ANTIMICROBIAL RESISTANCE IN G7 COUNTRIES AND BEYOND:

Economic Issues, Policies and Options for Action

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September 2015

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REFERENCE: This report was partially funded by the Federal Ministry of Health (Germany) to support the discussions of G7 Health Ministers on this topic.

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ACKNOWLEDGEMENTS

The work presented here was undertaken by the Organisation for Economic Co-operation and Development (OECD) to help inform the meeting of the G7 Ministers of Health organised in 2015 under the German Presidency. This work was carried out thanks to a voluntary contribution from the Ministry of Health of Germany (BMG). The work benefited greatly from the inputs and comments received from national experts and delegates to the Health Committee of Canada, France, Germany, Italy, Japan, the United Kingdom and the United States. Judith Haugwitz has facilitated contacts between the OECD Health Division and the German Presidency of the G7. At OECD, authors would like to thank Francesca Colombo, Rie Fujisawa, Valerie Paris and Franco Sassi as well as Stefano Scarpetta and Mark Pearson for their contributions and suggestions during the compilation of this report. Susannah Nash and Irit Perry provided invaluable editorial support.

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SUMMARY AND KEY FINDINGS

1. Since their discovery, antimicrobial therapies (AMTs) have played an essential role in the treatment of infections in humans and animals and have significantly improved population health. Many of the improvements in mortality and morbidity that modern medicine has secured are largely based on our ability to prevent and cure infections. The introduction of AMTs has, for example, markedly decreased the burden of infectious diseases (e.g. pneumonia and tuberculosis) and, by preventing hospital-acquired infections, has allowed the introduction of complex medical interventions such as organ transplantations, advanced surgery and care of premature babies.

2. All these applications are now endangered by the increasing spread of microbes that are resistant to antimicrobial medications. Resistance to antimicrobials is a natural phenomenon as old as the development of antimicrobials. However, in more recent years this phenomenon has been amplified and accelerated by a number of factors and **modern healthcare rely on AMTs that may become ineffective.** Inappropriate prescription of antibiotics, poor adherence to therapies and insufficient hygiene practices, all contribute to a rapid spreading of antimicrobial-resistant microorganisms (ARMs). The extensive use of AMTs in livestock production may further sustain the growth of ARMs; particularly because, worldwide, the bulk of antimicrobials is given to animals. Antimicrobial resistance (AMR) is a global threat that spans all countries; even those with lower consumption of AMTs. Intensified global trade and travel contribute to the spreading of ARMs across hospitals, cities or countries.

3. **Antimicrobial resistance is rapidly becoming a top health problem that could pose a significant challenge to the functioning of healthcare systems and their budget**. ARMs are highly prevalent in G7 and OECD countries. Patients infected by ARMs are more likely to develop complications and up to 3 times more likely to die. Hospitals spend, on average, an additional USD 10,000 to 40,000 to treat a patient infected by an ARM. The associated impact of lost economic outputs due to increased mortality, prolonged sickness and reduced labour efficiency are likely to double this figure. This means that compared to a world without AMR, OECD countries may experience cumulative losses for USD 2.9 trillion by 2050. If no effective strategy is put in place soon, it has been estimated that the health and economic burden produced by ARMs would be much larger.

4. G7 countries and the European Commission are deeply committed to fighting AMR. Multilateral and bilateral initiatives as, for instance, the Transatlantic Taskforce on AMR have been at the forefront of efforts to tackle AMR. At the national level, **all the G7 countries have developed specific policies to tackle AMR both in the human and animal sector.** National policies generally aim at: i) rationalising the use of antimicrobials with interventions targeting both doctors (e.g. stewardship programmes) and the general population (e.g. education/awareness campaigns); ii) preventing the spread of ARMs (e.g. through strengthened prevention practices); iii) encouraging the development of new AMTs; and iv) strengthening surveillance and monitoring systems to increase early detection of ARMs and monitor use of AMTs. Often, national policies also include a specific objective to increase collaboration with animal and agri-sector partners. Policy response to AMR is sparser outside G7 countries. **At the global level, only 25% of countries have implemented a national policy to tackle AMR** and less than 40% of countries have put in place infection prevention and control programmes for AMR.

5. **Interventions to tackle excessive or unnecessary use of AMTs as well as interventions to prevent the transmission of ARMs are needed to contain the health and economic burden caused by AMR.** Stewardship programmes, awareness campaigns for healthcare personnel and enhanced immunisation programmes have been effective at rationalising the consumption of antimicrobials. Fiscal incentives and behavioural approaches (e.g. delayed prescriptions) are increasingly scrutinised to ascertain

whether they may play a role in decreasing unnecessary antimicrobial consumption. Preventing and controlling transmission of ARMs may be effectively achieved through wider implementation of policies such as early detection of ARMs and enhanced sanitation in hospitals. The implementation of the 5 WHO principles on hand washing coupled with goal setting, incentives or accountability is an effective strategy for increasing adherence to hand washing guidelines which are cornerstone in a successful strategy to prevent the spread of nosocomial infections. For all reviewed interventions, though, the evidence on effectiveness and cost-effectiveness of scaling up interventions at the national level is still limited.

6. The research and development (R&D) pipeline for new antimicrobial therapies is drying up. Rapidly increasing rates of antimicrobial resistance (AMR) as well as increased attention to limiting the use of antibiotics has made investment in developing new AMTs unattractive. Innovative approaches are required to stimulate sufficient R&D activity in this area. Delinking incentives with eventual sales of the product is crucial in achieving this aim. A number of interventions to stimulate sufficient investment in this area are available. A hybrid approach, combining both upstream (e.g. milestone prizes and grants) and downstream (e.g. patent buyouts for successfully developed products) interventions, is needed to ensure development is supported along the entire value chain, from concept to approval, production and distribution.

7. The findings presented in this document show that there is a strong case for G7 action in the area of AMR. The G7 has consistently committed itself to tackling global health challenges, including the fight against infectious diseases, and positioned itself as a leading partner in reaching health-related Millennium Development Goals, by initiating and supporting many global instruments of response to threats posed by infectious diseases. The strong political will of G7 countries would offer the opportunity for moving forward in achieving the goals stated both in the 2014 resolution against AMR issued by the World Health Assembly and in the 2012 EC roadmap against AMR. G7 countries, in particular, can create significant added value and change the architecture of the international response to AMR in three main areas: rationalising use of antimicrobials in animals and humans; incentivising research and development of new AMTs; and addressing the potential economic consequences of AMR.

Key findings

- The spreading of ARMs from one country to others makes AMR a unique global health challenge requiring a multifaceted and comprehensive approach. It is in the interest of G7 countries to tackle this issue globally, supporting the implementation of comprehensive action plans beyond G7. Coordinating efforts with other partner economies in the G20 may offer an excellent opportunity to upscale efforts in an efficient manner.

- Worldwide, the bulk of antimicrobials is not consumed by humans, but rather given to animals. In the United States, for example, antimicrobial use in the livestock sector accounts for about 80% of total annual consumption. Between 2010 and 2030, global consumption of antimicrobials in the livestock sector is projected to increase by about 67%.

- Antimicrobial-resistant infections are generally highly prevalent in G7 countries. For example, about 31% of infections caused by a strain of *S. Aureus* (the leading cause of post-operative infections) are resistant to methicillin.

- Patients infected by ARMs are significantly more likely to develop complications (e.g. +13% limb loss and +71% complications in the central nervous system for infections by methicillin-resistant *S. Aureus*) and to die (e.g. up to 2-3 times higher mortality depending on the microorganism).

- The most recent estimates suggest that AMR has caused about 23,000 deaths in the United States (in 2013) and 25,000 deaths in EU countries (in 2011). Globally, 700,000 deaths may be caused each year by ARMs.
- More than half of extra healthcare expenditure caused by ARMs in humans is to cover additional nursing and medical care. Support services (e.g. food service, laundry, etc.) correspond to about 13% of additional costs, while additional diagnostic tests, including laboratory tests and imaging correspond to 12%. Pharmacy services (i.e. AMTs and other drugs) account for less than 2% of additional costs.
- Compared to a world with no AMR, the economic impact associated with current rates of AMR may reach about 0.03% of GDP in OECD countries in 2020, 0.07% in 2030 and 0.16% in 2050. This would result in cumulative losses of about USD 2.9 trillion.
- Trade and agriculture is among the sectors of the wider economy that is most likely to be affected by AMR. For example, in 2015 chicken sales in Norway dropped by 20% (for some distributors) following the news that a resistant strain of Escherichia coli (E. coli) was found in chicken meat.
- Only a minority of countries around the world have implemented response plans and policies to tackle AMR. One fourth of the countries have implemented a national plan, half of the countries have in place a surveillance system and less than 40% of the countries have currently in place effective policies to rationalise the use of antimicrobials or contain the spread of ARMs in humans.
- Well-designed and implemented stewardship programmes targeting hospital healthcare personnel may decrease antibiotic prescription and consumption by 20-40% and reduce the prevalence of ARMs by 9.4%

Key policy implications

- Strengthening existing G7 countries surveillance and monitoring systems should be a priority, particularly increasing the number of microorganisms that are monitored, expanding the monitoring of infections to outside the hospital sector and improving statistics on the consumption of antimicrobials
- The adoption of a globally agreed set of measurable targets related to the incidence of ARMs as well as to the efficient use of AMTs would provide political impetus to addressing AMR.
- Countries should strengthen their ongoing efforts to facilitate the upscaling of practices of proven effectiveness and efficiency at national level. All the G7 countries are implementing a number of actions to rationalise the use of antimicrobials in human health (e.g. stewardship programmes, educational campaigns) and to prevent the spread of ARMs (e.g. early detection and better sanitation).
- A concerted international approach to foster innovation as well as basic research in the antimicrobial sector is crucial to lower many barriers that currently hinder R&D in the antimicrobial sector and to increase the productivity of research at the global level. This approach should combine both upstream and downstream economic incentives; it should aim to de-link development incentives from sales, and encourage the participation of small to medium enterprises (SMEs) in R&D efforts. A good package would include establishing a global collaborative research platform, milestone prizes and grants, patent buyouts, and a globally coordinated approach to clinical trials.

- OECD, with its distinctive cross-sectoral expertise, is placed in a unique position to help G7 countries and their G20 partners in tackling AMR. The OECD can provide a forum where governments can discuss, develop and coordinate new strategies for prudent antimicrobials use in human medicine and agriculture. OECD can evaluate the detrimental economic impact caused by AMR. Finally, OECD can review and assess the most promising innovative actions to tackle inappropriate use of antimicrobials and to overcome barriers to innovation.

ACRONYMS

AMTs	Antimicrobial therapies
AMR	Antimicrobial resistance
ARMs	Antimicrobial-resistant microorganisms
ARIs	Acute respiratory infections
APEC	Asia-Pacific Economic Cooperation
CDC	Centers for Disease Control and Prevention
DTP	Diphtheria, tetanus and pertussis
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EMEA	European Medicines Agency
FAO	Food and Agriculture Organization
GDP	Gross domestic product
GHSA	Global Health Security Agenda
MDR-TB	Multidrug-resistant tuberculosis
MRSA	Methicillin-resistant *S. aureus*
MSSA	Methicillin-susceptible *S. aureus*
NPV	Net present value
OIE	World Organisation for Animal Health
PDPs	Product development partnerships
R&D	Research and development
ROI	Return of investment
RR	Relative risk
SMEs	Small-medium enterprises
TATFAR	Transatlantic Taskforce on Antimicrobial Resistance
TB	Tuberculosis
WHO	World Health Organization

1. The spread of antimicrobial resistance is a threat to human health and economies in the absence of new therapies

> "*Mr X has a sore throat. He buys some penicillin and gives himself, not enough to kill the streptococci but enough to educate them to resist penicillin. He then infects his wife. Mrs X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin the treatment fails. Mrs. X dies.*"
> Sir Alexander Fleming, 1945

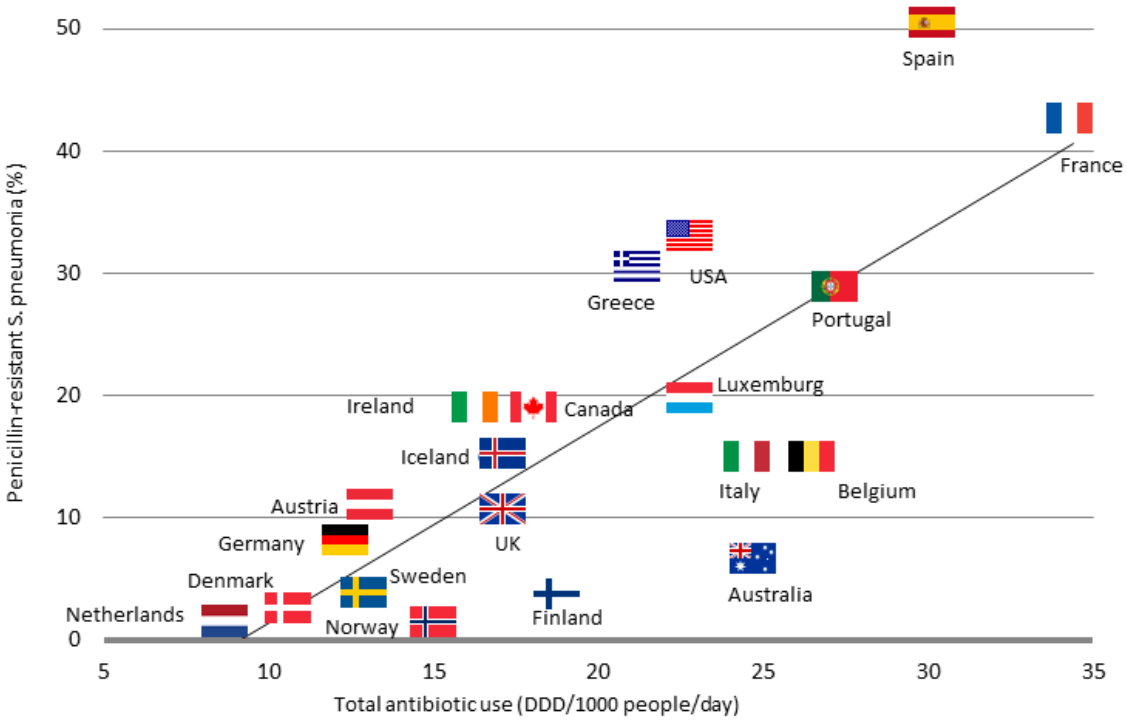
8. Sir Alexander Fleming used these words to close his Nobel lecture for the discovery of penicillin in 1945 (Fleming, 1964). The abovementioned example was used to warn colleagues and future generations on the unavoidable consequences derived by an ineffective use of the antibiotic he had discovered. Better than anything else, these words provide an accurate description of the threat imposed by antimicrobial resistance. Many of the improvements in mortality and morbidity that modern medicine has secured are fundamentally based on our ability to prevent and cure infections. Since their introduction, antimicrobial therapies (AMTs) have played a fundamental role in medicine and have significantly improved population health. The introduction of penicillin has, for example, dramatically changed the health outcomes of patients with bacteria-induced pneumonia and bloodstream infection from a case-fatality rate of about 90% to a survival rate of about 90% (Austrian & Gold, 1964).

