLES OF MECHANISMS AND ANTIBIOTIC TARGETS

BASIS OF RESISTANCE	MECHANISM	BACTERIAL PROTEINS/TARGETS RESPONSIBLE	ANTIBIOTIC TARGETS
Enzymes	Hydrolysis	ß-lactamases	ß-lactams
		Esterase	Macrolide
		C-P lyase complex	Fosfomycin
	Group transfer	Acetyltransferase	Streptogramins,
		Phosphotransferase	Aminoglycosides, macrolides
		Nucleotidyltransferase	Lincomycin, clindamycin, aminoglycosides
		Glycosyltransferse	Macrolides
		Ribosyltransferase	Rifampin
		Thiol transferase	Fosfomycin
	Redox process	TetX	Tetracyclines
Target modification	Structural alterations/ modifications	Penicillin binding proteins	ß-lactam antibiotics
		Cell wall precursors	Vancomycin
	Mutations in genes	Ribosomal subunits	Streptomycin
	Amino acid substitutions	RNA polymerase	Rifamycin
		DNA gyrase/topoisomerase	Quinolones
	Methylation	16S rRNA	Aminoglycosides
		23S rRNA	Macrolides
	Mutation	23S rRNA	Oxazolidinones
Reduced permeability	Reduced expression/ defective protein	Porins	ß-lactams, fluoroquinolones, aminoglycosides, chloramphenicol
Target protection	Ribosome protection	Ribosome protection proteins	Tetracycline
Efflux	Active extrusion	Membrane proteins	All major antibiotics

MULTI-DRUG RESISTANCE

Multidrug-resistant bacterial infections represent a major public health burden, not only in terms of morbidity and mortality, but also in increased expenses for managing patients and implementing extensive infection control measures.

Definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria were proposed to characterize the different patterns of resistance found in healthcare-associated, antimicrobial-resistant bacteria.

- MDR is defined as non-susceptibility to at least one agent in three or more antimicrobial categories.
- XDR is defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories).
- PDR is defined as non-susceptibility to all agents in all antimicrobial categories (i.e. no agents tested as susceptible for that organism)

MAINLY MULTI-RESISTANT BACTERIA

Methicillin resistant staphlycoccus aureus (MRSA)

Staphylococcus aureus (S. aureus) commonly colonises the skin and nose. MRSA infection is caused by a strain of S. aureus that has become resistant to the antibiotics commonly used to treat ordinary staphylococcal infections. Resistance to methicillin and other ß-lactam antibiotics is mediated by gene (mecA), which encodes a Protein Binding Penicillin (PBP) and it has low affinity for ß-lactams. MRSA can cause severe infections such as bloodstream infection, infective endocarditis, pneumonia and skin and soft tissue infections. Some of these infections are life-threatening and many result in considerable patient suffering and morbidity.

Vancomycin resistant enterococcus (VRE)

Enterococci form part of the normal flora of the human gastrointestinal tract. *Enterococcus faecium and Enterococcus faecalis* are the most prevalent in humans, accounting for greater than 90% of clinical isolates of Enterococci. Acquired resistance, most commonly to amoxicillin, aminoglycosides and glycopeptides, is increasing and glycopeptides such as vancomycin and teicoplanin have been the treatment of choice for invasive infections due *to E. faecium*. Initial reports of VRE first emerged from England and France in 1988 and from the United States in 1989. The proportion of *E. faecium* that are resistant to vancomycin has increased from 11% in 2002 to 37.4% in 2011.

Emergence of Enterococci with vancomycin acquired resistance coincided with an increase in the global usage of glycopeptides for the treatment of infections caused by MRSA and *Clostridium difficile*. In Europe the use of avoparcin, a glycopeptide antimicrobial used as a growth promoter for livestock has been proposed to explain the epidemiology of VRE. Until banned by the European Union in 1997, avoparcin had been used in several European countries and provided a selective pressure for the emergence and spread of vancomycin resistance genes.

Pneumococcus

ß-lactam-resistance in *S. pneumoniae* is caused by reduced affinity between the PBPs and ß-lactam antibiotics. Penicillin-resistant strains are also resistant to non– ß-lactam antimicrobial agents and are often multidrug resistant.

