

97039 - GLOBAL HEALTH, ANTIMICROBIAL
DRUGS AND VACCINES

Global Aspects of Antimicrobial Resistance

Russell E. Lewis, Associate Professor, Infectious Diseases, University of Bologna

11/26/2022

Contents

A brief history of antimicrobial resistance (AMR)	3
Global response to antimicrobial resistance	5
What are the drivers of antimicrobial resistance?	7
AMR in Low-Middle Income Countries (LMICs)	8
AMR situation in Italy	15
The global future of AMR	17
One-Health Perspective of AMR	18
Cross-border spread of AMR	29
Summary	31
Lecture Slides	31
References	31

A brief history of antimicrobial resistance (AMR)

Until the 20th Century, influenza and pneumonia, tuberculosis, and enteric infections were among the top three causes of death. The average life expectancy of an adult in Western Europe was less than 50 years, and 2% of children failed to live beyond 5 years of age due to deaths caused mostly by infectious diseases.

Industrialization and growing wealth during the 19th century brought improvements in drinking water and sanitation for many countries, leading to reductions in communicable enteric infections and dramatic improvements in life expectancy. By the early 20th century, advances in immunization further reduced mortality as vaccines for pertussis, diphtheria, yellow fever and tuberculosis were introduced. However, common bacterial infections remained a serious medical threat. Streptococcal throat infections were sometimes fatal, ear infections could progress to deafness, mastoiditis or meningitis, and even minor surgeries were associated with life-threatening infections. Maternal mortality during childbirth approached 1%.

Figure 1. Changes in life expectancy over 500 years. Data source: World Health Bank

Antibacterial resistance emerged with bacteria on earth approximately 2-2.5 billion years ago. In contrast, the first humans are believed to have existed around 2 million years ago. Therefore, it cannot be said that humans are the cause of

antimicrobial resistance. Antibiotic resistance pre-dates the use of antibiotics in medicine. Indeed, antibiotic use is inevitable. Any use of an antibiotic will eventually select for antimicrobial resistance.

The first recorded use of antimicrobial -like substances was by the early Egyptians, Greeks, and Chinese, who used natural products with antimicrobial activity for millennia to treat wounds and infections, even if the causes of these diseases were unknown until the 19th and 20th century..

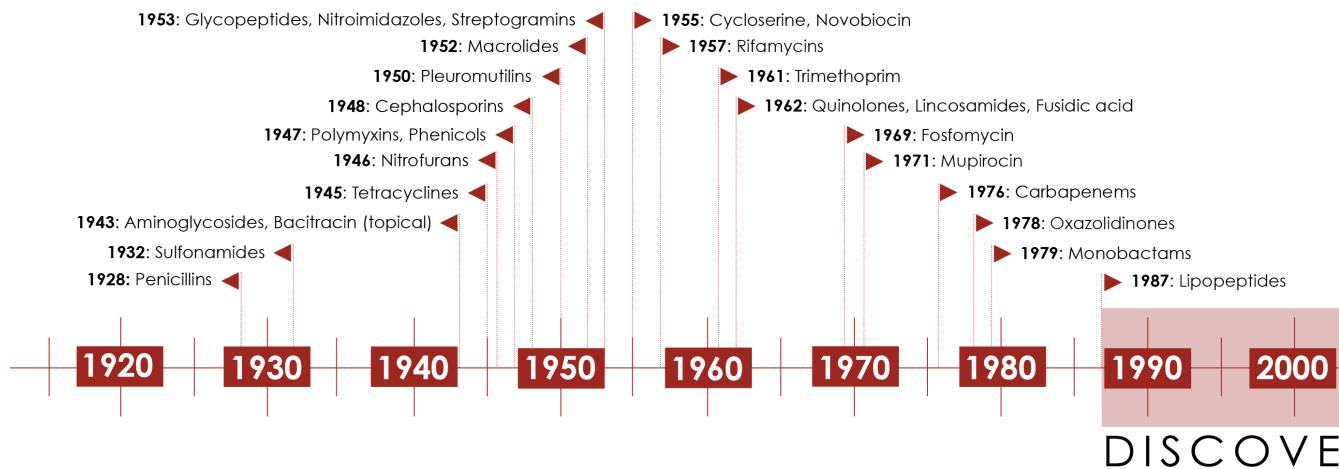
The microbiologist and immunologist Paul Ehrlich (1854-1915) is credited with the discovery and first medical application of a synthetic antibiotic arsphenamine (Salvarsan) for the treatment of a bacterial infection-syphilis. Yet it was the serendipitous discovery of penicillin in 1928 by Alexander Fleming, and its subsequent purification of the drug in quantities needed for clinical testing by Drs. Florey and Chain in the 1930s, that initiated the true start of the modern antibiotic era. Interestingly, the term *antibiotic* was actually coined by Selman Waksman, a biochemist and microbiologist who discovered the first effective treatment for tuberculosis, streptomycin, and was awarded the Nobel prize in 1952.

Alexander Fleming was among the first physicians to caution about the risks of resistance to penicillin if used too little or for a too short of period during treatment. In his Nobel Prize acceptance speech, Dr. Fleming noted:

“It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily under-dose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.” -Sir Alexander Fleming, Nobel Prize Lecture, December 11, 1945

By 1947, Fleming’s predictions had come true as the first cases of penicillin resistance were already being reported. Thus began the modern era’s “arms race” between new antibiotic discovery and increasing antimicrobial resistance.

Initially, antibiotic discovery seemed to keep pace with resistance as a host of new chemical classes were developed and introduced in the 1950s-1980’s. During this time, it was often possible to simply switch treatment in a patient who was failing therapy because of resistance to the current treatment to a newer antibiotic. Yet by the 1980’s, the discovery of new agents began to slow. The latest discovery of a new antibiotic class that has reached the market was in 1987. Since then, there has been a lack of innovation in the field, and today there are few novel antibiotic classes in the drug pipeline. In Module 2 we will examine the scientific challenges and market forces that have made new antibiotic discovery increasingly difficult and how access to newer antibiotics is limited in many parts of the world.



© ReAct Group 2015

Figure 2. Antibiotic discovery timeline. Source ReACT Group 2015.

Once antibiotic resistance develops, it can spread from one colonised patient to another patient if appropriate hygienic precautions (e.g., hand hygiene, isolation) are not followed. The risk of resistant bacteria spreading is enhanced in crowded environments, especially when people in the surrounding area are receiving antibiotics - a common scenario in hospitals especially in wards of critically-ill patients.

The consequences of faltering antibiotic discovery are now being felt worldwide as more and more bacterial infections are becoming harder to treat. Especially worrisome is the lack of antibiotics against common Gram-negative bacteria (i.e. *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*) that are increasingly resistant to all but last-line antibiotics. The rapid global spread of multi- and pan-resistant bacteria, also known in the lay press as “superbugs,” can cause infections that are not treatable with existing antibiotics.

Global response to antimicrobial resistance

Recognizing the growing global threat of antibiotic resistance (AMR) on human health but also the economy and human development, The World Health Organization (WHO) and The Organisation for Animal Health (OIE) developed in 2001 a Global Plan for Containment of Antimicrobial Resistance that subsequently led to a Global Action Plan for AMR in 2017 and more recently a “Call to Action on Antimicrobial Resistance” in 2021. The plan outlines 21 strategies and 5 strategic objectives action plans that should be implemented in member states to address AMR. These include:

1. Improvements in the awareness and understanding of antimicrobial resis-

- tance through effective communication, education and training
2. Strengthening of knowledge and evidence base of AMR through surveillance and research
 3. Reductions in the incidence of infection through effective sanitation, hygiene and infection prevention measures
 4. Optimization the use of antimicrobial medicines in human and animal health
 5. Development of an economic case for sustainable investment in AMR research that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions

The WHO also proposed a Priority Pathogen List for research and development of new antibiotics. This list includes bacterial pathogens that are considered to be the biggest threat to human health in addition to *Mycobacterium tuberculosis*. The WHO list breaks down pathogens into three groups:

Table 1. WHO priority pathogens

Priority	Pathogens included
Critical	<i>Acinetobacter baumannii</i> (Carbapenem-resistant) <i>Pseudomonas aeruginosa</i> (Carbapenem-resistant) Enterbacterales (3rd generation cephalosporin, carbapenem-resistant)
High	<i>Enterococcus faecium</i> , vancomycin-resistant <i>Staphylococcus aureus</i> , methicillin-resistant, vancomycin intermediate and resistant <i>Helicobacter pylori</i> , clarithromycin-resistant <i>Campylobacter</i> , fluoroquinolone-resistant <i>Salmonella</i> spp., fluoroquinolone-resistant <i>Neisseria gonorrhoeae</i> , 3rd generation cephalosporin-resistant, fluoroquinolone-resistant
Medium	<i>Streptococcus pneumoniae</i> , penicillin-non-susceptible <i>Haemophilus influenzae</i> , ampicillin-resistant <i>Shigella</i> spp., fluoroquinolone-resistant

These pathogens may exhibit multi-drug resistance (MDR), extensive drug resistance (XDR) or pan-drug resistance (PDR)¹. Difficult-to-treat resistance (DTR) is a newer definition used to define isolate resistance patterns that require the use of less-effective or more toxic “reserve” antibiotics- e.g., *Acinetobacter baumanii* susceptible only to colistin and tobramycin.².