9. The emergence and spread of antimicrobial-resistant microorganisms may now undermine many of these advances. Resistance means that an antimicrobial therapy becomes less effective, up to becoming completely ineffective, against the microorganism it targets (box 1). The development of resistance to an antimicrobial therapy is not necessarily a health problem as long as we can count on new, alternative, therapies that can replace less effective pharmaceuticals. This was the predominant situation during the second half of the 20th century when a number of new classes of therapeutics, and specific AMTs within these classes, were discovered. Over this period, physicians could count on the continuous introduction of newly available pharmaceutical products. However, since then, the development pipeline of new AMTs has progressively dried up and the number of new available AMTs is now only a fraction of what it was few decades ago.

Box 1. What is antimicrobial resistance? How does it develop and spread?

Antimicrobial resistance is a natural phenomenon part of the evolution of bacteria. As any living organism, bacteria can go through random evolutionary changes in their genes. Mutations in these genes can produce new or altered traits that may provide new abilities or capacities. These new traits are passed on to offspring during reproduction. In the case of bacteria, these genes may be also acquired 'horizontally' across two bacteria of the same generation through the exchange of mobile genetic elements. If a new trait results helpful for a bacterium's survival and reproduction the lineage descending from that bacterium becomes more common by replacing, through natural selection, bacteria that did not inherited that trait. In the case of animals or humans it may take millions of years before a new helpful trait becomes predominant. In the case of unicellular microorganisms, like bacteria, this process is much shorter as they can reproduce as often as every 20 minutes. For example, ampicillin, despite being only developed half a century ago, is now widely tolerated by many strains of microorganisms. Nearly 100% of hospital-acquired *Klebsiella* infections in developing countries are now ampicillin resistant (Laxminarayan et al., 2013)

Figure 1. Use of AMTs is strongly associated with resistance



Source: Adapted from Albrich et al., 2004

Note: G7 countries are represented with red dots

1.1 The selection and growth of antimicrobial-resistant microorganisms in humans is largely human-driven

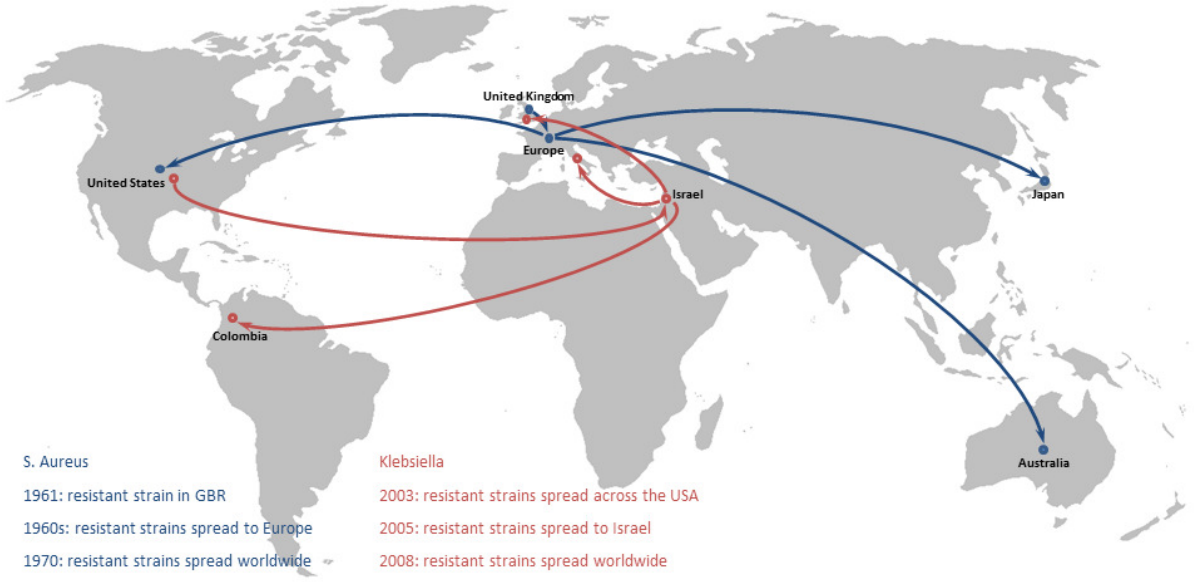
10. Humans are playing a crucial role in selecting antimicrobial resistant microorganisms and helping them grow. There is a clear association between consumption of antibiotics and the development of antimicrobial-resistant strains of microorganisms (figure 1). Inappropriate prescription of antibiotics (e.g. prescription of antibiotics for viral infections), poor adherence to the prescribed therapy (i.e. before the infection is fully eradicated), utilisation of counterfeit and sub-standard antibiotics (10% of the market of counterfeit antibiotics is directed towards European and North American countries (Delepierre et al., 2012) and insufficient hygiene practices in hospitals, all contribute to the selection and the spread of ARMs.

11. The extensive use of AMTs in livestock production may further sustain the growth of resistant microorganisms. Worldwide, the bulk of antimicrobials is, in fact, not consumed by humans, but rather given to animals. In the United States, for example, antimicrobial use in the livestock sector accounts for about 80% of the total annual consumption (FDA, 2010). Livestock producers use antimicrobial agents for a number of different objectives which range from treating sick animals to prevent the spread of infectious diseases, to increase growth rates and feed efficiency. Demand for animal protein is rising worldwide driving up the consumption of antimicrobials in the livestock sector. If current trends continue, between 2010 and 2030, the global consumption of antimicrobials in the livestock sector is projected to increase by about 67%. A significant part of this increase will be determined by a shift in farming techniques in major developing economies (Van Boeckel et al., 2015).

1.2 Antimicrobial resistance is a global health challenge

12. Antimicrobial resistance is a global threat that spans all countries, even those with lower consumption of AMTs. The epidemiology of resistance is multinational and there is consolidated evidence that resistant microorganisms do not recognize boundaries. Patients as well as medical personnel or even healthy people may bring ARMs to other hospitals, cities or countries. For example, the first strain of a methicillin-resistant variant of *S. aureus* (MRSA) was isolated in the United Kingdom 2 year after the introduction of methicillin in 1959. During the 1960s variants of this strain were isolated in many European countries and, then, during the 1970s in other parts of the worlds including Australia, Japan and the United States. MRSA is now a major cause of nosocomial infections worldwide (Deurenberg et al., 2007). Increased mobility and globalization are reducing the time needed for antibiotic-resistant microorganisms to spread. So, if half a century ago MRSA took about two decades to spread to Europe and, then to the rest of the world, a carbapenem-resistant strain of *Klebsiella* needed only 5 years to spread from the United States, where it was identified in 2003, to Israel (2005) to the United Kingdom, Italy and Colombia (2008) (McKenna, 2013).

Figure 2. Antimicrobial resistance is a global threat further increased by globalisation



Source: OECD analyses of Deurenberg et al., 2007 and McKenna, 2013

13. Countries' response to the antimicrobial threat needs to be global and multifaceted. Antimicrobial resistance is one of the very few public health issues in which actions and policies in one country have global ramifications on the health of the entire world. As figure 2 clearly shows, no country, acting on its own, has the power to protect the health of its citizens against antimicrobial resistance. To produce a sizeable effect, actions to tackle antimicrobial resistance should be strongly coordinated within countries and, at a higher level, across countries.

14. This OECD report outlines the economic and policy issues that are central to the current debate on tackling antimicrobial resistance in the human sector. More in detail, this report aims at providing a review of the available evidence that policy makers need to take informed decisions on how to most effectively tackle antimicrobial resistance. The focus of this report is on interventions in the human health sector and the geographical scope is primarily G7 and OECD countries. It is beyond the scope of this report to comprehensively assess potential policy options in the livestock sector as well as basic infrastructure aspects including, among the others, access to clean water and food, separation of drinking and sewage water.

15. The reminder of this report illustrates the health and economic effects caused by antimicrobial resistance, describes policies currently in place in G7 countries and provides an overview of what innovative actions can be but in place to tackle antimicrobial-resistant microorganisms. More in detail, section 2 describes the health and economic burden associated to antimicrobial resistance. Section 3 analyses the international and national policies already in place to tackle antimicrobial resistance. Section 4 looks at the innovative policy actions that can be put in place to avoid the development and the spread of antibiotic-resistant microorganisms in humans. Section 5 provides an overview of options to foster research and development of new AMTs. Section 6 concludes the document by discussing the key policy implications of this work.

2. The case for Policy action: The health and economic burden of antimicrobial resistance

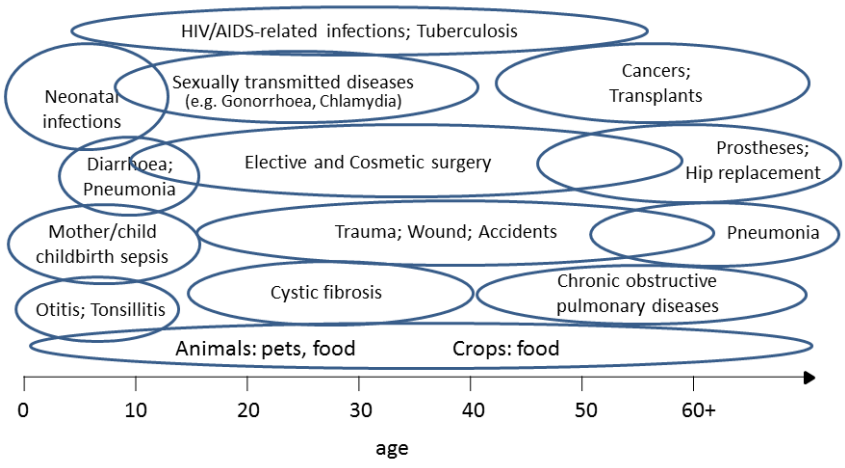
16. Antimicrobial resistance (AMR) is rapidly becoming a top health problem and poses a threat to the financial sustainability of healthcare systems as well as to the broader economy, globally. Antimicrobial-resistant microorganisms (ARMs) are highly prevalent in G7 and OECD countries and cause diseases like pneumonia, urinary tract infections, post-operatory infections and tuberculosis. Patients infected by ARMs are more likely to develop complications and up to 3 times more likely to die. The death toll in the United States and EU countries is estimated in about 50,000 lives a year (0.7 million globally). ARMs cost money: hospitals spend, on average, an additional USD 10,000 to 40,000 to treat a patient infected by an ARM. The associated impact of lost economic outputs is likely to double this figure. This means that compared to a world without AMR, OECD countries may experience cumulative losses for USD 2.9 trillion (corresponding to about 0.16% of their GDP) by 2050. If no effective strategy is put in place soon, it has been estimated that the health and economic burden produced by ARMs may be much larger.

17. This section presents an overview of the current and forecasted health and economic burden caused by AMR. First, the health effects caused by ARMs are discussed focusing on the diseases and the medical conditions caused by ARMs. This section will then illustrate how, compared to susceptible strains, resistant agents increase the morbidity and the mortality of affected patients. The final part presents the most recent estimates in terms of current and forecasted mortality caused by ARMs. Section two, instead, will focus on the economic burden caused by AMRs. The first part of this section will focus on healthcare costs and will describe what items drive the raise in healthcare expenditure. The second part will instead look at the societal costs caused by AMR with particular reference to the costs borne by patients and their families due to, for example, lost income. The final part will present current and forecasted estimates of the impact of AMR on the wider economy and GDP.

2.1 Antimicrobial resistance has a detrimental effect on population health

18. Since their discovery, AMTs have become an essential instrument in medical therapies and surgical treatments. The introduction of AMTs has, for example, markedly decreased the burden of infectious diseases (e.g. pneumonia and tuberculosis) and, by preventing hospital-acquired infections, has allowed the introduction of complex medical interventions such as organ transplantations, advanced surgery and care of premature babies. The number of clinical situations in which the use of AMTs is essential is countless and, as figure 3 shows, covers all the lifespan 'from cradle to grave'.

Figure 3. Use of AMTs over the lifespan



Source: Adapted from White AR, 2011

2.1.1 ARMs cause a number of highly prevalent diseases

19. AMR is the cause of significant detrimental consequences on the health of individuals in both developed and developing countries. The majority of the health burden is caused by a relatively limited number of agents. The WHO report on the global status of ARMs (WHO, 2014) identifies nine agents that would be responsible for most of this burden (table 1). At least, six out of these nine agents are highly prevalent in all G7 and OECD countries. *Escherichia coli* (*E. coli)* and *K. pneumoniae* are particularly common in hospitals where they cause infections, often in vulnerable individuals (e.g. neonates). *S. pneumoniae* is the leading cause of community-acquired pneumonia, which is one of the main killers among young children. *S. aureus* is also common in the community but it is the leading cause of post-operative infections and some strains can induce toxic shocks. Almost 5 million persons living in G7 countries were infected by *N. gonorrhoeae* in 2013. 1.5 million cases developed in the United States while France, Germany, Italy and the United Kingdom had about 0.5 million cases each (IHME, 2015). Worldwide, 106 million persons aged 15-49 were infected (WHO, 2011).

20. Drug resistant tuberculosis (TB) is less common in G7 countries but it is a re-emerging threat. Globally, 8.7 million people developed TB in 2012 and 1.3 million people died as a result of the disease (WHO, 2014). In the same year, the estimated number of multidrug-resistant TB (MDR-TB) cases was 450,000 which correspond to around 3.6% of all new cases and 20.2% of all previously treated cases of TB. The number of prevalent cases of TB in G7 countries is only a fraction of the global estimate: in 2013, the estimated number of persons with TB was about 122,000. However, two tendencies should not allow for complacency. First, between 2005 and 2010 and after years of decreasing trends, many G7 countries started experiencing growing incidence rates. Second, G7 countries show rates of MDR-TB that are comparable to the world average. The world prevalence of MDR-TB is 3.6% and 20.2% for, respectively, new and previously treated cases of TB. G7 countries have a prevalence of MDR-TB which ranges between 0.5% and 2.6% and between 1.6% and 21.0% for, respectively, new and previously treated cases.