Gram negative bacteria

Enterobacteriaceae is a term used to describe groups of Gram-negative bacilli that commonly live in the gastrointestinal tract and includes organisms such as: *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae,* and *Citrobacter freundii.*

The first plasmid-mediated ß-lactamase in *Enterobacteriaceae,* TEM-1, was described in the 1960s. Since then, ß-lactamase variants with expanded spectra of activity have been increasingly reported and are known as extended spectrum ß-lactamases (ESBLs). Since the 1980s, ESBLs have been increasingly detected in *Enterobacteriaceae.* ESBLs have disseminated worldwide. ESBLs are generally located on plasmids and are therefore easily spread between bacteria. ESBLs confer resistance to a range of ß-lactam antimicrobials including broad spectrum third- and fourth-generation cephalosporins. They may also confer resistance to monobactams, such as aztreonam and to ß-lactam/ß-lactamase-inhibitor.

A second group of broad spectrum ß-lactamases are AmpC ß-lactamases. In contrast to ESBL enzymes, AmpC enzymes are commonly found on chromosomes of many clinically relevant species within the *Enterobacteriaceae* family, such as E. coli, *Enterobacter* spp., *Citrobacter freundii, Serratia marcescens, Shigella* spp., *Providencia stuartii* and *Morganella morganii.* In recent years increasing numbers of AmpC ß-lactamase genes have been mobilised onto plasmids, which are subsequently transferred to species such as *K. pneumoniae*.

Carbapenem resistant *Enterobacteriaceae* (CRE)

As a result of increasing resistance to various groups of ß-lactams due to ESBLs and AmpC enzymes, there is increasing use of carbapenems for the treatment of infections caused by *Enterobacteriaceae* and other Gram-negative bacilli, such as Pseudomonas aeruginosa and *Acinetobacter* spp. Over the last decade, there has been an alarming rise in the reports of carbapenem resistant *Enterobacteriaceae.*

The majority of CRE are also resistant to other commonly used groups of antimicrobials such as fluoroquinolones and aminoglycosides.

Carbapenemases are a diverse group of broad spectrum b-lactamases. The most commonly encountered carbapenemases are:

- *Klebsiella pneumoniae* carbapenemase (KPC)

- New Delhi metallo-ß-lactamase (NDM)

- Verona Integron-encoded metallo-ß-lactamase (VIM)

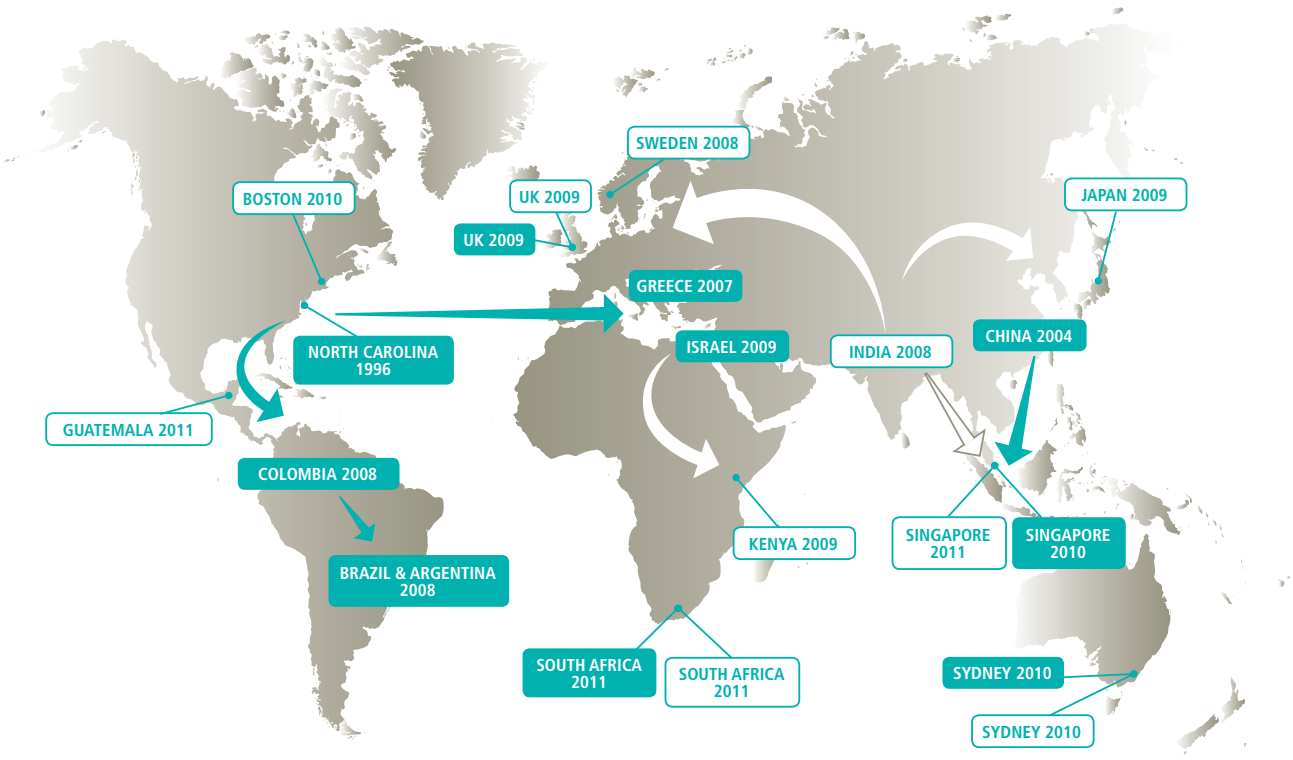
- Oxacillinase (OXA)