MDR- resistance to one agent in at least 3 antibiotic categories; XDR- resistant except to 2 or fewer antibiotic categories; PDR- resistant to all agents in all antibiotic categories; DTR-requires the use of less-effective or more toxic “reserve” antibiotics

Currently, both the WHO and OIE have also developed lists of antibiotics that are considered of “critical importance” for human and animal medicine. These lists help establish priorities for antimicrobial resistance surveillance and new drug development.

What are the drivers of antimicrobial resistance?

AMR is a natural phenomenon. Most antimicrobial drugs are naturally produced by micro-organisms, including environmental fungi and saprophytic bacteria, or are synthetic modifications of these natural products, with only a few drugs (e.g., sulphonamides and fluoroquinolones) being wholly synthetic. Yet AMR selection is accelerated by antimicrobial exposure in health care, agriculture, and the environment. Further transmission is affected by standards of infection control in healthcare settings, sanitation, access to clean water, access to assured quality antimicrobials and diagnostics, travel, and migration.

Antimicrobials are among the most commonly prescribed drugs used in human medicine, yet up to 50% of all antimicrobials prescribed to people are considered unnecessary. This use, misuse, or overuse of antimicrobial drugs is considered to be a major driving force towards antimicrobial resistance.

In medicine, the concentration of antibiotic prescribing might be highest in inpatient settings, with 30–40% of patients on antibiotics in European hospitals. However, the overall highest *quantity* of antimicrobial consumption is highest in the community setting.

Yet, more antimicrobials are used in food production than in human beings, with marked national differences in the number of antimicrobial drugs used in food producing animals. **It has been estimated that 73% of all antibiotic use per by weight is for food production in animal.³** Various studies have shown that antimicrobial resistance has, at least in part, emerged as a result of the selective pressure exerted by antimicrobial use outside of human medicine, namely in veterinary medicine, food-animal and fish production, and agriculture. Therefore to effectively AMR, a multifaceted or *ONE-HEALTH* approach is required.

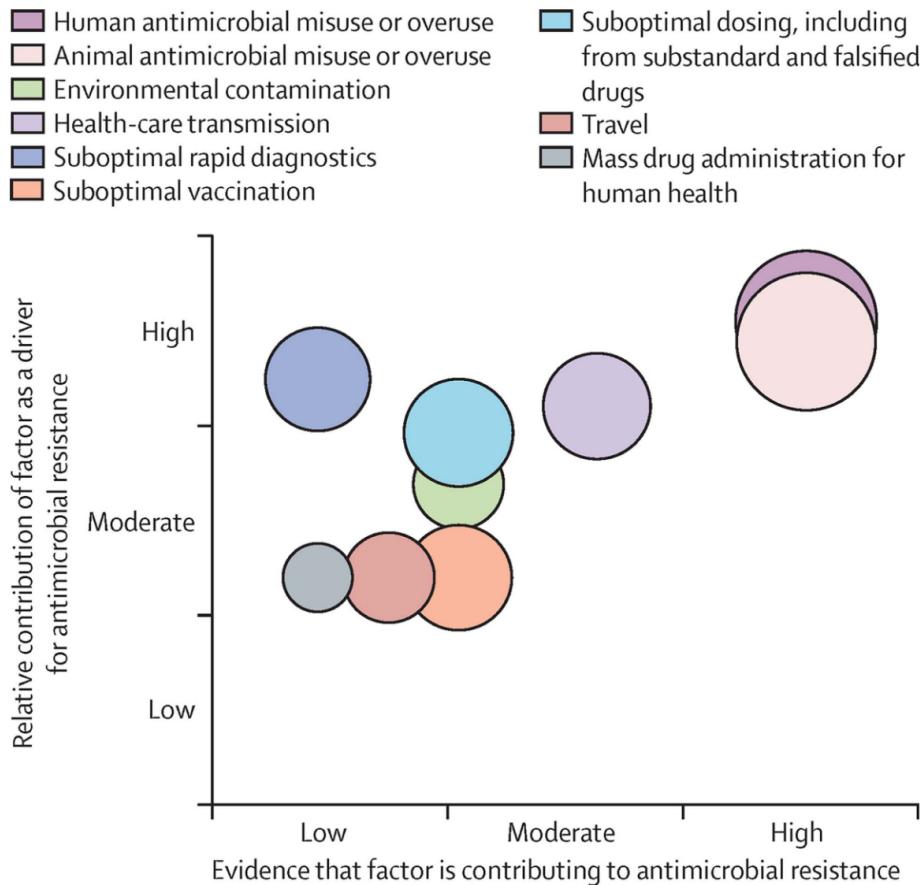


Figure 3. Modifiable risk factors that drive antimicrobial resistance.
Figure from Homes et al.⁴

AMR in Low-Middle Income Countries (LMICs)

COVID-19 has focused global attention on the inequitable access to the tools needed to control the pandemic, with high-income countries (HICs) and low- and middle-income countries (LMICs) at opposite ends of the scale. In the case of antibiotic resistance, a pandemic projected to cause four times more deaths per year than occurred from COVID-19 during 2020, inequity between HICs and LMICs is a major challenge:⁵

How is LMIC defined? The World Bank defines lower middle income economies as countries where the per capita gross national income (GNI) falls between \$1,026 and \$3,955. The countries that are part of the upper MIC

classification with a GNI that falls between \$3,956 and \$12,475.

LMICs are particularly susceptible to the emergence and rapid spread of AMR for several reasons:

- High population density
- Lack of access to clean water, suboptimal sewage systems, poor sanitation
- Poor healthcare infection control practices
- Increasing consumption of antimicrobials in humans
- Lack of regulation on antimicrobial use in farming, and pharmaceutical industry pollution

The health and economic impact of AMR is also more severe and longer lasting in LMICs versus HICs. AMR is generally associated with:

- Increased mortality and health costs
- Antibiotics effective against AMR are more expensive and not affordable for many patients
- Increasing use of antibiotics with efficacy against AMR leads to higher resistance to “last-line” antibiotics
 - In fact, carbapenem consumption is increasing at a rapid pace in poor economies.⁶

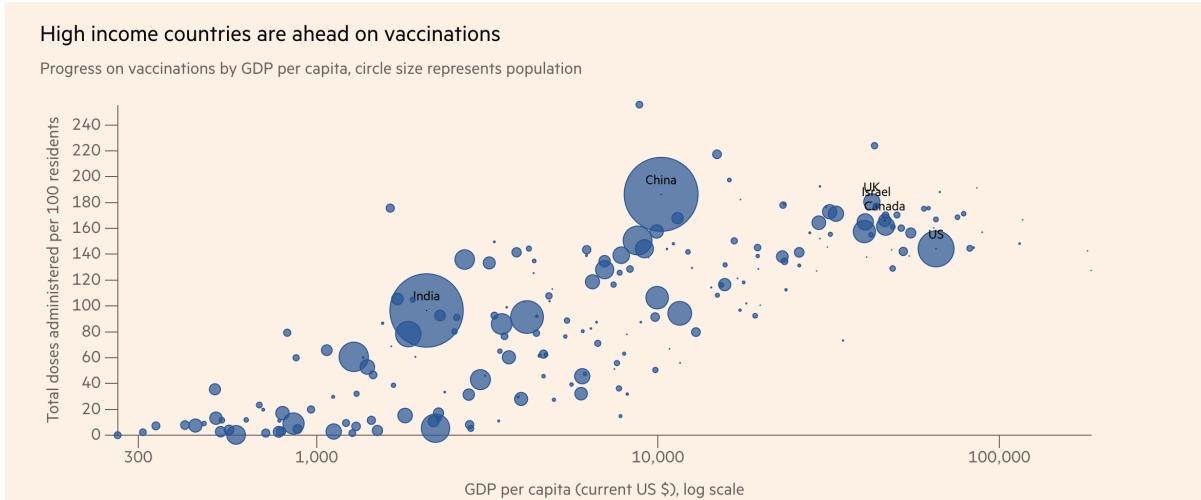


Figure 4. Progress on vaccinations by GDP per capita, circle size represents population. Source: Financial Times

- Lack of access to antibiotics in some poorer countries, a driver of mortality particularly in children under 5 years of age;
- Lack of access to newer, expensive antibiotics needed to treat the increasing toll of MDR and XDR bacterial infections;

- Inequity in ability to provide the basic public health interventions that drive many of the social determinants of infectious diseases in LMICs

The singular effectiveness of access to clean water, sanitation and hygiene, called WASH, in preventing the spread of disease is well understood, yet billions of people around the world still lack access to these necessities.⁷

- Currently, 2.1 billion people live without access to safe drinking water and 4.5 billion people are without access to adequate sanitation.
- Every day, 1300 children under 5 die from preventable diarrhoeal diseases, including cholera, caused by contaminated water and poor sanitation.
- 1 in 3 healthcare facilities lacks soap and water or hand sanitizer where staff provide patient care. Billions of patients worldwide must rely on these facilities.
- In some countries, up to 90% of women receive routine prophylactic antibiotics during childbirth, highlighting the conditions under which they are delivering their babies and what would cause the inevitability of infection

The cumulative lack of WASH adds up to children and adults not only getting unnecessarily sick—with the associated suffering, medical costs and loss of income or schooling—they are relying on antibiotics to get better.⁸ The challenge here is that WASH is a public works solution for a public health problem. WASH is not a pill or ‘quick fix’. It requires capital investment, system strengthening, and behaviour change to ensure that clean water and functional toilets are available and utilized day-in and day-out. These issues require a different set of skills than those possessed by medical and public health professionals.