2.1.2 Infections by ARMs increase population morbidity

21. Compared to infections susceptible to AMTs, antibiotic-resistant microorganisms (table 1) increase the population health burden in multiple ways (box 2). First, ARMs prolong morbidity and increase the time spent with the infectious disease. Second, ARMs increase the likelihood of developing other comorbidities or complications. Third, by requiring more intensive treatments, patients are more likely to experience adverse reactions or secondary effects. Finally, patients infected by ARMs experience higher mortality rates.

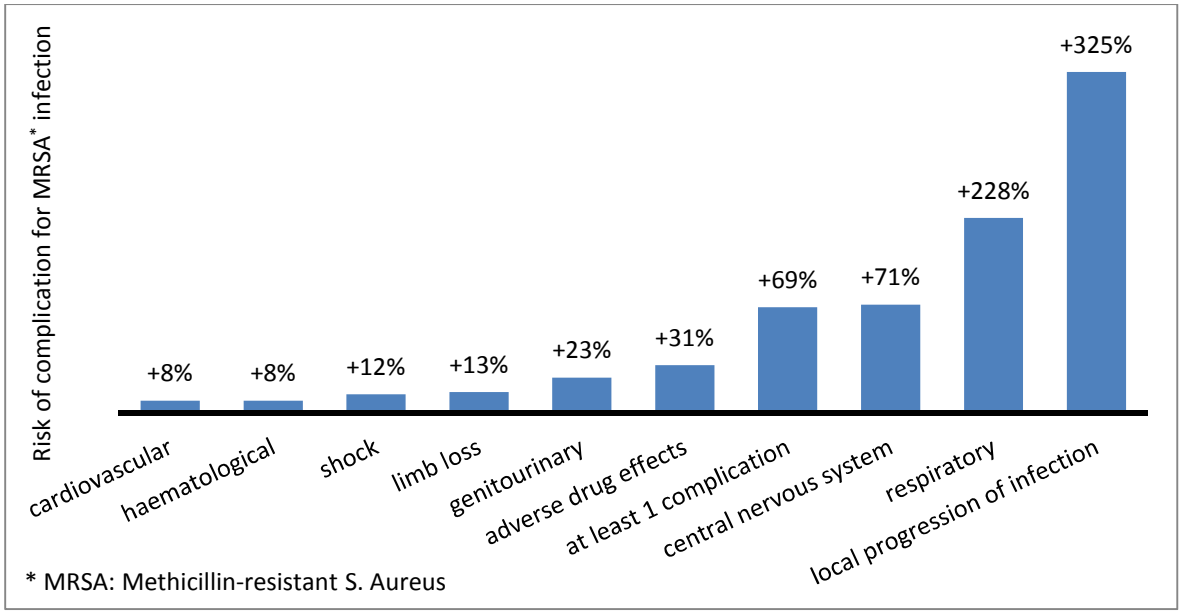
Box 2. Calculating the health and economic impact of AMR: identifying the right reference point

If not otherwise specified, the calculation of the health and economic burden caused by ARMs is intended as the additional marginal deaths or costs above the deaths and costs caused by infections caused by similar agents that are susceptible (i.e. not resistant) to antimicrobial therapies. From an economic perspective, calculating the pure cost of illness and treatment associated to an ARM would produce an overestimation of the costs due to resistance 'per se' because it should be assumed that the most likely alternative scenario would have been infection from a susceptible agent which would have also produced some additional costs compared to a scenario in which the patient would have not developed any infection. Conversely, the analysis of the cost-effectiveness of actions aimed at tackling AMRs, particularly of actions aimed at limiting the spread of ARMs, should also incorporate the positive effects on healthcare expenditure that such interventions have in limiting the spread of antibiotic-susceptible bacteria.

22. Inadequate and delayed therapies are the main causes underlying the increased burden of disease caused by ARMs. The identification of the correct therapy may take significantly longer for ARMs: up to six times longer, for instance, in the case of antibiotic-resistant *E. coli* and *K. pneumonia* (i.e. 72 hours versus 11 hours for the susceptible strains) (Lautenbach et al., 2001). Simultaneous resistance to multiple AMTs would increase further the probability of inadequate AMT and delay of the effective therapy (Hyle et al., 2005). A systematic review and meta-analysis showed that patients with infections from strains with extended resistance have a risk of delays in starting the effective therapy which is more than 5 times higher (relative risk 5.56, 95% confidence interval: 2.94 – 10.51) compared to patients with infections from antibiotic-susceptible strains (Schwaber & Carmeli, 2007).

23. Patients infected by ARMs are significantly more likely to develop complications and long-term sequelae (box 3). Once an infective microorganism enters a body, it can move from the primary site of infection to other sites. As previously mentioned, ARMs can usually benefit from extra time to multiply, spread to other organs and to develop complications. For example, patients infected by the methicillin-resistant (MRSA) strain of *S. aureus* have a risk of developing any complication which is 69% higher compared to similar patients infected by its methicillin-susceptible variant (MSSA)(figure 4). The single most frequent complication is a progression of the local infection (relative risk (RR) equal to 3.25 – i.e. a persons infected by MRSA is 3.25 times more likely to have a local progression of the infection compared to a person infected by MSSA). If the infective microorganism enters the circulatory system and spreads widely, it may cause sepsis (i.e. whole-body inflammatory response to an infection) and, eventually, a shock. Patients infected by ARMs are more likely to develop sepsis and 12% more likely to develop shock. Some other serious long-term complications that are more likely to develop include sequelae in the central nervous system (RR 1.7) or limb loss (RR 1.13).

Figure 4. Additional risk of developing complications for infections by a resistant strain compared to a susceptible strain: the case of S. aureus



Source: OECD calculations on Filicie et al. 2010

Table 1. List of key antimicrobial-resistant microorganisms, place of infection and resistance

Infectious agent	Common infection sites or clinical conditions	Common resistances	Resistance rates Average in G7 countries [min-max]
Escherichia coli	urinary tract, bloodstream, intra-abdominal (e.g. peritonitis), skin and soft tissues, meningitis in neonates, foodborne infections	3rd gen cephalosporins; carbapenem; fluoroquinolones,	3rd gen ceph: 12.1% [8.0% - 19.8%] fluoroquin: 27.7% [17.5% - 40.5%]
Klebsiella pneumoniae	urinary tract, bloodstream, meningitis in neonates	3rd gen cephalosporins, carbapenem, cotrimoxazole; fluoroquinolones	3rd gen ceph: 17.3% [4.0% - 45.9%] carbapenem: 5.5% [0.0% - 26.7%]
Staphylococcus aureus	skin, soft tissue, bone and bloodstream, postoperative wound infections, toxic shock syndrome and food poisoning	methicillin	30.5% [13.6% - 53.0%]
Streptococcus pneumoniae	Community-acquired pneumonia, acute otitis media, meningitis, bloodstream	penicillin	8.3% [0.1% - 42.2%]
Nontyphoidal shigella	Foodborne, gastroenteritis, enteric fever, diarrhoeal	fluoroquinolones	5.9% [0.0% - 17.6%]
Shigella	Gastroenteritis, neurologic disorders	fluoroquinolones, cotrimoxazole	fluoroquin: 9.8% [2.0% - 17.5%]
Neisseria gonorrhoeae	acute infection of the reproductive tract, pharynx and the rectum, newborn, including eye infections that may lead to blindness	3rd gen cephalosporins, penicillin, tetracycline, fluoroquinolones	3rd gen ceph: 7.5% [0.0% - 31.0%]
Mycobacterium tuberculosis	tuberculosis	streptomycin, isoniazid, rifampicin, fluoroquinolone	New cases: 1.3% [0.5% - 2.6%] Retreatments: 9.1% [1.6% - 21.0%]
Plasmodium malariae	malaria	chloroquine, pyrimethamine, mefloquine, amodiaquine, sulfadoxine-pyrimethamine	-

24. Infections caused by ARMs may also require more intensive and protracted treatments with second line therapies. In some cases, these AMTs may cause a higher number of adverse reactions or may have toxic secondary effects. For example, the multiresistant gram-positive pathogens have to be increasingly treated with linezolid which has a documented efficacy for treating this serious type of infections. However, a series of post-marketing studies documented that patients treated with linezolid often had adverse reactions including thrombocytopenia (deficiency of platelets in the blood causing bleeding and bruising), anaemia, gastrointestinal problems and peripheral neuropathy (Bishop et al., 2006).

Box 3. Overuse of AMTs beyond AMR: is there a link with obesity and chronic diseases?

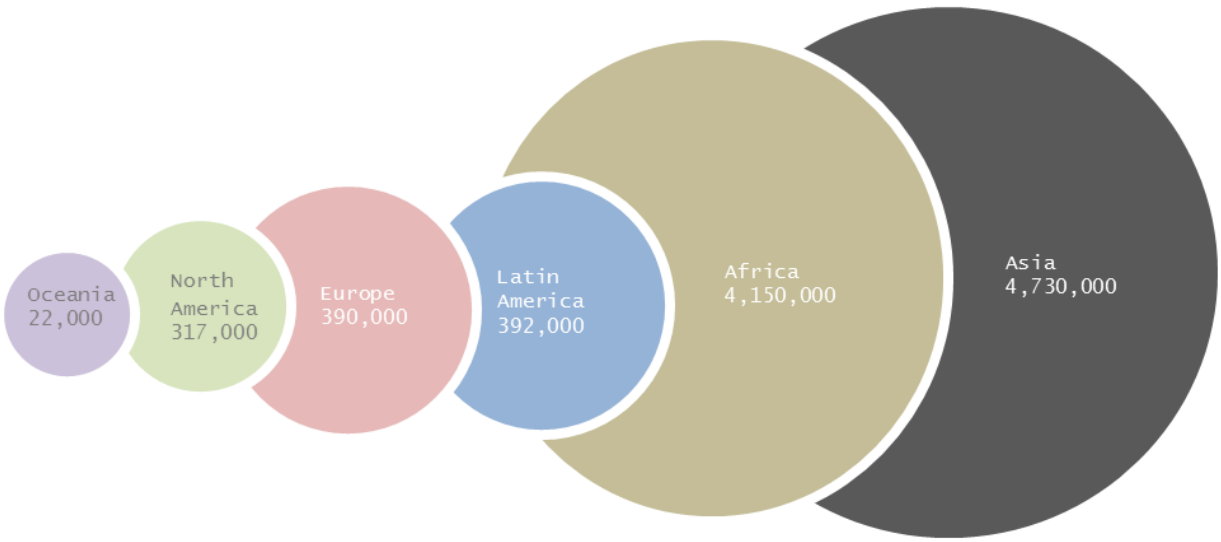
Obesity and associated chronic diseases like diabetes, cancers and cardiovascular diseases are a major cause of concern for population health and the economy of OECD countries. There is increasing evidence suggesting that use of antibiotics may be playing a role in the epidemic of obesity-related diseases. In particular, consumption of antibiotics may be altering the intestinal microbiota (i.e. the mix of bacteria living in the gut) and that these changes may influence human metabolism and contribute to weight gain (Jess T, 2014; Riley et al., 2013). This new stream of studies is still in its infancy and more research is needed but a large US cohort study has concluded that repeated exposure to broad-spectrum antibiotics in the first 2 years of life is associated with higher risk (+11% compared to non-exposed children) of childhood obesity (Bailey et al., 2014). A case-control study in Denmark has instead found a statistically significant association between exposure to antibiotics and development of type 2 diabetes (Mikkelsen et al., 2015). Both studies show that higher levels of exposure to antibiotics are more strongly associated with the health outcome under study.

2.1.3 Infections by ARMs increase population mortality

25. Patients infected by ARMs experience increased risk of mortality. Results of a meta-analysis conclude that, on average, patients infected by MRSA are 40% more likely to die compared to patients infected by MSSA (Cosgrove et al., 2003). Other reviews conclude that, patients infected by other ARMs may experience significantly higher (up to 2-3 times) risks of death due to the infection (WHO, 2014; Maragakis et al., 2008). Other factors that may affect the risk of fatality include whether the infection was acquired in the hospital or in the community (Wang et al., 2008), the presence of other comorbidities and the delay in starting an effective treatment. For example, Tumbarello (2007) concludes that mortality rates are 80% higher among hospitalised patients that develop an infection and do not receive an adequate initial antibiotic treatment, even when they do receive one at a later stage.

26. The death toll caused by AMR is already substantial but may become enormous (figure 5). CDC calculates that in 2013, 23,000 deaths were directly amenable to AMR in the United States while the most updated estimates for the EU suggest that 25,000 persons may have died in 2011 because of ARMs (ECDC & EMEA, 2009). Globally, a conservative estimate suggests that the death toll caused by AMR may be 700,000 people (Review on AMR, 2014). However, if no appropriate policies are put in place, the health burden caused by AMR may reach massive proportions. The United Kingdom review on AMR (Review on AMR, 2014) calculated that if current rates of resistance increased by 40%, we could expect an average of 10 million deaths per year between 2015 and 2050. Only 0.7 million of these additional deaths would occur in North America or Europe, with the largest numbers in Africa and Asia.

Figure 5. Number of deaths per year attributable to AMR by 2050 if current resistance rates increased by 40%



Source: KPMG, 2014

2.2 Antimicrobial resistance has a negative impact on the health budget and on the economy

27. The detrimental health effects produced by AMR go hand in hand with a negative impact on the budget of health systems and, more broadly, on the economy. From the micro-level to the macro-level, ARMs have a direct negative impact on many actors and economic dimensions. First, by requiring more intensive therapies, AMR increases health expenditures. Second, patients and their families may undergo additional non-healthcare related expenditures (e.g. travel time) or suffer from income loss due to ill-health. At the societal level, AMR negatively impact labour market outcomes due to absence from work which, down the line, negatively affect the broader economic performances of countries.