A worrisome aspect is the rapidity of international dissemination of carbapenemases, as exemplified by the importation of NDM-1 from the Indian subcontinent to the United Kingdom and other European countries as well as the global importation of KPC from the United States to various continents. The rapid spread of these carbapenemases is usually mediated by transfer of plasmids between strains or species and/or clonal dissemination of certain strains.

For serious infections caused by carbapenemase-producing Enterobacteriaceae, the treatment options are restricted and invariably rely on tigecycline and colistin of the polymixin antibiotic class. The emergence of plasmid mediated resistance to colistin heralds the breach of the last group of antibiotics use to treat severe infections.

In Europe, Greece is considered endemic for CRE, but significant problems of CRE dissemination have also been reported in almost all European countries.

GLOBAL DISSEMINATION OF KLEBSIELLA PNEUMONIAE CARBAPENEMASE-PRODUCING K. PNEUMONIAE
AND NEW DELHI METALLO-SS-LACTAMASE-1-PRODUCING ENTEROBACTERIACEAE



From Molton JS and all. The Global Spread of Healthcare-Associated Multidrug-Resistant Bacteria: A Perspective From Asia.

KPC POSITIVE *KLEBSIELLA PNEUMONIAE*

NDM-1 POSITIVE *ENTEROBACTERIACEAE*

The earliest reported cases in each continent are shown. Arrows indicate the significant international movements of these organisms.

Pseudomonas aeruginosa

Pseudomonas aeruginosa is a Gram-negative bacteria existing widely in the environment. It is present in diverse environmental sites (e.g. aquatic environments and soil) and is also known to colonize plants, animals and humans. *P. aeruginosa* can also survive for prolonged periods in moist environments such as taps, sinks and respiratory equipment.

P. aeruginosa is primarily described as an opportunistic pathogen causing disease in compromised hosts, for example patients in intensive care settings, patients with chronic lung disease or immunocompromised patients. *P. aeruginosa* represents a nosocomial pathogen of considerable importance. *P. aeruginosa* rarely colonizes healthy non-hospitalized individuals. However up to 50% of hospitalized patients exhibit colonization within the gastrointestinal or respiratory tracts. Infection due to MDR *P. aeruginosa* is associated with increased morbidity and mortality, prolonged length of stay, and increased costs.

Tuberculosis multi-resistant

Tuberculosis (TB) is among the most common infectious diseases and a frequent cause of death worldwide. TB is caused by the bacteria *Mycobacterium tuberculosis (M. tuberculosis)* and is spread most commonly through the air. With an estimated 9 million new infections and 2 million deaths per year, TB is the world's number one cause of human suffering attributed to a single infectious agent. Eighty percent of all infections occur in sub-Saharan Africa and Asia. In most cases, TB is treatable and curable with the available first-line TB drugs. However, in some cases, *M. tuberculosis* can be resistant to one or more of the drugs used to treat it. Multidrug-resistant TB (MDR-TB) is defined as resistance to isoniazid and rifampicin, the two most potent anti-TB drugs. MDR-TB is difficult and expensive to treat. The major factors driving TB drug resistance are incomplete or wrong treatment, short drug supply, and lack of new drugs

Extensively drug-resistant TB (XDR-TB), defined as MDR-TB with additional resistance to a fluoroquinolone and one or more of the injectable anti-TB drugs, has been reported in many countries.

To treat drug-resistant TB is complex and requires more time and more expensive drugs that often have more side effects.