In LMICs, an estimated 670 million people still practice open defaecation in 2017, and only one in three people have access to safe drinking water, resulting in high rates of diarrheal disease and equally large amounts of inappropriate antibiotic use.⁸ According to WHO surveys, vaccination, a cornerstone of infection prevention and reducing the need for antibiotic use, is suboptimal in both HICs and LMICs. In 2019, global third-dose coverage for childhood pneumococcal vaccination in 149 member states was only 48%, and global rotavirus vaccine coverage was estimated at 39%. In South Africa, middle-income country, procures less than 1 million doses of influenza vaccine for its annual influenza season, despite in excess of 10 million people being identified as high-risk for influenza and prioritized for vaccination.⁵

Optimizing infection prevention on farms and making improvements to housing conditions and feed to reduce illness in animals is also critical in food production to offset the need for antibiotic growth promotion or metaphylaxis in food production animals. While there has been progress in the reduction of antibiotic use in farms in the EU and other HICs, attention nor funding for such improvements in LMICs has not even been proposed. “It’s one thing being told to reduce your antibiotic use in food production, it’s another to have the means to do so, even for the most committed resource-poor farmer.⁵

As discussed above, the emergence of antimicrobial resistance (AMR) is a complex

phenomenon and is intensified by selective pressure through antibiotic use in humans, animals, and agriculture. The transmission of AMR to humans occurs from contact with animals (including food), other humans, and the environment. Transmission is facilitated by several factors, including high population density, lack of access to clean water, suboptimal sewage systems, poor sanitation, and poor healthcare infection control practices, all of which are more common in LMICs. With the increasing consumption of antimicrobials in humans, lack of regulation on antimicrobial use in farming, and pharmaceutical industry pollution, it may not be surprising that relatively higher levels of AMR among human pathogens are being reported from LMIC.

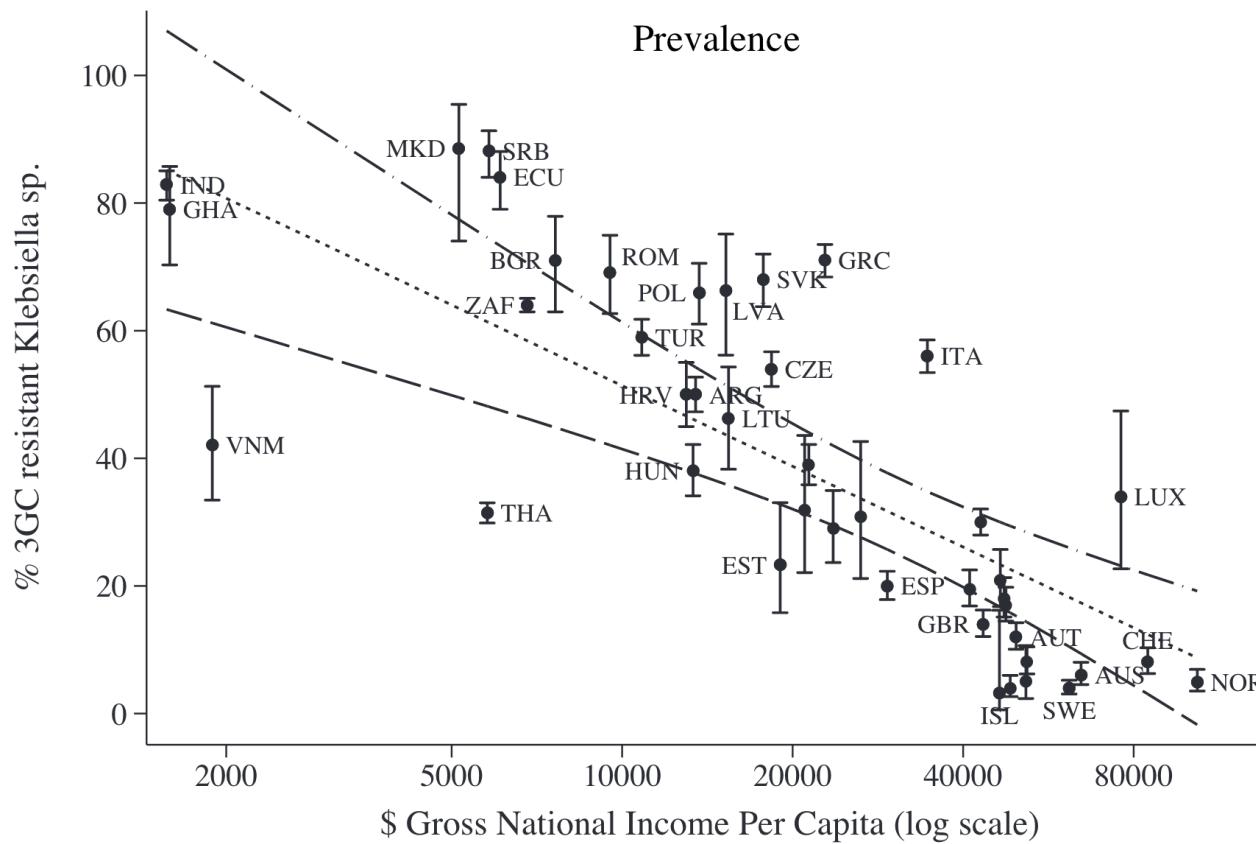


Figure 5. Prevalence of third-generation cephalosporin-resistant (3GCR) *Klebsiella* spp. by gross national income per capita and predicted values with 95% confidence intervals according to a linear regression model. Data are from reference.⁹

The impact of

The international focus on awareness, surveillance, infection prevention, stewardship and research and development (R&D) of new antibiotics is actually widening the equity gap by pouring millions of dollars into R&D of new antibiotics and surveillance systems, while the intervention that could benefit LMICs the most, infection prevention, has received a relatively few resources.

What are the possible solutions? Recently COVID-19 has refocused attention that in infectious diseases The Access to COVID-19 Tools (ACT)-Accelerator that we will discuss in Model 2 has shown that financial contributions from HICs to a LMIC-pool can improve equitable access to diagnostics, therapeutics and vaccines, but it is conceivable that the same model could be broadened to encompass tools that would support major social change for AMR.

How can the effectiveness of antimicrobials be preserved?

Strategies for the prevention and containment of AMR often focus on:

1. Improvement of infection diagnosis and prescription practices (antimicrobial stewardship)
2. Reduction of antimicrobial use in agriculture and environmental exposure in general
3. Development of new antimicrobials
4. Access to essential medicines of assured quality
5. Improvement of AMR surveillance

Antimicrobial stewardship is a coordinated program that promotes and focuses on the appropriate use of antimicrobials and strategies to improve patient outcomes, reduces antimicrobial resistance, and decrease the spread of infections caused by multidrug-resistant organisms. These programs may be implemented through the use of institution-specific treatment guidelines and an antibiotic stewardship team (typically infectious diseases physicians with a clinical pharmacist) who carry out full-time activities to promote and encourage appropriate antibiotic use. While these programs have been shown to be successful, many gaps remain in the knowledge of how to optimally design and sustain stewardship programs in the hospital, and such programs are rarely implemented in community settings where most antibiotic consumption takes place.