2.2.1 Infections by ARMs increase healthcare costs

28. Additional healthcare costs caused by AMR are driven by different factors, mainly related to an inadequate or delayed start of effective antimicrobial therapies and to the increased degree of severity of infections caused by ARMs. Reviews (Cohen et al., 2010; Sipahi, 2008; Smith & Coast, 2012; Tansarli et al., 2013; WHO, 2014) suggest that, compared to an antibiotic-susceptible infection, an antibiotic-resistant infection is responsible for about USD 10,000 to 40,000 extra healthcare costs. However, single studies may provide significantly different estimates ranging from less than USD 10 to more than USD 100,000. The main drivers underlying the additional expenditure are:

- Use of a more aggressive antimicrobial therapy based on either second-line AMTs (which are usually more expensive), or combinations of different AMTs or a series of tests with different treatment options before identifying the most effective strategy;

- Extra investigations as, for example, advanced laboratory tests to ascertain what is the most effective therapy for that specific agent or imaging to monitor the development of complications associated to the infection;

- More intensive forms of treatments as, for instance, hospitalization in the case of community-acquired ARMs or, if the patient develops the diseases while hospitalized, transfer to intensive care units and isolation rooms;

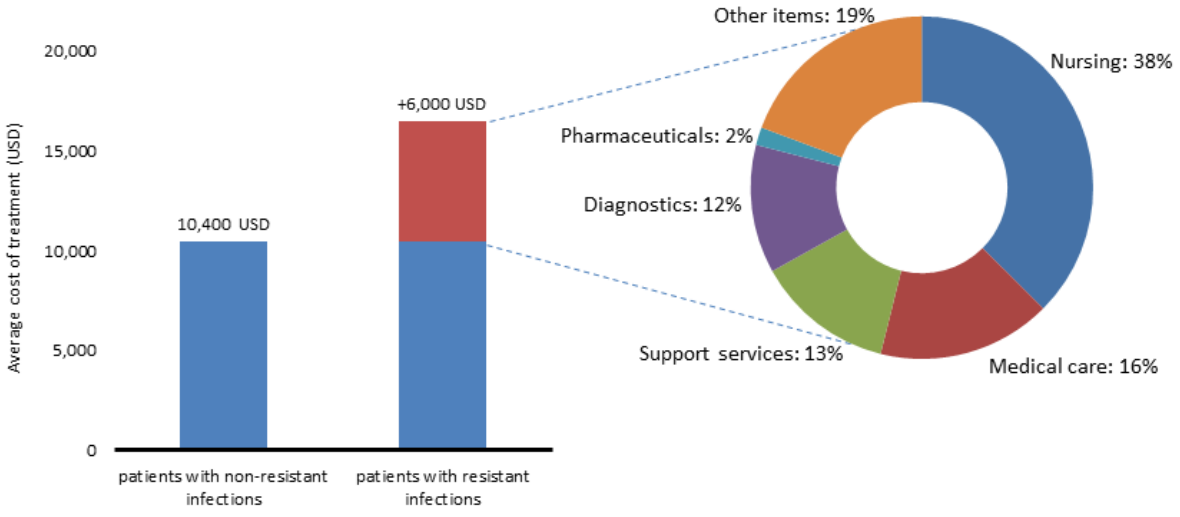
- More intensive medical procedures as, for example, an increased likelihood of undergoing surgery among patients infected with resistant organisms. Surgery may range from debridement of infected tissue to amputation (Cosgrove SE, 2006);

- Excess length of stay or treatment until the infection is eradicated. This entails additional medical and nurse care (and, consequently, time) as well as use of other additional hospital resources.

- Changes in physicians' prescribing habits that may start prescribing second-line antibiotics even to patients with first-line antibiotic susceptible infections, if the prevalence of ARMs is perceived as increased (McNulty et al., 2011)

29. Tumbarello and colleagues (2010) calculated the contribution of the different items concurring to the total healthcare expenditure of patients with an *E. coli* bloodstream infection (figure 6). More than half of the extra expenditure is to cover costs associated to additional nursing and medical care. Support services associated to the hospitality of patients (e.g. food service, laundry, etc.) correspond to about 13% of the costs while additional diagnostic tests, including laboratory tests and imaging correspond to 12% of costs. Pharmacy services (i.e. AMTs and other drugs or disposables) account for less than 2% of the additional costs. Other services, mainly to cover overhead costs and depreciation account for the remaining 20%.

Figure 6. Costs of hospitalisation for patients with E. coli antibiotic-resistant infection and underlying drivers



Source: OECD analyses on Tumbarello et al. 2010

30. The contribution of second-line therapies to the increase in health expenditure should not be underestimated. In the analysis by Tumbarello (2010) increased pharmaceutical costs represent only a tiny fraction (i.e. less than 2%, corresponding to USD 85) of the total additional expenditure. However, in some cases this expenditure may become much larger both in absolute and relative terms. Filice and colleagues (2010) found that, on average, the costs of AMTs to treat resistant strains of *S. aureus* was about seven times higher than treating a susceptible infection (i.e. USD 142 as opposed to USD 21).

31. In the United States, the cost associated with treating ear infections increased by 20% (equivalent to USD 216 million) between 1997 and 1998 because of increased resistance (Sharma & Towse, 2011). Treatment for MDR-TB provides another striking example. WHO (Fitzpatrick and Floyd, 2012) calculated that the cost of treating MDR-TB in the developed world can range between USD 35,000 and 41,000 per case. But this cost may become much higher in the case of extensively drug-resistant tuberculosis (XDR-TB). In the US, for example, there have been documented cases with treatment costs exceeding USD 200,000 and at least one case with a total cost close to USD 1 million (Chaulk and Kazandjian, 1998).

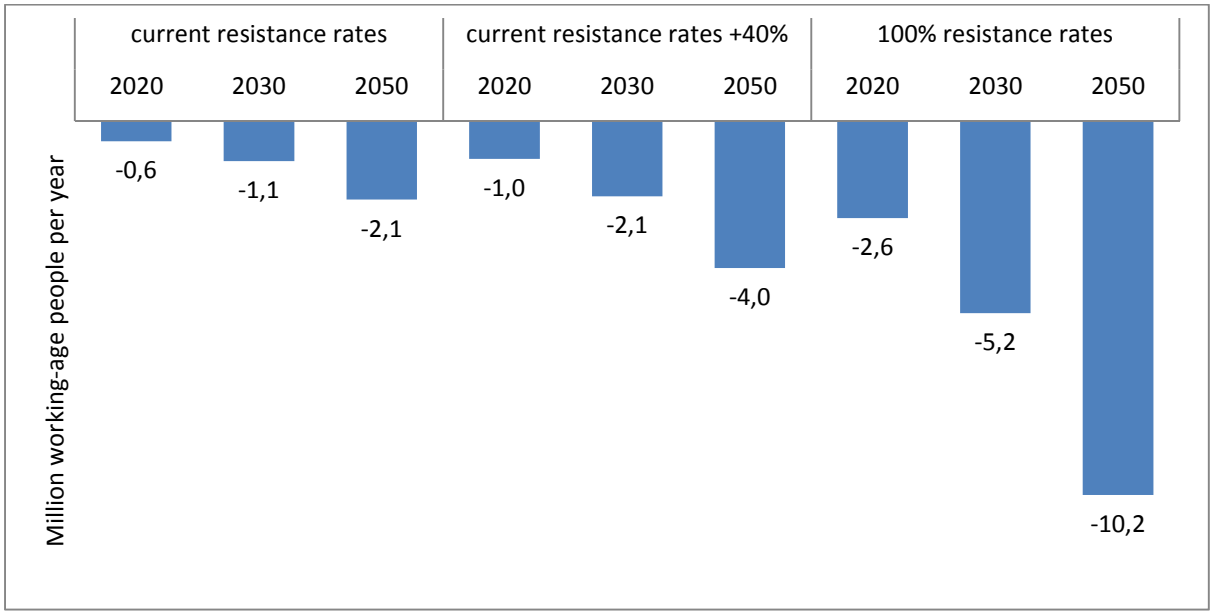
32. The impact of AMR on the budget of healthcare systems is significant. In Europe, ECDC and EMEA (2009) have calculated in about EUR 940 million the additional healthcare costs for treating the resistant strains of a limited set of the most common infective agents in 2007. The 2015 edition of the Canadian report on AMR (Government of Canada, 2015) suggests that the total medical care costs associated with AMR may be in the order of 1 billion CAD. The total healthcare costs are more difficult to calculate in the United States but the CDC (2013) reports that, under certain assumptions, they may be as high as USD 20 billion.

2.2.2 The impact of AMR on societal costs and labour force productivity are higher than health costs

33. Costs borne by patients and their families may be as high as healthcare costs. A second line of additional expenses produced by AMR is associated to societal costs amenable to lost income due to longer time away from work, the cost associated to ill-health and, eventually, to death. Both hospitalized patients and ill-persons that are not hospitalized because their infection does not require hospitalization bear this second type of costs. At the patient level, hospital expenditure may be significantly higher than other costs borne by patients and their families. However, when healthcare and non-healthcare costs are scaled up at the population level, non-healthcare costs may instead overshadow healthcare expenditure because of the very high number of infections that do not require hospitalization. For instance, community-acquired pneumonia is a very common disease with incidence rates ranging between 1 and 3 cases per 1000 persons per year in many G7 countries (Torres et al., 2013; Marrie & Huang, 2005). More than 95% of the cases of pneumonia are caused by bacterial infections (Marrie, 2014) and, on average, only one in ten patients requires admittance to an hospital (NHS, 2015).

34. Few studies estimated the societal costs of AMR and when this is done only a small fraction of the full societal cost is included. The effect that AMR has on the broader economy is mediated through increased mortality and increased morbidity (prolonged periods of sickness temporarily reduce the size of the global workforce and may lead to permanent reductions in labour productivity). Both of these drivers affect the productivity and the size of the labour force. In addition, increased morbidity may also affect the supply of labour if the condition requires the attention of a carer who would otherwise be economically productive. AMR, particularly if resistance rates increase substantially, could result in further costs. For example, people may choose not to undergo certain medical procedures because of the heightened risks involved.

Figure 7. Working-age population loss in OECD countries per year relative to no AMR (million people)



Source: Taylor et al., 2014

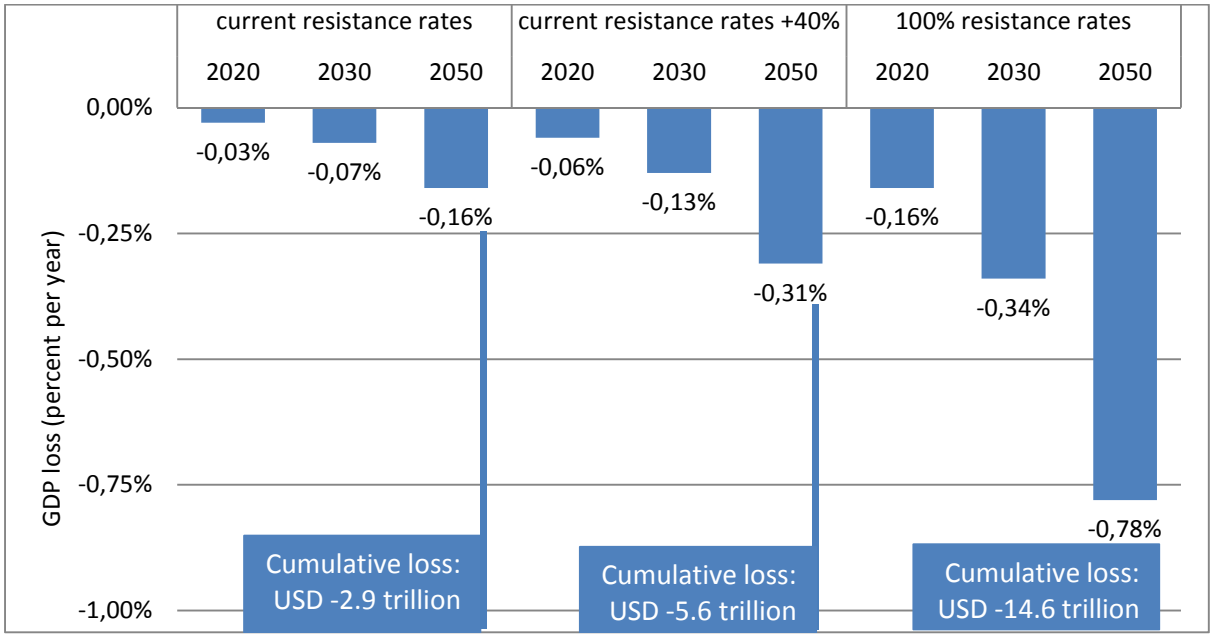
35. Figure 7 shows how the OECD population in working age could decrease over time under different AMR scenarios. If current resistance rate remained unchanged, in the 2020 OECD working-age population could be lower by 0.6 million people compared to a world without AMR. By 2050, the total loss in people in productive age would rise to 2.1 million. However, if no effective actions to tackle AMR are put in place in a timely fashion, current resistance rates may increase, even to significantly higher levels. The other two scenarios presented in figure 7 provide an idea of a possible realistic alternative (i.e. current resistance rates will increase by 40%) and of the worst-case scenario (i.e. 100% of resistance rates). Under these two assumptions, total deaths in working-age population may reach, respectively, 4 million and 10.2 million by 2050.

36. The impact of lost economic outputs due to AMR is likely to be higher than the associated medical costs. For example, Roberts and colleagues (2009) calculated the costs attributable to mortality and productivity loss during the extended time spent in hospitals for a cohort of US patients in 2000. The authors of this study concluded that the societal costs per patient with antibiotic-resistant infection would be of about USD 38,000 (2010), more than double of the medical costs. This estimate does not include other potential costs incurred by the families of hospitalized persons (e.g. travel time, absence from work to care for the patients, etc.). The authors calculated that scaling up these figures to the US national level would mean that the US population, in 2000, had lost about USD 35 billion (or about 0.35% of the national GDP) due to lost wages and premature deaths. This figure does not account for antimicrobial-resistant infections in the community. ECDC and EMEA (2009) calculated that, in Europe, productivity losses due to absence from work caused by AMR amounted to about EUR 600 million in 2007.

2.2.3 AMR has a negative impact on the economy

37. Figure 8 shows the potential impact on the GDP of OECD member countries of three AMR scenarios. Compared to a world with no AMR and if current resistance rates remained unchanged, OECD countries would experience a contraction of GDP equal to 0.03% in 2020, 0.07% in 2030 and 0.16% in 2050. This would result in cumulative losses for about USD 2.9 trillion which corresponds to about half of the negative macro-economic effects that AMR may produce globally by 2050 (i.e. the global cumulative GDP loss is calculated in USD 5.8 trillion). Under the other two scenarios (i.e. resistance rates increase by 40% and 100% of resistance rate) the GDP loss would be much higher and, by 2050, OECD countries would see their GDP 0.31% and 0.78% smaller compared to a world with no AMR.

Figure 8. Percent GDP loss in OECD countries per year relative to no AMR



Source: Taylor et al., 2014

38. These figures fail to capture the full health and economic burden caused by ARMs. For example, most of the studies can only assess the effects of a limited number of microorganisms and, for these agents, only the effects of resistance to a limited number of AMTs. We know that these estimates are only a piece of a bigger jigsaw. However, one of the greatest concerns about AMR is that modern healthcare heavily rely on AMTs that sooner rather than later may become ineffective. The knock-on effects of this event are difficult, if not impossible, to fully understand in their magnitude.