REFERENCES

- Antibiotics Currently in Clinical Development. July 2015. The Pew Charitable Trusts. http://www.pewtrusts.org/en/projects/antibiotic-resistance-project
- CDC. Antibiotic Resistance Threats in the United States, 2013
- Chen LF, Chopra T, Kaye KS. Pathogens resistant to antibacterial agents. Med Clin North Am. 2011 Jul;95(4):647-76
- Colson A. The Antibiotic Pipeline. www.extendingthecure.org
- Costa PM, Loureiro L, Matos AJF. Transfer of Multidrug-Resistant Bacteria between Intermingled Ecological Niches: The Interface between Humans, Animals and the Environment. Int. J. Environ. Res. Public Health 2013, 10, 278-294
- Davies J, Davies D. Origins and Evolution of Antibiotic Resistance. Microbiology And Molecular Biology Reviews, Sept. 2010, p. 417–433
- ECDC. Antimicrobial resistance surveillance in Europe 2012.
- Fair RJ, Tor Y. Antibiotics and Bacterial Resistance in the 21st Century. Perspect Medicin Chem. 2014 Aug 28; 6:25-64.
- FDA. 2011 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals.
- Gould IM. Antibiotic resistance: the perfect storm. International Journal of Antimicrobial Agents 34, S3 (2009) S2 S5.
- Hollis A, Ahmed Z. Preserving Antibiotics, Rationally. N Engl JMed, 2010; 369; 26: 2474-2476.
- IDSA. Bad Bugs, No Drugs. As Antibiotic Discovery Stagnates. A Public Health Crisis Brews. 2004
- Kaźmierczak Z, Górski A, Dąbrowska K. Facing Antibiotic Resistance: Staphylococcus aureus Phages as a Medical Tool. Viruses 2014, 6, 2551-2570
- Laxminarayan R, Duse A, Wattal C and all. Antibiotic resistance—the need for global solutions. www.thelancet.com/infection Published online November 17, 2013
- Laxminarayan R. Antibiotic Effectiveness: Balancing Conservation against Innovation. Science. 2014 Sep 12;345(6202):1299-301
- Levy SB. The Challenge of Antibiotic Resistance. Scientific American, March 1998, p. 43-56.
- Liu YY, Wang Y, Walsh TR and all. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect Dis 2015 Published Online November 18, 2015 http://dx.doi.org/10.1016/S1473-3099(15)00424-7
- Magiorakos AP, Srinivasan A, Carey R. B., and all. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012; 18: 268–281.
- Molton JS, Tambyah PA, Ang BSP, Ling ML, and. Fisher DA. The Global Spread of Healthcare-Associated Multidrug-Resistant Bacteria: A Perspective From Asia. Clinical Infectious Diseases 2013;56(9):1310–8
- O'Neill. Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations. 2014.
- Perros M. Infectious disease. A sustainable model for antibiotics. Science. 2015 Mar 6; 347(6226):1062-4.
- Sosa AJ, Byarugaba DK, Amabile-Cuevas CF, and all. Antimicrobial Resistance in Developing Countries. Springer. 2010. New York.
- Todar K. Todar's Online Textbook of Bacteriology
- Vasoo s, Barreto JN, ToshPK. Emerging Issues in Gram-Negative Bacterial Resistance: An Update for the Practicing Clinician. Mayo Clin Proc. 2015 Mar; 90(3):395-403.
- Verraes C, Van Boxstael S, Van Meervenne E. and all. Antimicrobial resistance in the food chain: a review. Int J Environ Res Public Health. 2013 Jun 28;10(7):2643-69.
- WHO. Antimicrobial resistance. Draft global action plan on antimicrobial resistance. 12 December 2014.
- WHO. Drug resistance. Infographic. http://www.who.int/drugresistance/publications/infographic-antimicrobial-resistance-20140430.pdf?ua=1
- WHO. Drug resistant-TB. Surveillance & Response. 2015
- WHO. The evolving threat of antimicrobial resistance. Options for action. 2012
- Woolhouse M, Ward M, van Bunnik B, Farrar J. 2015 Antimicrobial resistance in humans, livestock and the wider environment. Phil. Trans. R. Soc. B 370:20140083. http://dx.doi.org/10.1098/rstb.2014.0083
- Woolhouse MEJ, Ward MJ. Sources of Antimicrobial Resistance. Science 341, 1460 (2013)
- Wittebole X, De Roock S, Opal SM. A historical overview of bacteriophage therapy as an alternative to antibiotics for the treatment of bacterial pathogens. Virulence. 2014 Jan 1;5(1):226-35

Publisher
Paolo De Martin

life@scor.com

SCOR Global Life

SCOR Global Life
5, avenue Kléber - 75795 Paris Cedex 16
France
www.scor.com