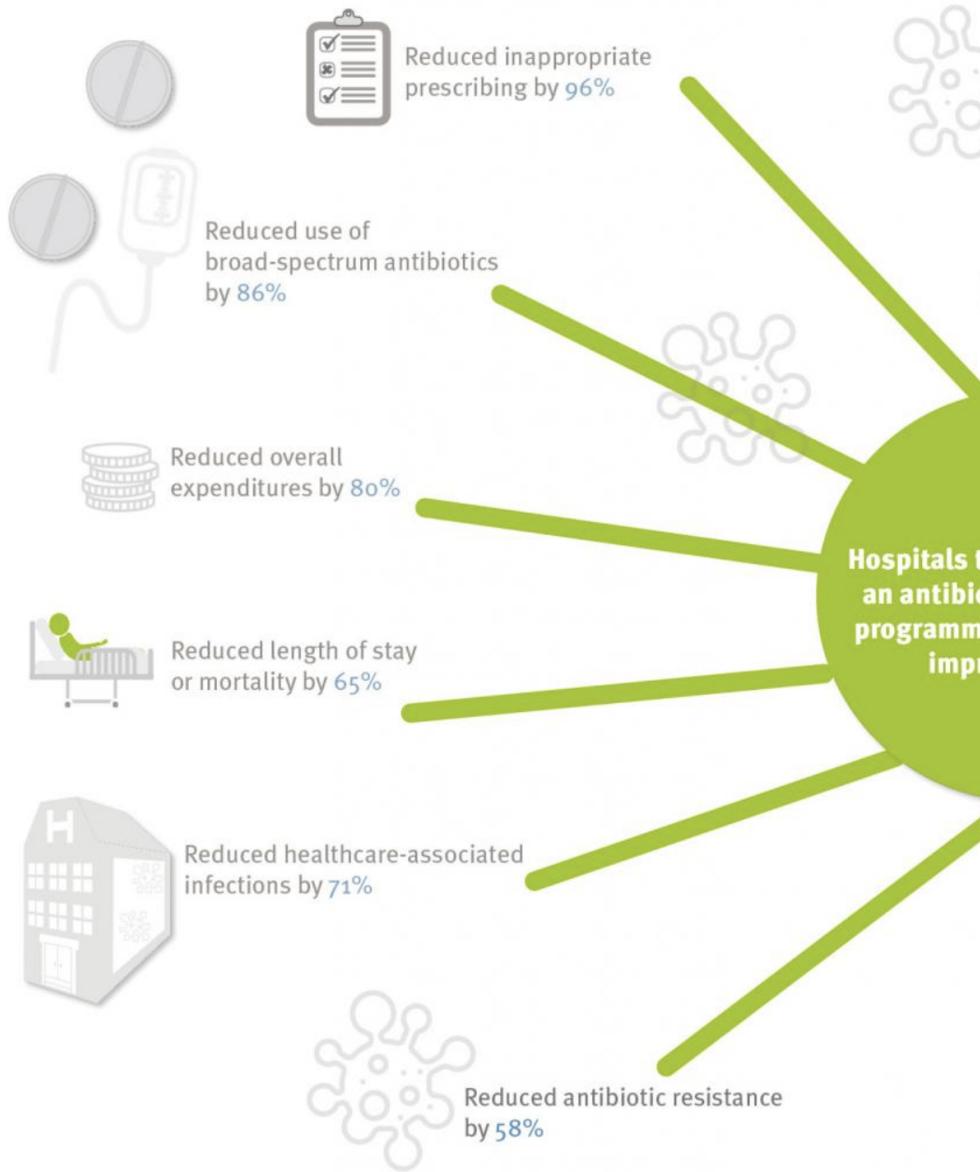


Figure 6. Examples of antimicrobial stewardship efforts and outcomes.
Source: ECDC

AMR situation in Italy

Southern Europe, including Italy, has among the highest rates of resistance for pathogens included on the WHO Priority Pathogen list. For example, surveillance data from the European Centres for Disease Control (ECDC) have reported a dramatic increase in multidrug-resistance (MDR) in Italy since 2009, with now more than one-third of *Klebsiella pneumoniae* resistant to previously-considered last-line antibiotics such as carbapenems. An interactive ECDC resistance atlas showing differences in resistance rates between countries for common antibiotics can be found here. Similarly, the Italian Antimicrobial Surveillance system (Micronet Resistance Surveillance) has reported:

- 26.4% of *Escherichia coli* are resistant to 3rd generation cephalosporins
- 29.5% of *Klebsiella pneumoniae* are resistant to carbapenems (including 33.1% resistant to multiple drug classes)
- 15.9% of *Pseudomonas aeruginosa* are resistant to carbapenems
- 80.8% of *Acinetobacter* spp. are resistant to carbapenems with 78.8% of species resistant to multiple drug classes
- For the Gram-positive organism *Staphylococcus aureus*, the percentage of methicillin-resistant isolates (MRSA) remained stable, around 34%, while a worrying trend continues to increase in the percentage of *Enterococcus faecium* isolates resistant to vancomycin, which in 2020 was equal at 23.6%
- For *Streptococcus pneumoniae* there was a slight increase in both the percentage of isolates resistant to penicillin (13.6%) and those resistant to erythromycin (24.5%).
- Overall, higher antimicrobial resistance rates (around 40%) are observed in ICUs versus general medical wards for both carbapenem-resistant *K. pneumoniae* and methicillin-resistant *S. aureus*.

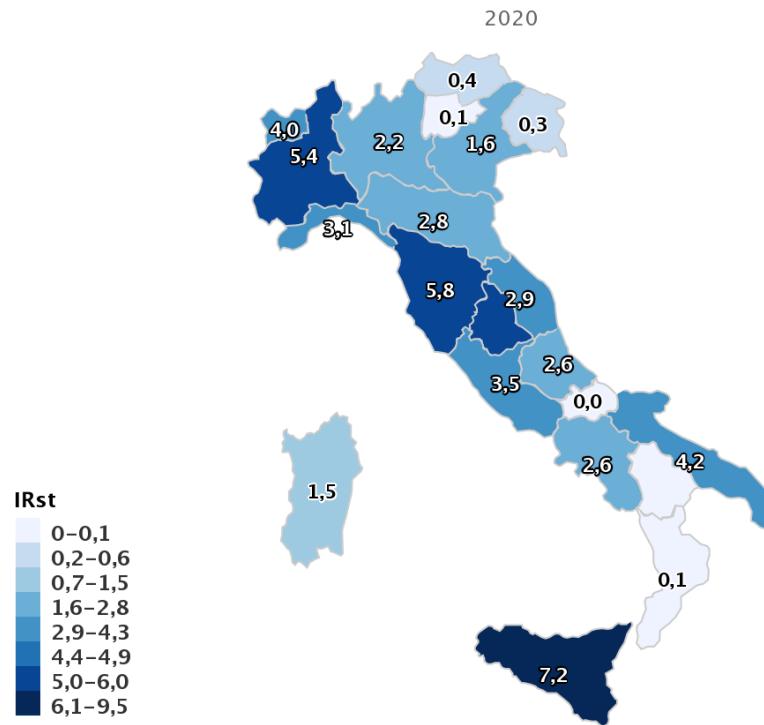


Figure 7. Regional differences in carbapenem-resistant Enterobacteriales (CRE) bloodstream infection- 2020 incidence per 100,000 residents in Italy. Source Micronet Resistance Surveillance Program

In 2017, a report by the ECDC noted that the AMR situation in Italian hospitals and regions poses a major public health threat to the country. The levels of carbapenem-resistant Enterobacteriaceae (Enterobacteriales) (CRE) and *Acinetobacter baumannii* have now reached hyperendemic levels in many hospitals. Together with increasing methicillin-resistance among the Gram-positive species *Staphylococcus aureus* (MRSA), these resistance trends has led to Italy's ranking as one of the Member States with one of the highest level of antibiotic resistance in Europe. Factors noted by the ECDC that contributed negatively to the poor control of antibiotic resistance in Italy include:

- Little sense of urgency about the current AMR situation from most stakeholders and a tendency by many stakeholders to avoid taking charge of the problem
- Lack of institutional support at national, regional and local level
- Lack of professional leadership at each level
- Lack of accountability at each level
- Lack of coordination of the activities between and within levels.

The global future of AMR

- Drug-resistant infections already cause at least 700,000 deaths globally a year, including 230,000 deaths from multidrug-resistant tuberculosis. **The estimated total number of deaths due to AMR could climb to 10 million deaths globally per year by 2050 under current projections.**
- Increasing resistance could lead to an unthinkable future of untreatable infections, reversing more than a 100 years of medical progress. Routine medical procedures or surgery will become more dangerous and associated with higher complication rates. Immunosuppression, cancer chemotherapy and transplantation may carry unacceptable risk for many patients if infections cannot be effectively prevented and treated.
- Economic and social progress in many countries will be dramatically impacted by increasing AMR leading to political and social instability. The initial short-term economic damage of uncontrolled antimicrobial resistance will be comparable to the economic shocks experienced during the 2008-2009 global financial crisis and result in dramatically-increased healthcare expenditures; reductions in food and feed production, reduced economic output, and increased poverty and inequality. The economic impact of antimicrobial resistance is predicted to be even greater and longer lasting on low-and middle-income (LMIC) countries.