39. Increasing rates of AMR are likely to have negative effects in other areas of the economy that, so far, have remained unexplored. Experts recognize that, in the future, AMR may end up following patterns similar to those of epidemic outbreaks developing into pandemics (Anderson RM, 1999; Spellberg et al., 2008). Studies looking at the effect of pandemics outbreaks have concluded that the area of travelling and leisure, trade and agriculture and finance and banking, may all experience substantial losses (Jonas, 2013; CBO, 2006). A recent example supporting this hypothesis may be drawn from Norway where, in 2015, chicken sales have dropped by as much as 20% (for some distributors) following the news that a resistant strain of *E. coli* was found in chicken meat (Dahle et al., 2015). Similarly, poultry consumption dropped by about 20-25% in several Asian countries, including Singapore, China and Thailand during the 2003 avian flu outbreak (Bánáti, 2011).

3. Responding to the Rise of antimicrobial resistance: G7 Countries and International Policy Plans

40. Antimicrobial resistance (AMR) requires multifaceted policy intervention. Global efforts to tackle the negative effects of AMR on human health are coordinated by WHO that has recently published the global action strategy to tackle AMR. Besides their role as members of WHO, G7 countries are also involved in a series of bilateral or multilateral initiatives. For example, the EU and the United States have established a Transatlantic Taskforce on the subject. Other notable examples include the Global Health Security Agenda and initiatives carried out through the Asian-Pacific Economic Cooperation Forum. At the national level, all the G7 countries have developed specific policies to tackle AMR. Canada (Government of Canada, 2014), Germany (BGM et al., 2015), the United Kingdom (Department of Health, 2013), the United States (The White House, 2015) and the EU (EC, 2011) have specific AMR action plans or strategies. France (République Française, 2011) has national plans focused on AMTs, whereas Italy (Ministero della Salute, 2014) has incorporated some AMR objectives and activities within the National Prevention Plan 2015-2018. Japan, finally, has issued a set of national recommendations which focused on the prevention of nosocomial infections (MHLW, 2015). Policy response to AMR is much sparser outside G7 countries. At the global level, only a quarter of countries have implemented some national policy to tackle AMR and less than 40% of countries have put in place infection prevention and control programmes for AMR.

41. This section describes the action plans currently in place in G7 countries and at the international level. The first part focuses on international plans. More in details, this section will first describe WHO and EC efforts to tackle antimicrobial resistance and it will then illustrate other bilateral (i.e. TATFAR) and multilateral actions (i.e. GHSA and the APEC forum) in which G7 countries play a key role. The second part focuses on G7 national plans. National strategies or action plans are reviewed and compared in terms of targets, level of enforcement and priorities. In particular, priorities are divided into 7 different dimensions: i) antimicrobial stewardship; ii) prevention of the spread of antimicrobial-resistant microorganisms; iii) surveillance and monitoring; iv) research and innovation; v) interventions in the livestock sector; vi) cross-country collaboration and international efforts; vii) awareness, education and training. The third part provides an overview of the level of response to AMR at the global level with particular regards to the implementation of effective practices and policies.

3.1 International plans and efforts to tackle antimicrobial resistance

42. International efforts to tackle AMR have existed for a number of years (figure 9). Early WHO efforts include the 1998 World Health Assembly Resolution, urging Member States to develop measures for containing antimicrobial use and strengthening legislation surrounding their use. Further key efforts include the 2001 global strategy publication (WHO, 2001), which focused on containment guidelines, as well as the 2015 country situation analysis report (WHO, 2015), which analysed existing initiatives on AMR and determined where further work is required (WHO, 2015) amongst WHO regions. The most recent WHO global action plan spans from 2015 until 2019. In recent years WHO has also joined forces with other relevant UN agencies, notably FAO (Food and Agriculture Organization) and OIE (World Organisation for Animal Health), to better coordinate global activities to address health risks (FAO et al., 2010).

43. At the EU level, the European Council called for a comprehensive AMR action plan in 2009, which was subsequently delivered by the European Commission in 2011 (EC, 2011). Amongst a breadth of actions (table 2) surrounding AMR issues in humans, the action plan also focuses on antimicrobial use in agricultural practices and includes regulatory and legislative changes in the animal and agriculture sector. Subsequent activities in human health highlighted in the 2015 Road Map (EC, 2015) and 2015 Progress Report (EC, 2015) include a wide-ranging set of actions to promote surveillance systems, to foster research and to develop recommendations and guidelines. Particular attention is devoted to collaboration both across different agencies within the EU (i.e. the European Centre for Disease Prevention and Control, the European Surveillance system of Antimicrobial consumption, the European Antimicrobial Resistance Surveillance Network) and with other countries (e.g. China and Russia). The existing action plan timelines span from 2011 until 2017.

44. In addition to plans established by intergovernmental organizations as the WHO and the EU, there are several existing joint efforts amongst G7 countries (box 4). The United States and EU established the Transatlantic Task Force on Antimicrobial Resistance (TATFAR) which issued a set of recommendations (TATFAR, 2011) for collaboration on AMR issues. Such recommendations are planned to be revised every five years. Canada, Germany, the United Kingdom, Italy, Japan and the United States have committed to action packages on AMR via the Global Health Security Agenda (GHSA, 2014). Canada, Japan and the United States also support AMR efforts via the Asian-Pacific Economic Cooperation Forum (APEC), where a set of guidelines on effective control and prevention (APEC, 2014) have been issued. The need to intensify joint international efforts to tackle AMR has been also recently confirmed during the June 2015 meeting organized by the G7 German Presidency. In that occasion G7 leaders committed to develop or review and effectively implement national action plans, share their national plans and support other countries develop their own national action plans (G7, 2015).

Box 4. Joint country efforts

TATFAR (Transatlantic Taskforce on Antimicrobial Resistance) was established at the 2009 EU summit by the United States and EU countries, and focuses on dialogue and information exchange regarding technical and scientific aspects in relation to the appropriate use of AMTs, prevention of AMR, surveillance and improving the pipeline for new AMTs. Members of the task force include various US and EU agencies (more recently Canada and Norway have been invited to attend) and the secretariat has been alternatingly hosted by the European Centre for Disease Prevention and Control (ECDC) and Centre for Disease Control (CDC). Activities are centred on information exchange, best approaches and practices as well as the development of peer relationships. TATFAR does not impose binding positions, but it does issue recommendations for executive bodies together with timelines (TATFAR, 2011). TATFAR also coordinate implementers for specific action areas, oversees their implementation and delivers a progress reports (TATRAR, 2014). The original mandate from 2011-2013 was extended until 2016.

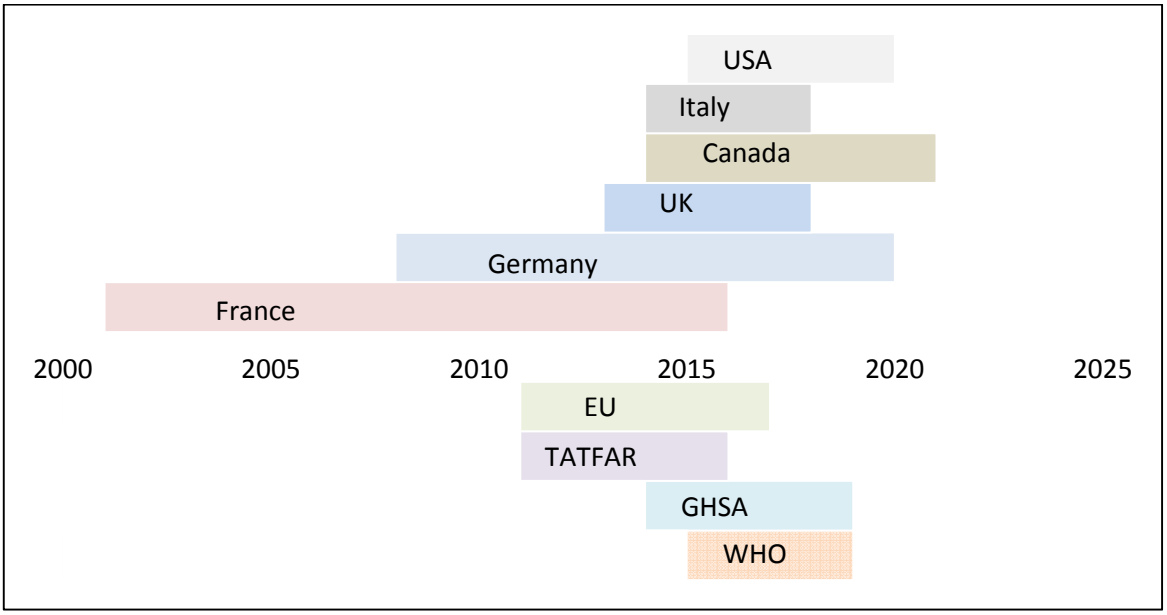
GHSA (Global Health Security Agenda) was launched in 2014 with the aim of advancing a world safe and secure from infectious disease threats. The GHSA Steering Group is currently chaired by Finland, with further country representation by Canada, Chile, India, Indonesia, Italy, Kenya, the Kingdom of Saudi Arabia, the Republic of Korea and the United States. Key efforts surrounding AMR include the 2014 Washington meeting commitments to develop and integrate a global package of AMR activities. These focus on establishing comprehensive national plans, strengthen surveillance systems and laboratory capacities as well as antibiotic stewardship. Implementation of action packages and reaching 2019 targets, draws on the engagement of nations, government agencies, international organisations and private stakeholders.

The APEC Forum has been providing advisory support on the effective prevention and control of AMR, specific to the Asian-Pacific Region. Key efforts on AMR have included 2012 APEC leaders declaration to support cross-sector efforts, as well as the issue of guidelines for member countries.

3.2 National plans and efforts to tackle antimicrobial resistance in G7 countries

45. National plans to tackle AMR have a relatively recent history (figure 9 and table 2). France has issued three national plans, publishing the first targeted plan in 2001 (République Française, 2001). Germany has issued two national plans, publishing its first national strategy in 2008 (BGM et al., 2008;) and the most recent plan (BGM et al., 2015) already integrates actions proposed in the WHO global action plan. G7 countries show sustained commitment to AMR plans, which currently encompass a 5-year plan by Canada, Germany, France, the United Kingdom and the United States, and a 4-year plan by Italy. Italy is also preparing a specific, multiannual and integrated plan to fight AMR, which includes many of the priorities highlighted in the WHO Plan.

Figure 9. National and International plans to tackle AMR: year of implementation and duration



Source: OECD analyses on national and international plans (references to plans in table 2)

3.2.1 AMR national policies in G7 countries: enforcement and ownership

46. The enforcement of policies varies amongst G7 countries. Canada, France, Germany and the United States are considering or plan to use legislative or regulatory changes to implement policies. In the United Kingdom most proposed policy actions are voluntary (DH, 2011), however the United Kingdom has now strengthened legislation (DH, 2015) to reflect the vital role of infection prevention (including cleanliness) in optimising antimicrobial use and reducing antimicrobial resistance. Germany introduced legislative changes (BGM et al., 2015) in hospital and certain outpatient-settings in 2011, which include the detection and isolation of high risk patients, as well as the reporting of specified bacteria and antibiotic use. The United States plans to streamline regulatory processes surrounding approval of devices used to test bacteria susceptibility to AMTs. This will facilitate use of up-to-date criteria in determining bacterial resistance and encourage the development of new antimicrobials (e.g. with the Limited-Population Antibacterial Drug pathway). Some legislative proposals in the same area are also under consideration. France plans to limit antibiotic prescriptions in both human and veterinary sectors and is considering strengthening the protection of AMTs through a special drug status framework. Canada plans to update and strengthen the veterinary drug regulatory framework as part of the overall action plan but regulation is not considered as the main mechanism for policy implementation. Besides, Canada considers the possibility of using the orphan drug framework to help incentivise filing of new AMTs. The orphan drug framework has facilitated approval requirements, such as smaller clinical trials, for drugs that meet the legislative criteria. In respect to veterinary and agricultural practices, Japan continuously conducts and reinforces risk management measures based on the risk analysis framework; Canada and the European Union plan to strengthen the regulatory framework.

47. Overall, country action plans stress the need for multi-stakeholder efforts for the implementation of plans, which widely spans across governments, healthcare authorities, organisations, practitioners, researchers, pharmaceutical and biotech companies, the community as well as patients. Further specifics regarding ownership of the AMR plans however also differ amongst G7. In Italy emphasis is placed on the Regions but the new national plan, currently under elaboration, is expected to better define the actions and the roles of both the national Ministry of Health and of the Regions. Canada highlights the key role of Provinces and Territories for delivery of healthcare, approval of AMTs for medical coverage and the regulation of antimicrobial use in agriculture and

veterinary medicine. Canadian Provinces and Territories also set standards and guidelines that support the appropriate use of AMTs and undertake awareness activities. Germany also stresses the importance of Länder in vigilating the implementation. The United States and United Kingdom highlight the need for partnership across groups, including public and private sector partners for implementation. Further to this, the United Kingdom established a High Level Steering Group (HLSG) consisting of governmental departments, agencies and NHS organisations, for reporting progress, driving delivery and ensuring cross-sector engagement amongst delivery partners. The United States have, instead, put in place the President's advisory council on AMR and the CARB (combating antibiotic-resistant bacteria) task force.

3.2.2. AMR national policies in G7 countries: evaluation processes and targets

48. Countries are at different stages and have different approaches for evaluating the progress and successes of their implemented plans. Germany and the United Kingdom have already published progress reports on their plans (BGM et al., 2011; DH, 2014). In particular, the United Kingdom is monitoring progress against published outcome measures. A key role is played by the new English surveillance programme on antimicrobial utilisation and resistance (ESPAUR) which measures the impact of surveillance systems and antimicrobial stewardship on resistance. ESPAUR has been producing annual reports since 2014. Each year since 1998, France has issued progress reports focused on antibiotic consumption (Observatoire National des Prescriptions et Consommations des Médicaments, then Agence Nationale de Sécurité du Médicament et des produits de santé, since 2008)(Ministère du Travail, de l'Emploi et de la Santé, 2006). Since 2002, France also produces annual reports on antibiotic consumption in veterinary sector. The United States sets out to provide annual updates on progress to the President in addition to the issue of yearly reports on progress regarding reduction of inappropriate antibiotic use as well as prescribing trends. Canada also plans to make regular updates on progress being made and reviews include evaluations on the effectiveness of the 2014 AMR awareness campaign by the Public Health Agency of Canada. At the international level, the EC and TATFAR have already published progress reports (EC, 2015; TATFAR, 2014), WHO is due to present their report for 2017 and GHSA also plans to measure success.