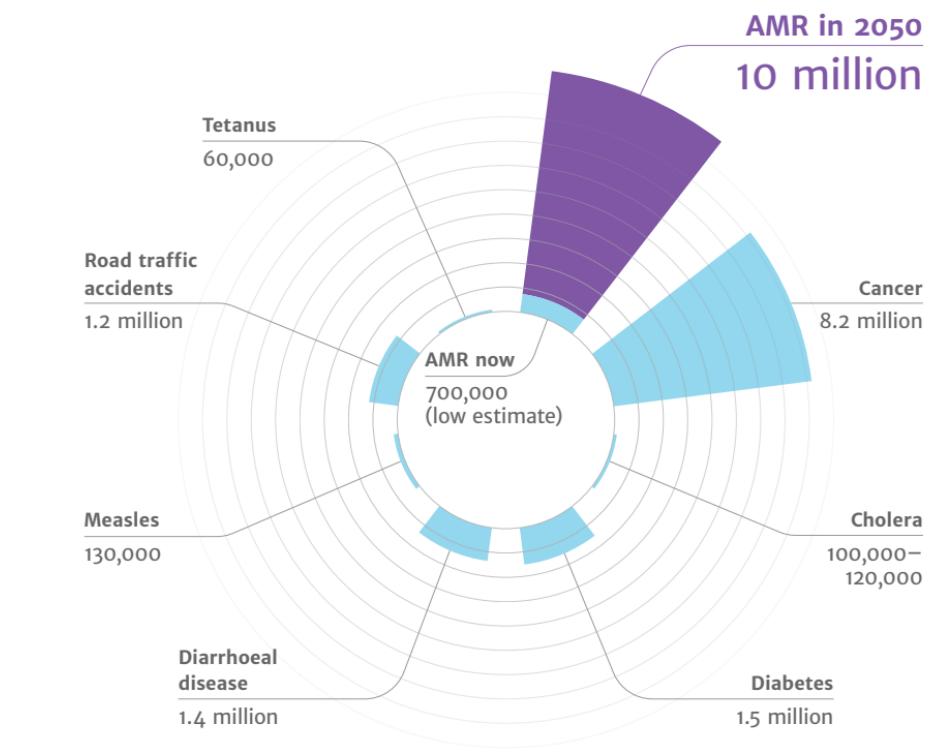


Figure 8. Projected deaths due to antimicrobial resistance in 2050.
Source: O’Neil Report.¹⁰

One-Health Perspective of AMR

Because the drivers of antimicrobial resistance lie in humans, animals, plants, food and the environment, a sustained One Health response is essential to engage and unite all health and environmental sectors around a shared vision and goals. “One Health” refers to designing and implementing programmes, policies, legislation and research in a way that enables multiple groups engaged in human, terrestrial and aquatic animal and plant health, food and feed production and the environment to communicate and work together to achieve better public health outcomes.

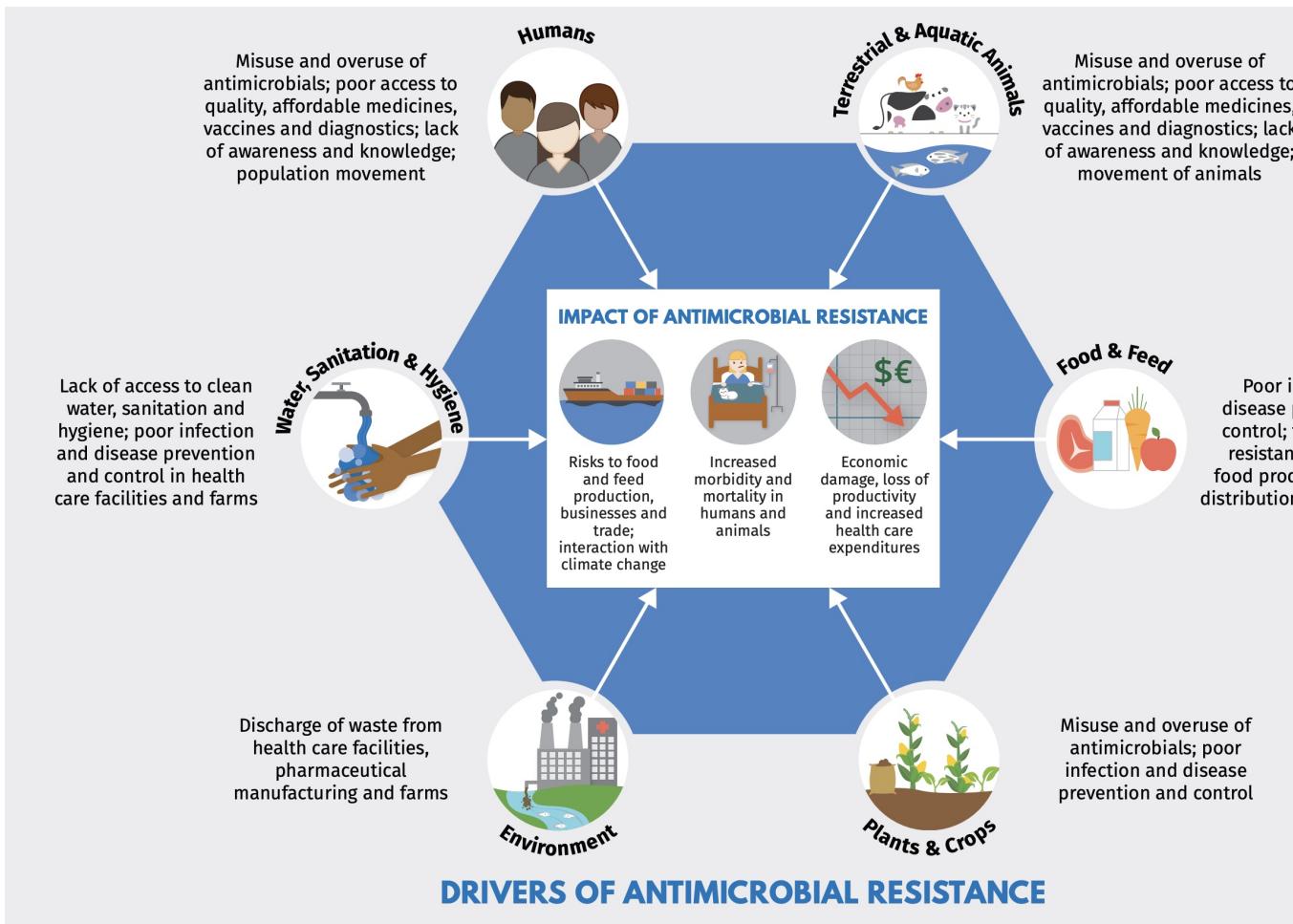


Figure 9. Rationale for one-health model for addressing AMR. Source: WHO

Antibiotic use in animal food production

Few antimicrobial classes are reserved exclusively for humans. The vast majority of antibiotics are used both in humans and animals, including domestic mammals, birds, farmed fish and shellfish, honeybees and others. As noted earlier, **73% of all antibiotic consumption per weight is used for food production in animals.**³ Critically, two-third of all human infectious diseases that have emerged or re-emerged in recent decades are zoonotic-i.e. they originated in animals.¹¹ Therefore the transmission of antibiotic resistance organisms from the foodchain to humans is a major health concern.

In horticulture, tetracyclines, streptomycin, and other antimicrobials are used

for the prophylaxis and treatment of bacterial infections that affect plants (e.g., fire blight *Erwinia amylovora*)

In veterinary medicine, there are major differences in the way antibiotics are used for companion animals (e.g., dogs, cats, pet birds, horses) versus food-producing animals. Antibiotic use in companion animals is broadly similar to humans for the treatment of infections or in select cases prophylaxis, such as post-surgery. In the case of food animals, if some animals are infected antibiotics may be administered through feed or water to the entire group for reasons of practicality or efficiency. *Metaphylaxis is a term used to describe therapeutic/prophylaxis antibiotic treatment at a group level.*

The most controversial type of group treatment in food animals is long-term, low-dose mass antibiotic treatment for purposes of growth promotion. This practice has a high propensity to select for antimicrobial resistance and is driven by economic factors rather than treatment of clinical infection. The practice was banned by the EU in 2006 but still continues in some countries such as the United States and China.



Figure 10. Pigs in cages, Quanzhou, China. As the largest consumer of veterinary antimicrobials, China is critical for combating antimicrobial resistance (AMR). From Van Boekel et al.¹²

The reported benefits of using antibiotics for growth promotion is controversial and reports of the beneficial effects in terms of weight gains vary widely widely in the literature (1-10%). Concerns have been expressed that antimicrobial growth promoters are often used to compensate for poor hygiene/housing and healthy management.¹³

Unfortunately, use of antibiotic for growth promotion has increased dramatically with the growing demand in meat-based diets. Since 2000, meat production has plateaued in high-income countries but has grown by 68%, 64%, and 40% in Africa, Asia, and South America, respectively.³ The transition to high-protein diets in low- and middle-income countries (LMICs) has been facilitated by the global expansion of intensive animal production systems, in which antimicrobials are used routinely to maintain health and productivity.

There are 4 factors that typically determine the health of animals, (e.g., chickens):

1. The genetic stock of the animals
2. Adequate nutrition
3. Hygiene of living conditions
4. Adequate veterinary care

While antibiotics may be able to improve deficiencies in 1 of the 4 areas, if multiple aspects are missing then antimicrobial resistance is unlikely to improve animal health or growth. Thus, antimicrobials are often surrogates for good hygiene on farms. Ideally, a key goal to reduce antibiotic use in animals is to further strengthen the 4 non-antibiotic aspects that are important to animal health so antibiotic use can be avoided.

Historically, governmental regulations have focused on toxicological dose-response data and the presence of antimicrobial residues in animal tissue, milk or other edible products (i.e. eggs) from treated animals - *so called minimum residue levels (MRLs) compatible with acceptable risk in humans*. While MRLs are well-understood and enforced with testing programs and penalties, these programs do not take into account selection of antimicrobial-resistant pathogens.

The WHO has advocated for the termination of using antimicrobials for growth promotion. A recent report from the ECDC has suggested some progress in addressing this problem. Using surveillance data from 2017, the EU/EEA population mean antibiotic consumption in the 29 countries was 130 mg per kg of estimated biomass in humans and 108.3 mg per kg in food-producing animals (Fig 1.6). *This first time since the agencies began publishing the joint reports in 2011 that antibiotic use in humans has exceeded use in livestock.* Consumption of third- and fourth-generation cephalosporins, fluoroquinolones, and aminopenicillins was considerably higher in human medicine, while consumption of macrolides was similar, and consumption of tetracyclines and polymyxins—a last-resort class of antibiotics that includes colistin—was significantly higher in food-producing animals.

In 2022, new EU legislation will prohibit all forms of routine antibiotic use in

farming, including preventative group treatments and medicated feeding except in extraordinary circumstances.

Figure 11. Antibiotic use in livestock reported in 2010. Source: Our World in Data.

The impact of animal antibiotic use on human AMR

Case study-cephalosporins

Third generation cephalosporins (ceftotaxime, ceftriaxone) are widely used for serious infections in humans, including the treatment of urinary tract, abdominal, lung and bloodstream infections. These antibiotics are classified as “critically-important” for human health (WHO AGISAR). Cetiofur, cefpodoxime, and cefoperazone are similar cephalosporins approved veterinary antibiotics and used predominantly for treating bacterial infections in food-producing animals including chickens and cattle.

Resistance to 3rd generation cephalosporins is mediated by extended-spectrum beta-lactamases (ESBLs) and AmpC enzymes. ESBL genes are highly mobile and transmitted on plasmids, transposons and other genetic elements that can spread horizontally (to surrounding bacteria and different bacterial species) and vertically (to daughter cells through replication). Consequently, resistance can spread rapidly from patient-to-patient and among different bacterial species. In recent years, growing resistance to 3rd generation cephalosporins is common among *Escherichia coli* and *Klebsiella pneumoniae* has required greater reliance on the few remaining classes of antimicrobials such as carbapenems.

A number of studies comparing isolates from animals, food and human infections have found a high genetic similarity or clonal isolates that carry the same ESBL genes and plasmids colonizing animals used for food production and isolates causing clinical infections in patients.¹⁴

Ceftiofur is frequently injected in small quantities to hatching eggs or chicks as metaphylaxis for *Escherichia coli* infections and/or yolk sac infections.¹³ (Fig1.7) This practice has been shown to select for cephalosporin resistance in *Salmonella enterica* serovar Heidelberg- an important cause of human illness in many countries that is typically associated with consumption of contaminated poultry products.¹⁵



Figure 12. Chicken farm in the United States of America. Image source: The Guardian

Studies conducted by the Canadian Integrated Program for Antimicrobial Resistance Surveillance detected a high degree of temporal correlation in trends of resistance to ceftiofur and ceftriaxone (a drug of choice for the treatment of severe cases of salmonelloses in children and pregnant women) among *Salmonella* Heidelberg from clinical infections in humans, from poultry samples collected at retail stores, and in *E. coli* from poultry samples collected at retail stores¹⁶. Voluntary termination of ceftiofur metaphylaxis in hatcheries in the province of Quebec was followed by a precipitous drop in the prevalence of resistance to ceftiofur; subsequent reintroduction of ceftiofur in a more limited way was followed by a return to higher levels of resistance (Fig 1.9)

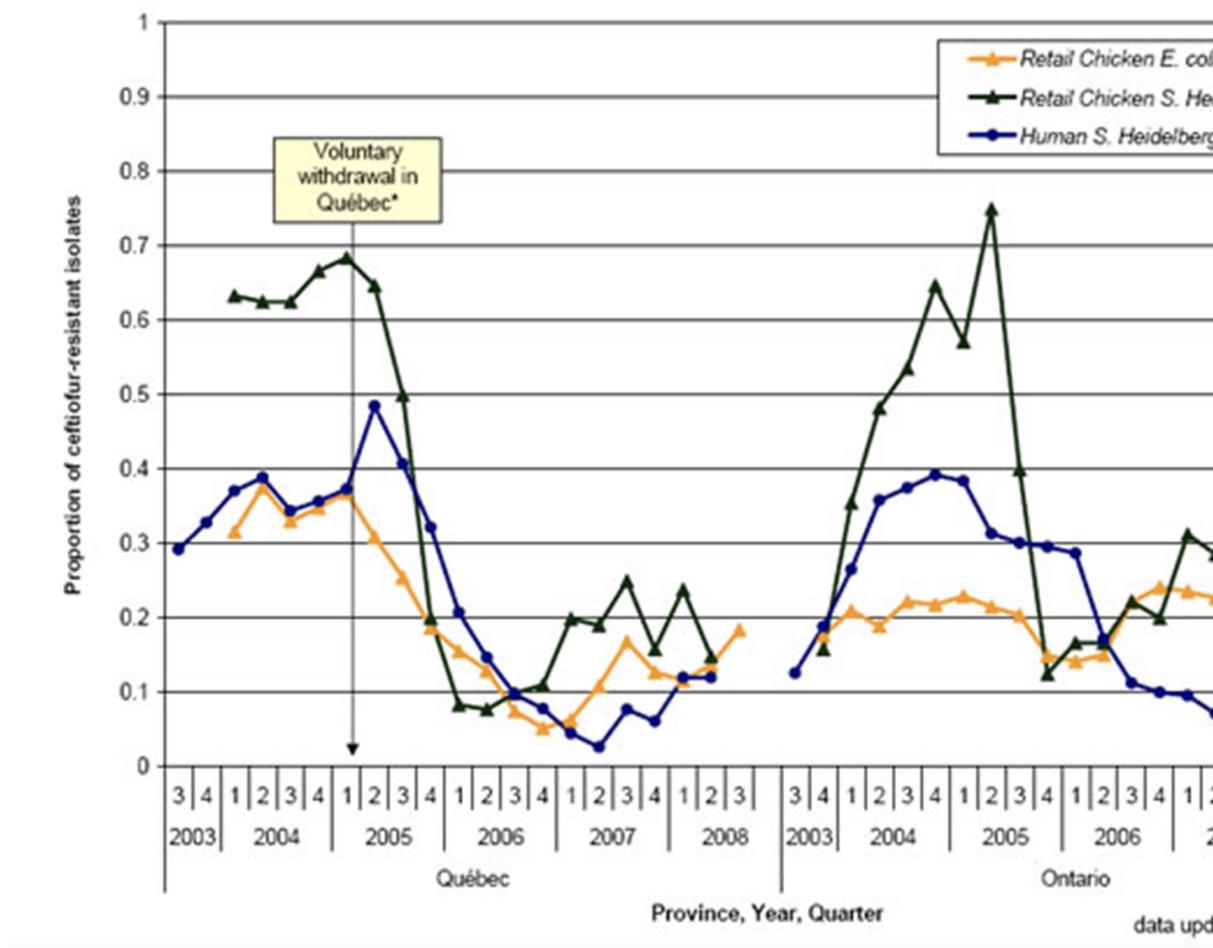


Figure 13. Ceftiofur resistance in chicken and human *Salmonella* Heidelberg and chicken *E. coli*.¹⁶

In Japan, voluntary withdrawal of the off-label use of ceftiofur in hatcheries in 2012 was also associated with significant decrease in broad-spectrum cephalosporin resistance in *E. coli* from chickens prepared for cooking. Some other countries (e.g., Denmark) have placed voluntary restrictions on its use. The label claim for day-old injection of poultry flocks was withdrawn in Europe, while some countries have banned off-label use of third-generation cephalosporins, and in other countries there is a requirement that use be restricted to situations where no other effective approved drugs are available for treatment.

These examples illustrate the danger of using antibiotics from the same class as critical therapies used to treat human infections for metaphylaxis or treatment

in large numbers of animals. A similar pattern in poultry was also observed with mass medication of poultry flocks using fluoroquinolones antibiotics and selection of fluoroquinolone- resistant *Campylobacter jejuni* infections in humans.¹⁷

Case study- colistin

Colistin is a member of the polymixin class of antibiotics, which have been used in both human and veterinary medicine for over 50 years. Until relatively recently, polymixins were rarely prescribed beyond topical or inhalational therapy in rare cases because of dose-limiting neurotoxicity and nephrotoxicity of the drugs.

However, use of intravenous colistin has surged in the last decade with the increase in carbapenem-resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*. Even as human use has increased, colistin continues to be used in Brazil, Europe and China as a growth promoting and antibiotic treatment for pigs, poultry and calves.