49. Some countries have detailed targets with quantifiable measures. France has set targets for 2016 to reduce antibiotic consumption by 25% from 2011 estimates. The same goal of 25% has been also set for the veterinary sector (République Française, 2012). Furthermore, quantitative indicators on prescribing practices to help measure and tackle AMTs over-prescription in the community has been implemented (République Française, 2006). For practitioners these new aims are set to limiting antibiotic treatment to 37% of patients aged between 16 and 65, with the exception of patients suffering from long-term illnesses. The United States have set targets around incidence of ARMs categorised as presenting urgent or serious threats, that are to be reached by 2020 (The White House 2015). For urgent threats, targets are to reduce overall incidence of *C. Difficile* and resistant-Enterobacteriaceae infections by 50 and 60% compared to 2011 estimates (The White House, 2015). Further *N. gonorrhoeae* infections are to be maintained below 2% compared to 2013 estimates. For serious threats, targets have been set to reduce incidence or rate of disease amongst specified ARMs by 15-50% compared to previous estimates. A national target of 50% reduction in inappropriate use of antibiotics for outpatient settings has also been set to be achieved by the United States in 2020.

3.2.3 AMR national policies in G7 countries: unified overall goals and policy plans, yet diverse priorities

50. The majority of G7 countries have targeted strategies or action plans to address this issue and most have implemented national plans (table 2) to achieve AMR policy objectives. The majority of policy objectives focus on human health in both hospitals and the community, and address these aims by:

1. Preventing new cases

2. Conserving use of current AMTs

3. Supporting research and development of novel treatment approaches

51. Overall, G7 countries are strongly committed to tackling AMR and have aligned plans, however for some actions their priorities vary, based on country-specific issues. Appropriate antimicrobial stewardship, prevention as well as surveillance and monitoring are priorities for all countries, yet few have specified quantifiable targets. France has amongst the highest AMT prescription rates in Europe. In addition, bacterial infection resistance remains high for some ARMs (e.g. the *S. aureus*) despite the recent significant decreases in the incidence of infections caused by MRSA. Tackling prescriptions and prevention for reducing the spread of AMR features strongly. Research and innovation is also a focal point on most action plans, and particularly prominent amongst Germany, the United Kingdom, the United States and the EU. One-health approaches are incorporated on most action plans and notably marked amongst Canada, Germany, France, Italy, the United Kingdom, the United States and EU. International efforts are priorities for Canada, Germany, France, the United Kingdom and the United States. The UK has established an independent review on AMR with a global focus to look at issues around the new drug pipeline. Awareness, education and training efforts are also incorporated in existing country action plans, and features strongly amongst Germany, the United Kingdom and the EU. The reminder of this section provides a detailed review and cross-country comparison of the different priorities of national plans to tackle AMR in G7 countries. To facilitate cross-country comparison, priorities are divided into seven homogeneous categories.

Table 2. Policy plans and priorities in G7 countries, EU, WHO

	WHO	Canada	Germany	France	Italy	Japan	United Kingdom	United States	European Union
Reference documents	WHO global strategy: 2014	Federal Action Plan, 2015; Federal Framework for Action, 2014	DART 2020; 2015	Plan national d'alert sur les antibiotiques 2011-2016	National prevention plan 2014-2018	MHLW recommendations on AMR, 2015 (focus on prevent nosocomial infect)	UK 5-year AMR strategy: 2013-2018 (DH, 2013)	National Action Plan for Combating Antibiotic-Resistance: 2015	Action Plan Against the rising threats from Antimicrobial Resistance; 2011
Antimicrobial stewardship	optimize the use of antimicrobial agents	strengthen the promotion of appropriate use of AMTs (human & vet)	Improve feedback on antibiotic use data; develop guidelines on use & communication between doctor & patient	Reduce & improve antibiotic prescriptions in hospitals & GPs; certification to improve quality & safety of care in health facilities		antimicrobial stewardship for healthcare personnel	optimise prescribing practice in human and animal health sector	CDC "get smart about antibiotics" programme	strengthen the promotion of the appropriate use of AMTs in human medicine in all member states
Prevention and control (P&C) of ARMs	reduce the incidence of infections	Conserve effectiveness of existing treatments through infection P&C guidelines, education, awareness, regulations & oversight	Disrupt infection cycles and avoid infections	The 2015 National Action Plan to Prevent Health Care-Associated Infections (Propias) aims at reinforcing control of ARMs	regions should put interventions in place for preventing AMR (include media campaigns & education)	infection control; outbreak response	improve infection P&C practices	slow the emergence and prevent spread of ARMs	infection P&C in healthcare; develop & strengthen multilateral & bilateral commitments for P&C of AMR in all sectors
Surveillance & monitoring (S&M)	strengthen knowledge through S&M	establish & strengthen S&M systems to id new threats & changing patterns in AMR use (human & vet)	Early detection of resistance developing	Establish network dedicated to right use of antibiotics; revision of indicator on antibiotics in hospital	Put in place S&M system to measure consumption of antibiotics in hospitals & community	Strengthen surveillance	better use & access to S&M data in human and animal health sector	CDC, FDA & USDA implementing surveillance programmes	strengthen S&M system on AMR & AMTs consumption in human medicine
Innovation, Research & Development (R&D)	strengthen knowledge through research	Creating new solutions to counteract loss in antimicrobial effectiveness through R&D	Improve & receive therapy options; support R&D	France would encourage EC to create a specific procedure for antibiotics			develop new AMTs & diagnostics; better identification & prioritisation of AMR research needs	develop & use rapid & innovative diagnostic tests; new AMTs; other therapeutics & vaccines	promote, reinforce & co-ordinate collaborative R&D for AMTs

	WHO	Canada	Germany	France	Italy	Japan	United Kingdom	United States	European Union
Animal & agriculture sector, including one-health approach		work with vet & agri partners to strengthen regulation of vet medicines & medicated feeds; facilitate access & adoption of alternatives to reduce use of AMTs	Strengthen one-health-initiative at national & international level	EcoAntibio plan dedicated to vet sector started in 2012; links between human & vet sectors on fight against AMR.	Regions to implement interventions to rationalise use of AMTs in livestock and a national information system to track vet AMTs	implementation of risk management measures of AMR based on risk assessment & risk analysis principle; prudent use guidelines for vet medicine; Japanese vet AMR monitoring system(JVARM)	Publication of: "UK one health report: antibiotics use in humans and animals"	strengthen national one-health surveillance efforts to combat resistance	reinforce vet drugs regulation; introduce recommend for prudent use in vet medicine; EU animal health law proposal; promote analyses of new vet AMTs; strengthen surveillance systems on AMR & AMT consumption in vet med
Cross-country collaborat & international efforts		promote innovation through funding collaborative R&D on AMR domestically & internationally	Capacity building as well as R&D with international partners	research in European & international context and encouragement at national level			strengthened international collaboration; co-sponsorship of 2015 WHO resolution	improve international collaboration and capacities for AMR surveillance, P&C and antibiotic R&D	
Increase awareness & education	improve awareness & understanding of AMR	Infection P&C; awareness activities	Promote awareness; strengthen capacities	Public campaigns were launched in 2002, then in 2010, with a new slogan		Enlightenment to the public	Public/professional European AMTs awareness day; activity with Royal Colleges	CDC Get Smart programme	
Training (tr) of health professionals (HPs)			Establish AMR online platform for HPs; strengthen tr on hygiene; incorporate AMR into clinical tr	Good use of AMTs & ARM are part of tr for health students; infectious diseases & prevention taught in schools (e-Bug project).		Strengthen role of health professionals (infection control nurses)	Improve professional education, tr & public engagement	CDC to inform & physicians, agricultural workers, and members of the public; CDC to train HPs	Strengthen communication, education & tr; survey & comparative effectiveness research
Financial sustainability	ensure sustainable investment in countering AMR	-	-	-	-	-	-	-	-

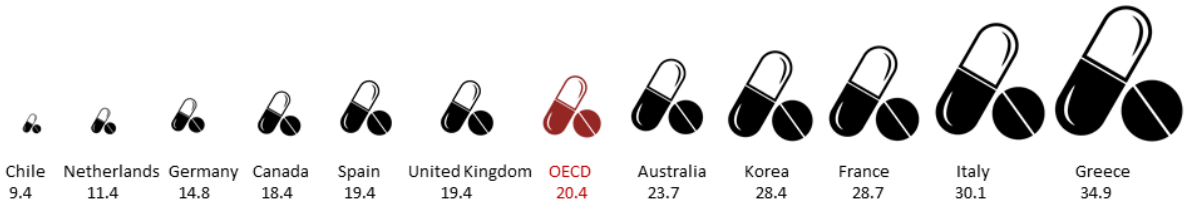
3.2.3.1 Policy priorities: promoting antimicrobial stewardship

52. Volumes of antimicrobial consumptions in humans vary widely across OECD countries (figure 10) with Chile and Netherlands reporting the lowest volume and Greece and Italy reporting volumes around 1.5-1.7 times the OECD average. All G7 countries incorporate antimicrobial stewardship programmes (i.e. educational interventions among healthcare personnel to rationalize antimicrobial prescription) in their plans and most have targeted approaches. Canada, France, the United Kingdom and the United States specifically plan to enhance appropriate prescribing of AMTs.

53. Canada plans to maintain antibiotics centre on infection prevention and control guidelines, education, awareness, regulation and oversight. In 2013 antimicrobial use was the highest amongst young children (0-5 years), with use in this group being 30% higher than the general population (Government of Canada, 2014). For this age group healthcare professionals and patients play a key role, hence Canada plans to evaluate the effectiveness and expand reach of their 2014 pilot awareness campaign targeted at these two groups. Further prospective measures include the promotion of optimal use amongst consumers through labelling of products with recent AMR knowledge.

54. In 2009, France had the third highest antibiotic consumption amongst EU countries, hence set a target to reduce consumption by 25% in order to be aligned with other EU levels, and particularly focuses on reducing prescription rates at the general practitioner level (République Française, 2011). The current plan includes establishing a network dedicated to the right use of antibiotics with the help of regional (agence régionale de santé [ARS]) structures, using certification tools to improve the quality and safety of care as well as evaluate professional practices regarding AMTs. Use of rapid diagnostic tests is also supported in order to facilitate appropriate use of AMTs and prevent use amongst patients with viral infections.

Figure 10. There is a high variability of antibiotic consumption across OECD countries. Antibiotic consumption in 2013 (defined dose per 1000 inhabitants per day)



Source: Authors' analyses on OECD Health Data

55. United Kingdom focuses on optimising prescribing practices with the potential use of genomic technologies for diagnostics. The United Kingdom National plan also includes the development of a framework on optimising prescriptions and antimicrobial prescribing quality measures have also been established, which aim to reduce prescribing and promote use of narrow spectrum antibiotics over broad spectrum use (DH, 2014). Community and hospital prescribing practices also aim to be improved and supported via enhanced data collection and feedback mechanisms. Further, the United Kingdom also plans to evaluate a pilot study and target behavioural changes amongst community prescribers and the public. Targets on antimicrobial prescribing have been set to return to 2010 levels in the primary care setting and 2012 levels in secondary care (DH, 2014).

56. By 2020 the United States plans to increase and expand ongoing antibiotic stewardship programmes (e.g. the CDC get smart about antibiotics programme) in hospitals and improve practices across all healthcare settings. Targets have been set to reduce inappropriate antibiotic use by 50% amongst outpatients and 20% amongst inpatients (The White House 2015).

3.2.3.2 Policy priorities: preventing the spread of antimicrobial-resistant microorganisms

57. Prevention features strongly amongst G7 countries AMR plans, yet individual approaches are quite varied. Germany focuses efforts on hygiene and aims to disrupt infection cycles early. Länder will be supported in developing their existing regional networks and by providing expertise on ensuring hospital hygiene standard compliance. Plans also include ensuring that Länder employ hygiene specialist staff in clinical facilities and supporting the development of hygiene standard indicators (BGM et al., 2015).

58. France plans to control spread of resistance by strengthening alert response mechanisms between diagnostic laboratories, clinical teams and hygiene specialists via regional (ARS) and national (direction générale de la santé [DGS]) structures (République Française, 2011). Plans also specify that ARS will oversee the application of recommendations on outbreak control.

59. Italy places ownership of prevention on the regions and highlight media and educational campaigns. Japan and the United Kingdom plan to prevent cases through improved infection control. Further to this, Japan particularly plans to improve outbreak responsiveness in medical institutions. Japan is also promoting efforts to establish a regional cooperation network among medical institutions to increase the level of infection control in the whole region. The United Kingdom plans to strengthen accountability and issue guidance on prevention to health professionals. This also includes strengthening the legislative framework on infection prevention and control, where compliance is to be overseen by care quality commissions of the Department of Health (DH, 2014).

60. The United States plans to implement AMR specific public health programmes across individual States, monitoring and feeding back on regional resistance trends, as well as providing technical assistance for healthcare facilities (The White House 2015). The EU particularly focuses on strengthening prevention and control commitments, with the healthcare setting being a central feature.

3.2.3.3 Policy priorities: surveillance and monitoring

61. Surveillance and monitoring are focal points in G7 country action plans. All countries have systems for monitoring AMR incidence and antibiotic use in humans, however capacities vary and there are only a limited number of international efforts as well as a limited standardization between surveillance efforts. Two notable exceptions are the EU EARS-net (European Antimicrobial Resistance Surveillance Network) and the ESAC-net (European Surveillance of Antimicrobial Consumption Network) systems, two European-wide networks of national surveillance systems, providing reference data on, respectively, antimicrobial resistance and antimicrobial consumption. Obtaining and reaping full benefits of surveillance data on AMR remains a challenge for countries even where systems are well developed. For example, in the United Kingdom only 60% of data has been obtained from medical laboratories and standard methods for analysing this data have yet to be incorporated (DH, 2015). Canada, France and Italy plan to establish and strengthen dedicated surveillance systems, whereas Germany, the United Kingdom and the United States particularly aim to expand and improve existing dedicated capacities.

62. For Canada this entails establishment of the Canadian Antimicrobial Surveillance System (CARSS), which coordinates and integrates existing AMR and antimicrobial use surveillance systems. Further to this, CARSS will also review and confirm priority microbes to be included on the existing AMR organism surveillance list, which currently includes *C. difficile*, MRSA, *S. aureus*, and Vancomycin-resistant Enterococci (Government of Canada, 2015).

63. France's plans on surveillance and monitoring of AMR include strengthening alert response mechanisms, and evaluating prescribing practices (see previous two sections).

64. Germany focuses on early detection of resistant pathogens (e.g. MRSA, *E. Coli*, etc.). This includes adding further resistant organisms to the existing obligatory register and identifying barriers as well as possible solutions for improving diagnostics (blood-borne infections and *C. difficile*). Further plans include expansion of existing surveillance systems (covering national resistance data on in- and out-patients and prescriber-feedback systems), strengthening national reference centres and laboratories as well as a pilot project on the inclusion of viruses and fungi in existing systems (BGM, 2015). With regards to animal health, existing national monitoring capacities being delivered under the German national monitoring program (GERM-Vet) are to be expanded and include further resistant bacterial species (BGM et al., 2015).

65. Italy is introducing an electronic prescription system for all the veterinary drugs, AMTs included. The system is designed to link sales data with prescriptions so to increase the effectiveness of pharmaco-surveillance and monitoring of use of AMTs in the livestock sector (Ministry of Health - Italy, 2015).

66. Japan is promoting the Japan Nosocomial Infection Surveillance (JANIS) programme to collect and make available to medical institutions a range of information on the incidence and prevalence of nosocomial infections and ARMs. Participation of the medical institutions to the project is on a voluntary basis.

67. The United Kingdom aims for better access and use of surveillance data. This includes developing the capacity for collection and analysis of baseline data on prescribing trends and monitoring of resistance, which will facilitate measuring outcomes of overall interventions (DH, 2014). Further to this, new quality measures and national indicators are being developed by the United Kingdom's executive health agencies to help improve standards in care and patient outcomes (DH, 2014).

68. The United States particularly aim to strengthen national surveillance and integrate one-health into their surveillance efforts (The White House, 2015). This includes improved data sharing as well as expansion and improved coordination of existing services being delivered by the National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMs) collaboration between the CDC, FDA and U.S. Department of Agriculture (USDA). Further plans include standardisation of resistance testing via a regional laboratory network, provision of genetic bacteria characterisation capacities, as well as enhanced monitoring of antibiotic sales and usage.

3.2.3.4 Policy priorities: research and innovation

69. Canada, Germany, United Kingdom, United States and the European Union have made research and innovation an important feature in their action plans. France particularly plans to support research on AMTs and AMR at the international level (see section 3.2.3.6 for international efforts) and encourage efforts at the national level.

70. Canada prioritises development of vaccines in their innovation plans, hence aiming to reduce dependence on antibiotics (Government of Canada, 2015). Further efforts in support of this include enhanced collaboration between PHAC (the Public Health Agency of Canada) and the Canadian Institutes of Health Research, for the establishment of the Canadian Immunization Research Network (CIRN). This national network aims to develop and test methodologies on the evaluation of vaccines. Commercialisation of innovative drugs, diagnostics and other technologies related to AMR are being supported at the federal level, and prospects of similar frameworks as the agreement between Canada and the Bill and Melinda Gates Foundation on HIV are under consideration for application with AMR. Nationally and globally, barriers to innovation will also to be assessed to identify areas requiring support.

71. Germany particularly wants to support R&D, improving therapy options. For supporting R&D, resistance causing agents and characteristics are to be analysed in overarching areas between humans, animals and the environment (box 5). For humans this includes research on the spread of resistance, flagship projects on training for medical staff, application of national and local guidelines as well as determining the efficacy of interventions. Working with the research and pharma industry and within the framework of the 'Pharmadialog', a task force on antibiotic research is to be established, and barriers to R&D are also to be identified. Under the G7 presidency, Germany also addresses questions concerning the development of new AMTs, alternative treatment options and diagnostics.

72. The United Kingdom focuses on developing new drug treatments and diagnostics as well as identifying and prioritising specific AMR research needs. This includes commission of a review into the antimicrobial drug pipeline and diagnostics across the NHS, establishment of a new AMR Research Funders Forum under the Medical Research Council (MRC) lead, as well as a research unit under the National Institute for Health Research (NIHR) lead (DH, 2014). The UK has also initiated a review looking at the economic issues surrounding AMR, including how to incentivise the drug pipeline and how to better use AMTs to treat illness. The review aims at identifying a range of proposals that can form the basis of a new, strengthened, global effort (AMR-Review, 2015).

73. The United States want to focus on development and use of diagnostic tests specific to the identification and characterisation of AMR, as well as accelerate research from basic to applied research on AMTs, other therapeutics and vaccines. The United States have accelerated efforts to advance the discovery and development of novel antimicrobials through adding or increasing funding mechanisms by National Institute of Health, the Defence Threat Reduction Agency, and the Biomedical Advanced Research and Development Authority at Health and human Services.

74. The EU plan to promote collaborative R&D efforts on new AMTs as well as reinforce and co-ordinate research efforts.

3.2.3.5 Policy priorities: the contribution of the livestock sector

75. Virtually all the reviewed policy plans contain specific sections about what usually goes under the name of 'one-health' approach (box 5). For completeness' sake, this section provides an overview of the policy priorities on this topic in G7 countries.

76. Canada wants to strengthen the regulatory framework surrounding veterinary medicines and medicated feed as well as facilitate access and support research and innovation on alternatives such as vaccines for animals. Agriculture and Agri-Food Canada's also plan to support and conduct research on improvement in animal production practices in addition to disease prevention and treatment.

77. One-health features strongly in Germany's plans, and approaches include addressing AMR issues such as waste water management through continuation of the interministerial AMR working group, supporting research on zoonoses through renewed research agreements between Ministries. Further plans entail, various monitoring activities, including monitoring resistance of zoonoses beyond those obligatory by the EU, expanding and standardising laboratory capacities, implementing laws on use of AMTs in animals, and continued antibiotic consumption registration amongst veterinary doctors. Developing further legislation on use of antibiotics amongst animals, early disruption of transmission through improved animal husbandry and vaccination are also included. Regional programmes are to be supported and flagship models are to be promoted, as well as targeting food-chains by determining efficacy of control programmes and developing hygiene criteria and research on hygiene measures in food-chains. Finally, there are also extensive research and development plans, focused on preventing emergence of resistance and prevention of transmission.

78. France's plans on reducing AMR in veterinary medicine centre on five axes (République Française, 2011). The first aim is to promote good practice and raise awareness, provide training on biosafety and proper use of AMTs, as well as the developing self-assessment tools for livestock farmers and technicians. The second aim is to develop alternatives to antibiotics, including promotion of good practice and research programmes for new solutions such as preventive use of vaccines amongst animals. The third aim is to reinforce controls and reduce high-risk practices, which includes improving evaluation of marketing of antibiotics, particularly with regards to generics, as well as measures such as inclusion of health education messages on antibiotic packaging and veterinary prescribing restrictions for AMTs critically important in human medicine. The fourth aim is to consolidate monitoring systems on antibiotic consumption and AMR by measures such as continued and intensified monitoring of antibiotic sales, incorporating the age of livestock treated and set up of an observatory on antibiotic use in veterinary practice. The fifth aim is to promote European approaches and international initiatives on livestock and veterinary practices.

79. Italy stresses the need for regions to implement interventions on the rationalisation of antibiotics in livestock. In addition, there are plans to develop a national information system which aims at tracking the use of drugs, including AMTs, for veterinary use.

80. Japan's response to rising rates of AMR in the livestock sector is based on a three-pronged approach. First, Japan has based the development of specific policies and risk management measures in the area taking as reference point the risk analysis principles mentioned in the code of practice developed by the Codex Alimentarius Commission (Ministry of Agriculture, Forestry and Fisheries, 2012). Risk management measures are continuously conducted and reinforced in accordance with the risk level. Second, in response to international concern about the impact of AMR on public health, Japan has established in 1999 the Japanese Veterinary Antimicrobial Resistance Monitoring system (JVARM). JVARM monitors levels of AMR in zoonotic and animal pathogenic bacteria and monitors quantities of AMTs used in animals. JVARM collaborates with JANIS (Japan Nosocomial Infectious Surveillance: AMR surveillance for human health sector). Finally, Japan has published the Prudent Use Guidelines for veterinary AMTs (Ministry of Agriculture, Forestry and Fisheries, 2013). The guidelines aim i) to keep animals healthy by observing high hygiene standards (based on the animal infectious diseases control law) and to prevent infectious diseases with vaccinations or other means; ii) to determine treatment measures only after veterinary diagnosis; iii) to choose appropriate AMTs after a microbial sensitivity test; iv) to preserve critically important AMTs (e.g. fluoroquinolones and cepharosporins) and use them only after a first ineffective treatment; v) to monitor AMTs' efficacy over time so to adapt therapy if necessary; vi) to share information and raise AMR awareness in all the stakeholders.

81. The United Kingdom incorporates one-health approaches throughout their 7-point action plan, and examples include strong infection control and prevention practices to control cross-infection and educational programmes for veterinary teams. Further, encouraging and supporting animal keepers to improve animal husbandry and bio-security practices through measures such as appropriate housing design and isolation of sick animals. Preventive measures include better use of intelligence and early warning systems as well as cost-effective use of vaccines. Surrounding antimicrobial stewardship, local prescribing practices will be audited to assess the effects programmes on animals and preventive antibiotic use is to be minimised in animals through advocacy and guidance. AMR research needs in animals are to be identified by Defra's Antimicrobial Resistance Co-ordination Group (DARC), and international efforts of the FAO and OIE are to be supported. The United Kingdom has also published a surveillance report (Public Health England & Veterinary Medicines Directorate, 2015) which brings together the most recently available data on AMR rates in key bacteria that are common to animals and humans. The report also includes details on the amount of antibiotics that are sold for animal health and welfare as well as antibiotics prescribed to humans.

82. The United States also incorporate one-health approaches throughout their action plan. Specific goals include eliminating use of medically-important AMTs for growth promotion in food producing animals by 2020. The United States have already spearheaded voluntary efforts to remove medically important antibiotics from animal food and water. Particularly strengthened surveillance and monitoring efforts feature strongly with respect to one-health approaches.

83. The EU plans to revise legislation on veterinary medicine and medicated feed, as well as issue recommendations on prudent use in veterinary medicine. Revised legislation covers market authorisation and use of veterinary AMTs, preservation of certain antibiotics for human use, requirements on information sourcing and prohibition of preventive antimicrobial use in medicated feed (EC, 2015). EU recommendations cover use of critically important antibiotics (quinolones, cephalosporines and macrolides) which are used to treat both humans and animals. Further, existing and revised legislative obligations are being verified amongst member states, with plan to present findings in a 2016 report.

Box 5. One-Health approach

'One-Health' is a concept which acknowledges that human health is interconnected with animals, agriculture and the environment. It has been known for many years that diseases can pass between animals and humans, and that use of AMTs can further drive resistance. Achieving one-health therefore requires closer collaboration between human and veterinary health professionals.

International efforts have been made by the EU, the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE). EU institutions including the European Medicines Agency (EMEA), European Centre for Disease Prevention and Control (ECDC) and European Food Safety Authority (EFSA) have issued guidance on infection prevention and control. Further, the European Commission have issued practical guidelines for member states focused on preventing overuse and misuse of antibiotics in the veterinary sector (EC, 2015). The FAO and OIE have issued various guidelines on surveillance of resistance and prudential use of antibiotics in animals (FAO, 2005; FAO, 2011; OIE, 2014).

3.2.3.6 Policy priorities: cross-country collaboration and international efforts

84. As described in the section on "international plans and efforts to tackle antimicrobial resistance" and in box 4, G7 countries and EC play a central role in the global fight against antimicrobial resistance. More in detail, Canada, Germany, France, the United Kingdom and the United States specifically incorporate international efforts into their national plans. Canada and France particularly plan to promote R&D activities with international collaboration. Germany has used their G7 presidency to promote international collaboration on AMR. The United Kingdom has focused international efforts on the WHO resolution being adopted and for the GHSA AMR action package to be developed. The United States focuses their international collaboration on prevention, surveillance, infection control and R&D.

85. Canada's international support includes the 'Joint Programming Initiative on Antimicrobial Resistance' which is a collaborative platform of 19 countries seeking to overcome fragmentation of national research programmes on AMR by coordinating resources and actions.

86. Germany's international plans include supporting select countries in implementing their own Global AMR action plan and supporting AMR efforts during Germany's G7 presidency.

87. International efforts surrounding surveillance of antimicrobial use is being coordinated by TATFAR and carried out by two of the TATFAR member institutions: CDC and ECDC. Recent recommendations by TATFAR (TATFAR, 2014) included the establishment of standard methods for measuring antimicrobial use in hospitals.

3.2.3.7 Policy priorities: awareness, education and training

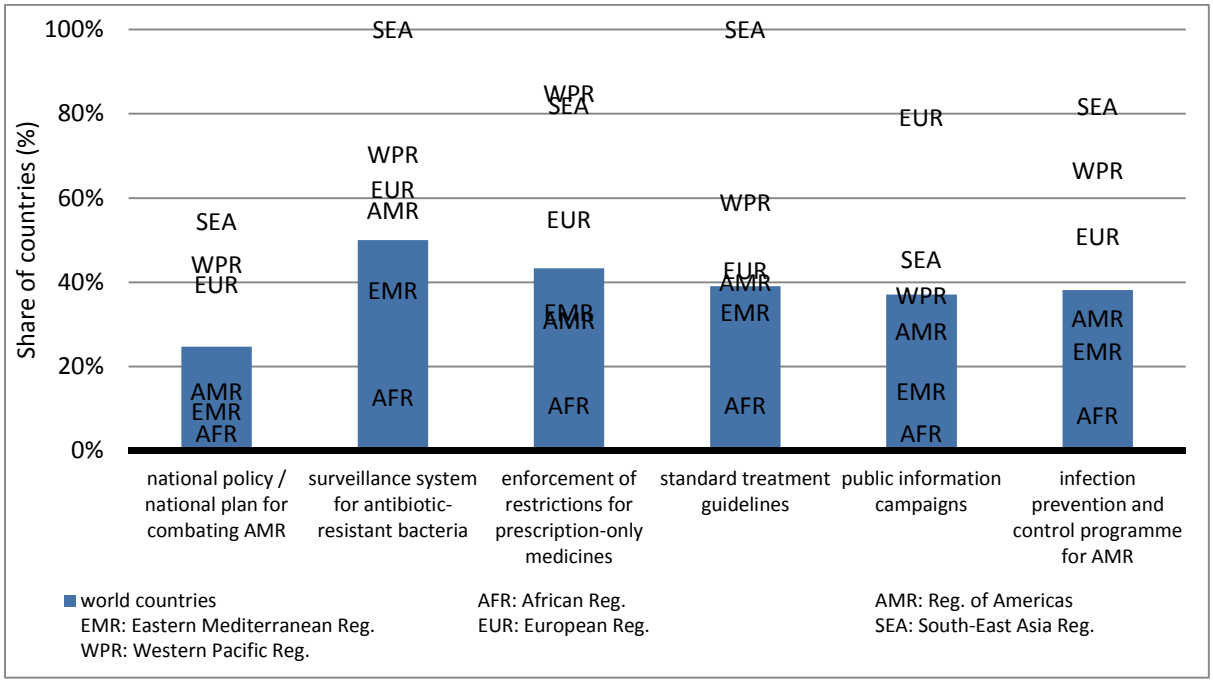
88. Overall, all G7 countries incorporate awareness, targeted at the population, as well as education and training, targeted at the medical community, within their plans. Germany, the United Kingdom and the EU have further specified details.