- In 2014, colistin use in EU member states in animals was higher than humans with a reported 485 tonnes- 99.7% in oral form or oral medicated feed.¹⁸ In China, with the world's largest production of pigs and poultry, an estimated 12,000 tonnes of colistin was used in the food production industry.¹⁹
- In 2015, Lui and colleagues reported plasmid-mediated colistin-resistance gene, *mcr-1*, in *Escherichia coli* isolates obtained from animals, food and human bloodstream infections in China.¹⁹ Alarmingly, the resistance gene has also been detected in 5% of healthy travellers from China in other parts of the world.²⁰
- The *mcr-1* gene has also been detected in isolates obtained from wildlife and surface water samples, demonstrating environmental contamination.²¹
- Additional plasmid-mediated colistin-resistance genes have been reported in many other bacterial species and countries, including *mcr-2* from pigs in Belgium, and *mcr-3,4,5* in other countries.²²
- Colistin illustrates important *One-Health Dimensions* of AMR that differ from third generation cephalosporins. Specifically, large volumes of colistin use in animals, rather than humans, have probably driven colistin resistance now observed in humans. Using large quantities of colistin for group treatment or growth promotion in animals has probably lead to antimicrobial resistance problems in human health, even through colistin was considered in the past to be less important because other less toxic treatments were still available.
- In 2017, China banned the use of colistin as a food additive for animals. Colistin is currently not approved as a food additive in Europe or the United States, but is still be used in LMICs as a growth promoting agent.

Antimicrobial resistance in animals in LMICs

Many farmers in LMICs are sustenance farmers, and their livelihood is at stake if an animal becomes ill. Therefore, they may not have the resources for optimally nutritious feed and housing space/conditions. These challenges, combined with looser regulations on veterinary drugs, may facilitate the use of antimicrobials in feeding.³

Figure 14. Global hotspots of antimicrobial resistance in animals.
Data source resistancebank.org

The largest hotspots of AMR in animals were in Asia and India. Asia is home to 56% of the world's pigs and 54% of the chickens. Other growing hotspots of AMR are found in central India and Kenya, where resistance to multiple drugs has appeared but not yet reached 50%.

These data suggest that in areas such as Asia, targeted interventions such as legislative action and subsidies to improve farm hygiene could reduce the need for antimicrobials in animal production, thereby preserving important drugs for human medicine and the treatment of sick animals. In these regions, meat consumption is still low and animal production is gradually intensifying. Here, there may be a window of opportunity to contain AMR by imposing strict hygiene standards in newly built farms. This approach could reduce the risk of the spread of resistant pathogens such as *mcr1*-carrying *E. coli* that have emerged in regions where intensive meat production has been facilitated by enormous quantities of veterinary antimicrobials.

In Africa, resistance maps reveal the absence of major AMR hotspots, except for the Johannesburg metropolitan area. This suggests, on the basis of the regions surveyed, that Africa probably bears proportionately less of the current global burden of AMR than high- and upper- to middle income countries. Policy-makers coordinating an international response to AMR might therefore spare Africa from the most aggressive measures, which may undermine livestock-based economic development and rightfully be perceived as unfair.

Clearly the transition to sustainable animal production in both HIC and LMICs with improvements in farm-level biosafety and biosecurity are essential to reduce the future risk of AMR.

For further study: In the 1990s avoparcin, a glycopeptide antimicrobial, was widely used in growth promotion in pigs and poultry production that was not initially thought to be of public health importance. Surveillance and research were eventually able to show that avoparcin use in animals contributed to the selection and wide dissemination of what type of resistance?

Environmental concerns

One health considers possible environmental drivers of AMR in addition to human and animal health.¹³ Many resistance mechanisms such as beta-lactamases

are millions of years old and pre-date antibiotics. Soil and other environmental sources are rich sources of highly-diverse populations of bacteria and genes.

Antimicrobial resistance to a wide variety of drugs has been demonstrated in environmental bacteria isolated from the pre-antibiotic era, as well as from various sites (e.g., caves) free of other sources of exposure to modern antimicrobials. Yet there is abundant evidence that humans have an impact on the *resistome*- the totality of resistance genes in the total environment.²³

Hundreds of thousands of tonnes of antimicrobials are produced annually and find their way into the environment. Waste from treatment plants and the pharmaceutical industry especially if inadequately treated, has been shown to release high concentrations of antimicrobials into surface water. Residues and metabolites of antimicrobials are constituents of human sewage, livestock manure, and aquaculture, along with fecal bacteria and resistance genes. Sewage treatment and composting of manure reduce concentrations of some but not all antimicrobials and micro-organisms, which are introduced to soil upon land application of human and animal bio-solids.²⁴

In developed countries with good-quality sewage and drinking water treatment, and where most people have little to no direct contact with food-producing animals, transmission of bacteria and resistance genes from agricultural sources is largely foodborne, either from direct contamination of meat and poultry during slaughter and processing, or indirectly from fruit and vegetables contaminated by manure or irrigation water. In countries with poor sewage and water treatment, drinking water is likely to be very important in the transmission of resistant bacteria and/or genes from animals. Poor sanitation also facilitates indirect person-person water-borne transmission of enteric bacteria among residents as well as international travellers who return home colonized with resistant bacteria acquired locally. Through these and other means, including globalized trade in animals and food and long-distance migratory patterns of wildlife, antimicrobial-resistant bacteria are globally disseminated.

General measures to address antimicrobial resistance in the wider environment include improved controls on pollution from industrial, residential, and agricultural sources. Improved research as well as environmental monitoring and risk assessment are also required to better understand the role of the environment in the selection and spread of antimicrobial resistance and to identify more specific measures to address resistance in this sector.

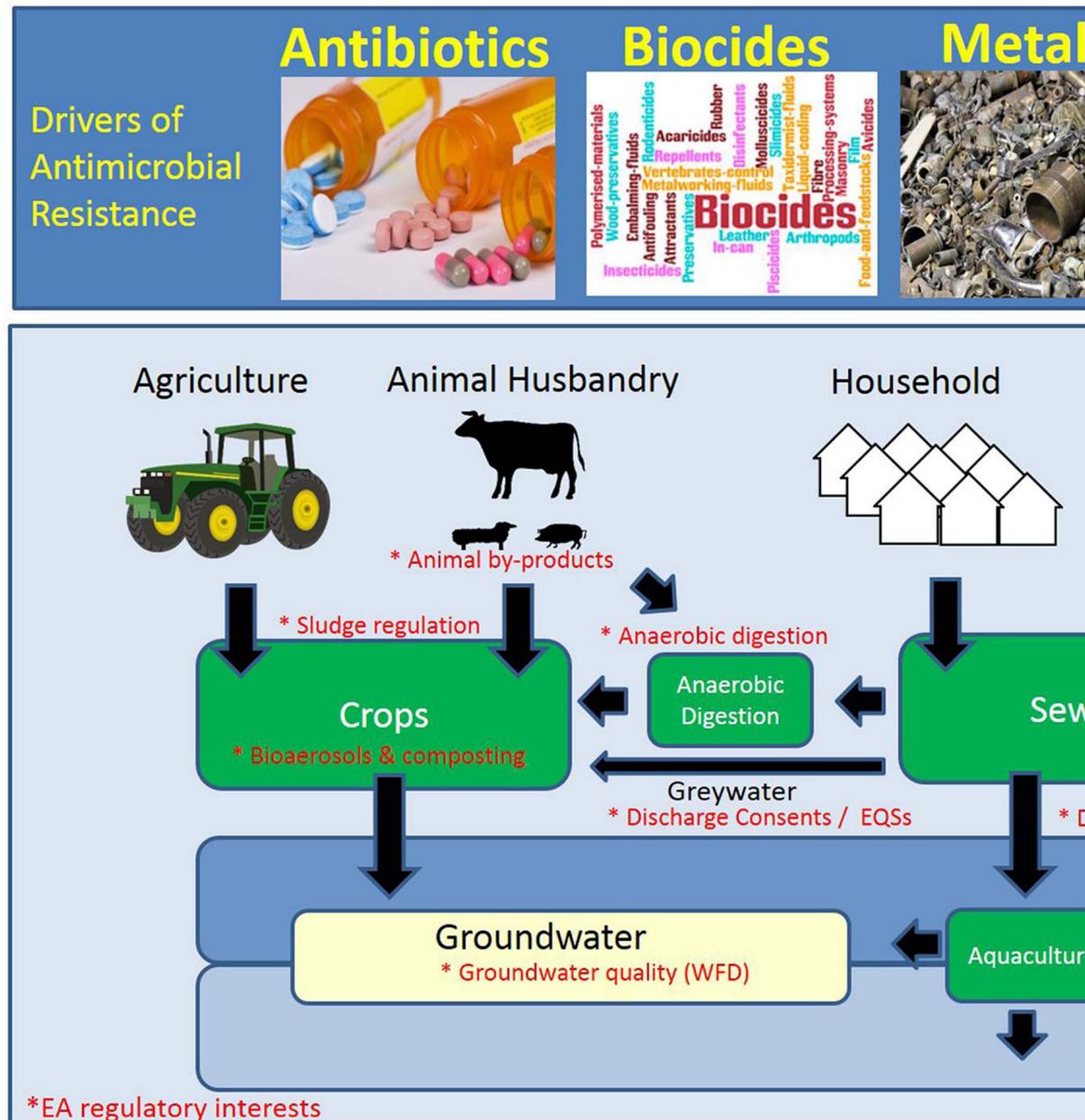


Figure 15. Hotspots of antimicrobial resistance.

Cross-border spread of AMR



Figure 16. World airline travel routes in 2014. Photo credit Jpatokal/Wikimedia (CC BY-SA 2.5)

The COVID-19 pandemic has exposed the limitations of global collaboration and response within existing global health frameworks, pointing to a clear need for more rules-based global governance to be able to effectively prevent, prepare and respond to health emergencies in a more just equitable way. However, valuable lessons from COVID-19 pandemic could enhance actions against AMR. (Table 1.2). Clearly, actions taken by one country have had substantial consequences for others. governments should significantly bolster global and national capacity to prevent and respond to global cross-border health threats more broadly.

Table 1.2 Global successes and shortcomings in the multilateral response to the COVID-19 pandemic. Table is from Jit et al 2021²⁵.

Domain	Successes	Shortcomings
Research collaboration and information sharing	<ul style="list-style-type: none"> Sharing of information by researchers International research collaborations Public data repositories 	<ul style="list-style-type: none"> Many regions and countries slow to learn policy lessons from elsewhere Lack of systemic global research governance Duplication of research studies
Vaccine discovery and development	<ul style="list-style-type: none"> Multinational initiatives to fund efforts such as the Coronavirus Global Response and the Coalition for Epidemic Preparedness Innovations Approval of vaccines and adjuvants Establishing the principle of equitable vaccine distribution through the COVAX Facility (despite failures in implementation) 	<ul style="list-style-type: none"> Most funding from national efforts Most vaccine doses secured by rich countries through bilateral deals Trade barriers around vaccines and raw materials
Travel policies	<ul style="list-style-type: none"> Travel restrictions delayed spread from China in early 2020 	<ul style="list-style-type: none"> Dissonant COVID-19 response policies between highly connected nations Restrictions on travel to countries of high COVID-19 incidence contribute little to control in these countries

The actions of the EU during the pandemic illustrate the tension between short-term nationalistic incentives and long-term imperatives for cooperation towards achieving global public goods such as reducing antimicrobial resistance. The EU has struggled to balance preferences of individual member-states (and those of their political leaderships), with the collective interests of all member-states. Such tensions are especially challenging when health care and health policy issues are involved, given how these have hitherto remained largely the responsibility of the member-states. In a pandemic, this can lead to inertia and political indecisiveness at the EU level, with member-states filling the gap with potentially contradictory or competing decisions.

Looking ahead, it is likely that there will be several changes to the global health architecture, possibly including a new pandemic treaty and additional international collaborative mechanisms to promote preparedness and coordinate responses. In the following sections, we explore what those developments might look like in three key areas.

Summary

The post-COVID-19 world must overcome the serious setbacks from the pandemic to hard-fought progress in reducing poverty and inequality. Health infrastructure and human resources vital for fighting AMR have been overburdened and will take many years to recover, particularly if governments impose austerity measures as they seek to recover from fiscal expansion during the pandemic.

Decades of funding neglect, combined with continuously increasing global antibiotic consumption, poor surveillance data, and weak pipelines for new drugs, vaccines and diagnostics, has left the world dangerously vulnerable to a pandemic of resistant and untreatable infections.

Therefore, strong multilateral collaboration is essential for the world to absorb these shocks and refocus on the silent but growing pandemic of AMR. Pandemics are opportunities to re-imagine governance structures and learn from previous experiences. COVID-19 has shown the importance of multilateral collaboration in diverse areas, including research and knowledge sharing, discovery, development and distribution of vaccines and medicines and access to diagnostics and medicines. Action is needed now to reverse the unthinkable future of untreatable infections.

Lecture Slides

References

1. Magiorakos, A.-P. *et al.* Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. *Clinical Microbiology and Infection* **18**, 268–281 (2012).
2. Kadri, S. S. *et al.* Difficult-to-Treat Resistance in Gram-negative Bacteremia at 173 US Hospitals: Retrospective Cohort Analysis of Prevalence, Predictors, and Outcome of Resistance to All First-line Agents. *Clinical Infectious Diseases* **67**, 1803–1814 (2018).
3. Boeckel, T. P. V. *et al.* Global trends in antimicrobial use in food animals. *Proceedings of the National Academy of Sciences* **112**, 5649–5654 (2015).
4. Holmes, A. H. *et al.* Understanding the mechanisms and drivers of antimicrobial resistance. *The Lancet* **387**, 176–187 (2016).

5. Mendelson, M. BSAC Vanguard Series: Inequality and antibiotic resistance. *Journal of Antimicrobial Chemotherapy* (2021) doi:10.1093/jac/dkab426.
6. Klein, E. Y. *et al.* Assessment of WHO antibiotic consumption and access targets in 76 countries, 2000–15: An analysis of pharmaceutical sales data. *The Lancet Infectious Diseases* **21**, 107–115 (2021).
7. Bürgmann, H. *et al.* Water and sanitation: An essential battlefield in the war on antimicrobial resistance. *FEMS microbiology ecology* **94**, (2018).
8. Denny, L. BSAC Vanguard Series: Clean water- the world's best medicine for disease and drug-resistant infection. *Journal of Antimicrobial Chemotherapy* (2021) doi:10.1093/jac/dkab414.
9. Alvarez-Uria, G., Gandra, S. & Laxminarayan, R. Poverty and prevalence of antimicrobial resistance in invasive isolates. *International Journal of Infectious Diseases* **52**, 59–61 (2016).
10. O'Neill, J. *Tackling drug-resistant infections globally: Final report and recommendations.* (2016).
11. Woolhouse, M. E. J. & Gowtage-Sequeria, S. Host range and emerging and reemerging pathogens. *Emerging Infectious Diseases* **11**, 1842–1847 (2005).
12. Van Boeckel, T. P. *et al.* Reducing antimicrobial use in food animals. *Science (New York, N.Y.)* **357**, 1350–1352 (2017).
13. McEwen, S. A. & Collignon, P. J. Antimicrobial Resistance: A One Health Perspective. *Microbiology Spectrum* **6**, 6.2.10 (2018).
14. Lazarus, B., Paterson, D. L., Mollinger, J. L. & Rogers, B. A. Do human extraintestinal Escherichia coli infections resistant to expanded-spectrum cephalosporins originate from food-producing animals? A systematic review. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* **60**, 439–452 (2015).
15. Smith, K. E. *et al.* Outbreaks of Salmonellosis in Minnesota (1998 through 2006) Associated with Frozen, Microwaveable, Breaded, Stuffed Chicken Products. *Journal of Food Protection* **71**, 2153–2160 (2008).
16. Canada, P. H. A. of. ARCHIVED - UPDATE - Salmonella Heidelberg Ceftriaxone-Related Resistance in Human and Retail Chicken Isolates - 2006 to 2008. (2009).
17. Endtz, H. P. *et al.* Quinolone resistance in campylobacter isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine. *The Journal of Antimicrobial Chemotherapy* **27**, 199–208 (1991).
18. Agency, E. M. *Updated advice on the use of colistin products in animals within the European Union: Development of resistance and possible impact on human and animal health.* (2016).

19. Liu, Y.-Y. *et al.* Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: A microbiological and molecular biological study. *The Lancet Infectious Diseases* **16**, 161–168 (2016).
20. Laxminarayan, R. *et al.* Antibiotic resistance—the need for global solutions. *The Lancet Infectious Diseases* **13**, 1057–1098 (2013).
21. Zurfuh, K. *et al.* Occurrence of the Plasmid-Borne mcr-1 Colistin Resistance Gene in Extended-Spectrum- β -Lactamase-Producing Enterobacteriaceae in River Water and Imported Vegetable Samples in Switzerland. *Antimicrobial Agents and Chemotherapy* **60**, 2594–2595.
22. Borowiak, M. *et al.* Identification of a novel transposon-associated phosphoethanolamine transferase gene, mcr-5, conferring colistin resistance in d-tartrate fermenting *Salmonella enterica* subsp. *Enterica* serovar Paratyphi B. *The Journal of Antimicrobial Chemotherapy* **72**, 3317–3324 (2017).
23. O’Neil, J. *Antimicrobials in agriculture and the environment: Reducing unnecessary use and waste. The review on antimicrobial resistance.* (2015).
24. Rahube, T. O. *et al.* Persistence of antibiotic resistance and plasmid-associated genes in soil following application of sewage sludge and abundance on vegetables at harvest. *Canadian Journal of Microbiology* **62**, 600–607 (2016).
25. Jit, M. *et al.* Multi-country collaboration in responding to global infectious disease threats: Lessons for Europe from the COVID-19 pandemic. *The Lancet Regional Health – Europe* **9**, (2021).