89. Germany plans to use education measures amongst the population, as well as targeting patients with specific information. Hospitals are also obliged to incorporate information on hygiene standards in their quality reports that are comprehensive to the public. Communication strategies between clinician and patient are also to be developed. Further measures targeting medical professionals include online AMR platforms, strengthened training with focus on outpatient services and discussions on obligatory AMR training. Japan also plans to address the role of health professionals including infection control nurses. In Italy and the United Kingdom, plans span across professional education and training to public engagement. In the United Kingdom, measures include and updated e-learning programme on infection and prevention within the 2002 established 'Skills for Health' organisation and a revision of training guidelines on infectious disease and microbiology by the Royal Colleges. The EU plans to enhance communication, education and training as well as establish comparative effectiveness research.

3.3 National plans and efforts to tackle antimicrobial resistance beyond G7 countries

90. Although globally recognised as a key priority, only a relatively small number of countries have implemented response plans and effective actions to address the rising issue of AMR (figure 11). Worldwide, only 48 countries (25% of the 194 WHO member countries) have put in place national plans or national policies to tackle AMR. Regions of South-East Asia (55%), Western-Pacific (44%) and Europe (40%) are the areas with the highest proportion of countries with such plans. Conversely, only a small share of countries in the Regions of the Americas (14%), Eastern-Mediterranean (10%) and Africa (4%). The implementation of well-financed action plans is the first step, and one of the principal tools, to fight AMR. Action plans should embrace a multisectoral and multifaceted actions.

Figure 11. Percentage of countries at the global and regional level that have implemented relevant actions and programmes to tackle AMR



Source: OECD analyses on WHO, 2015

91. National surveillance mechanisms are key for understanding and monitoring the spread of antimicrobial-resistant microorganisms. Effective surveillance systems can be used to analyse the patterns and trends of spreads of resistant microorganisms and are an essential tool to put in place, in a timely fashion, responses to the emergence of infectious diseases outbreaks caused by resistant agents. Globally, only half of world countries (97 countries) have put in place a surveillance system to monitor antibiotic-resistant microorganisms. While the majority of countries in the Regions of South-East Asia (100%), Western-pacific (70%), Europe (62%) and Americas (57%) have implemented surveillance systems, the Eastern-Mediterranean (38%) Region and the African Region (13%) still face large implementation gaps.

92. Only 40% of world countries implements effective actions aimed at tackling AMR. The fight against AMR requires the implementation of effective actions aimed at rationalising the use of antimicrobials and at preventing the spread of antimicrobial-resistant microorganisms (see section 4 for an in-depth review of actions). Still, only a minority of countries have currently in place policies as: i) enforcement of restrictions for prescription-only medicines; ii) use of standard treatment guidelines for communicable diseases; iii) public information campaigns to educate the population on the correct use of AMTs; and iv) prevention and control programmes to limit the spread of infections. Countries in the Regions of South-East Asia and Europe are generally more likely to have implemented some of these actions. Contrariwise, only about 10% of counties in the African Region and less than one third of countries in the Eastern-Mediterranean Region report having such programmes in place.

4. Tackling antimicrobial resistance: what works in preventing the development and the transmission of ARMs

93. Interventions aimed at avoiding the emergence of new antimicrobial-resistant microorganisms (ARMs) and at limiting their transmission play a key role in containing the health and economic burden caused by antimicrobial resistance (AMR). Overuse of AMTs is a principal factor for the emergence of AMR. Antimicrobial stewardship programmes have been shown to decrease consumption of antibiotics both in the hospital sector (up to 40% in some settings) and in the community. Programmes to increase immunisation rates may play a role to decrease consumption of antibiotics but, currently, no vaccines exist for the most important ARMs. Carefully designed fiscal policies may be effective in increasing the price and in decreasing consumption of antibiotics but how to best target only inappropriate use is still to be determined. Actions aimed at preventing the spread of infections present further opportunities to reduce antibiotic use. For example, early detection through point-of-care testing and rapid diagnostics would allow precise diagnoses in primary care and targeted therapies. Measures to reduce infectivity and to enhance hygiene and sanitation in hospitals would, instead, avoid transmission across patients.

94. This section provides an overview of the key actions that G7 and OECD countries can put in place to avoid the emergence and to limit the transmission of ARMs. The focus is on presenting evidence on the effectiveness and cost-effectiveness of interventions. The first part presents options aimed at avoiding the emergence of ARMs and, more in details, it examines the effects of stewardship programmes, enhanced immunisation and the use of fiscal policies. Part two, instead, looks at actions aimed at limiting the transmission of ARMs. This part examines the effects of measures to allow an early detection of ARMs, of measures to reduce infectivity and, finally, of measures to enhanced hygiene and sanitation in medical facilities.

95. Actions to tackle the spread of AMR reviewed in this report fall under two main categories: i) avoiding the emergence of resistance and; ii) preventing transmission of ARMs (table 3). Available evidence on these two categories tends to heavily centre on hospital and community interventions. More in detail, hospital settings are often considered ‘hotspots’ for the clinical manifestation of problems related to AMR, where most of the consequences and excessive costs are incurred. Hence, many interventions specifically focus on this setting. However, the community setting also plays a vital part in tackling AMR, particularly in relation to preventing the emergence of resistance. The overall implementation of successful interventions in these two settings is contingent upon two factors. First, there is the need for a strong and wide consensus on actions, particularly in relation to guidelines and legislation, where the medical community plays a key role. Second, there is the need for a strong commitment on these actions, in order to secure long-term effects, which can be ensured through solid leadership, funding and continuous review of progress.

Table 3. Overview of actions aimed at preventing the emergence and the transmission of ARMs

	Preventing emergence				Preventing transmission		
	Rationalisation of prescriptions	Immunisation	Alternative treatments	Early detection	Reducing infectivity	Increasing hygiene	Reduce susceptibility
Aims	conserving precious antimicrobial resources for cases with clear clinical indication	preventing infections and enhancing heard immunity (existing and new vaccines)	very varied (e.g.; probiotics for recolonization of healthy bacteria)	enhancing provision of information. From diagnostics (POC testing) to surveillance	containing infections	decontamination (cleaning practices) and preventive barriers	from boosting immune system (supplements/foods) to promoting health (exercise)
Examples of interventions	tax/price incentives regulation of prescriptions behavioural interventions educational campaigns delayed-prescriptions antimicrobial cycling	uptake of existing vaccination programmes (school-based)	probiotics (Lactobacillus and Bifidobacterium yoghurts) cranberry juice as prophylaxis for UTI's	enhanced provision of testing (e.g.: TB rapid molecular assay) enhanced infrastructure and new devices	isolation of patients (predominantly hospital setting) decolonisation	improved cleaning practices (specialist staff) OH-based hand hygiene contact precautions (gowns, gloves, masks)	probiotics health promotion campaigns
Target group	prescribers, patients, community, pharma and R&D community	children in community (acknowledging parents role in uptake)	varied; from patients to community	medical community; GP and hospital level as well as executive agencies for surveillance	patients	medical community, patients, public	community, patients, schools
Potential bottlenecks	consensus on guidelines and legislation ownership on patients/community (shared decision-making)	developing vaccines for major resistant infections (MRSA, *C.difficile)* ensuring population coverage	strengthening evidence base	consensus on metrics funding; deep analysis on cost effectiveness protecting patient data	addressing psychological / ethical aspects of patient isolation	sustained efforts ensuring long-term commitment	reaching target group impact
Overarching bottlenecks	1. consensus on implementation (medical community key role in this), guidelines, legislation (need to foster dialogue) 2. commitment to plan (funding, review) 3. ensuring long-term effects 4. leadership						

4.1 Avoiding the emergence of antimicrobial-resistant microorganisms

96. Key interventions include the rationalisation of antibiotics prescription and utilization, increasing immunity and, when feasible, using alternative treatments (table 4). Overuse of antibiotics is a principal driving factor for AMR, and there is a correlation between national consumption and resistance rates (BGM, 2015), hence the rationalisation of antibiotics prescription and utilization features very strongly in in the policy plans of G7 countries. It has been found that between 51-80% of cases with respiratory tract infections are prescribed antibiotics, despite the fact that these are often caused by viruses and hence antimicrobial use is not appropriate (Shapiro et al. 2014; BGM, 2015). Further avenues preventing the emergence of resistance include limiting the overall need to use AMTs by increasing immunity with measures such as enhanced vaccination uptake. Alternative treatments also present further option, and simple actions can be effective such as consumption of cranberry juice for preventing urinary tract infections (Smith & Coast, 2012).

Table 4. Common interventions to avoid the emergence of antimicrobial-resistant microorganisms

Rationalisation of prescriptions and utilization	increasing the tax/price of antibiotics marketing/advertising restrictions of antibiotics reducing over-the-counter / online sales training of medical staff (educational, reminders) guidelines (restrictive vs. persuasive, stewardship) feedback (peer-review and monitoring systems) education of patients/public (mass media campaigns) delayed-prescriptions
Immunisation	existing vaccination uptake
Alternative treatments	probiotics (lactobacillus and bifidobacterium) cranberry juice as prophylaxis for urinary tract infections

4.1.1 Antimicrobial stewardship programmes

97. Excessive and unnecessary use of AMTs are key driving factors for AMR, hence the rationalisation of antibiotics prescription focuses on conserving these precious resources, thereby limiting the emergence of AMR. It is important to stress that these approaches aim to ensure continued access to antibiotics however their use should be limited to cases where there is clear clinical indication. Antibiotic stewardship programmes include interventions on regulation, guidelines, monitoring, education and campaigns to increase awareness among healthcare personnel. Prescribers in the medical community play an particularly important role, both in the hospital and community setting, however interventions also target a holistic spectrum of groups, including government, regulators, patients, as well as individuals within the population.

98. Both in the hospital and community setting, there is a large body of evidence and strong case for support on antimicrobial stewardship programmes. In the hospital setting a Cochrane review (Davey et al., 2013) showed that not only can AMR be reduced by interventions that aim to lower excessive antibiotic prescribing, but actions promoting effective prescribing practices can also improve clinical outcome on a short- and long-term basis. Antimicrobial stewardship formed a key part of a recent Californian flagship

programme, which achieved a 9.4% decrease in MRSA rates over a 3-year period (Epson, 2015). Further to this, hospital based programmes have demonstrated a 20-40% reduction in antibiotic prescriptions (Laxminarayan et al., 2013). In the community setting, a Cochrane review (Arnold & Strauss, 2009) found that evidence on bundles of interventions targeting prescriptions are strong, yet the evidence on effectiveness amongst individual interventions remains inconclusive. Nationwide programmes have great potential for impact. France, has achieved a 26% decrease in antibiotic prescriptions during the course of a multifaceted programme from 2002 to 2007, which particularly targets prescribers (Sabuncu et al., 2009; Bartlett et al., 2013).

99. Bottlenecks that need to be overcome include removing barriers such as overly-precautious prescribing practices and addressing the perceived demands of patients amongst prescribers. Clearer guidelines and consensus on prescribing practices, as well as improved diagnostic tests, may strengthen confidence in treatment choices. Further, behavioural interventions offer novel complimentary avenues for tackling AMR (box 6). Interventions that focus on patients and individuals in the community (e.g. interventions challenging the need for prescriptions) place ownership on individuals in an area where people may not have the necessary training or knowledge to take the correct decision. These are challenges that can be addressed through education as society faces an era of increasing shared decision-making and an evolving relationship between patient and healthcare professional.

Box 6. Behavioural interventions to tackle AMR

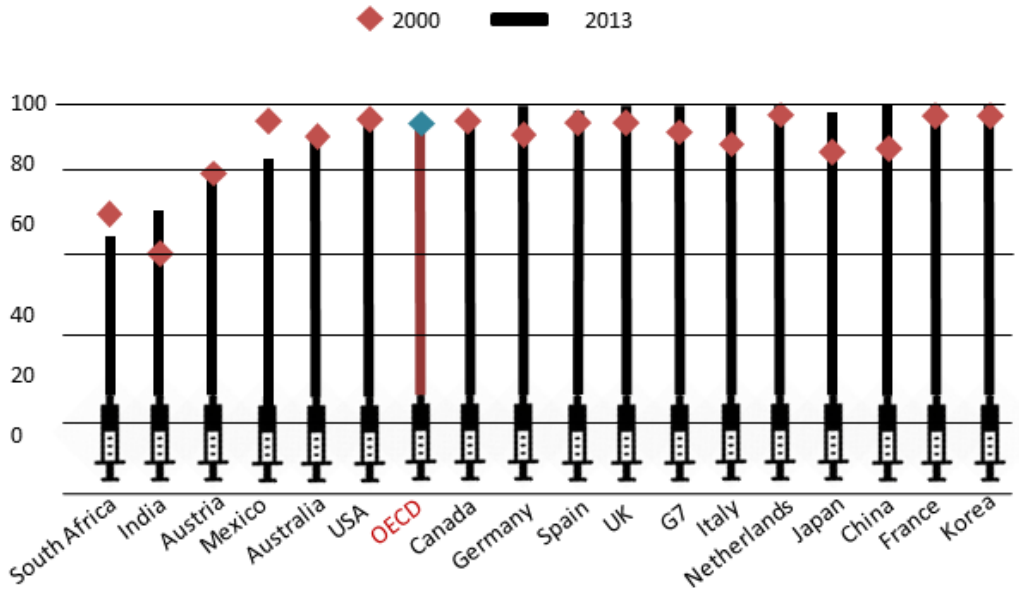
Behavioural interventions seek to complement measures on preventing emergence and spread of AMR. Behavioural interventions largely target prescribers, healthcare workers and the general public through measures that, through minimally invasive interventions (e.g. providing information, setting the correct behavior as the default option, etc.), encourage behaviour to be in unison with designated policies. Interventions include education, introduction of dedicated AMR improvement teams, compliance and feedback measures (e.g. through peer comparison). Behavioural interventions tend to be introduced as bundles of interventions, hence effectiveness of individual interventions is difficult to assess, however a systematic review (Aboelela et al., 2007) found that these bundles may significantly reduce healthcare associated infections or colonisation rates.

The United Kingdom has employed behavioural interventions to tackle AMR, which include a pilot on GP feedback mechanisms as well as the 'Antibiotic Guardian campaign', an antimicrobial stewardship awareness campaign. The pilot study underway targets prescribing practices and tests the impact of feedback letters from the Chief Medical Officer to GP's on their prescribing rates in comparison to national norms (DH, 2014). Effectiveness of these interventions have yet to be assessed, yet early success can be seen, with the Antibiotic Guardian campaign achieving over 10,000 pledges by the public and health professionals to follow stewardship principles.

4.1.2 Enhanced immunisation

100. Immunisations programmes aim to prevent infections and enhance herd immunity, hence also preventing the need to use AMTs as well as preventing transfer of ARMs. Most interventions are implemented in the community and include selective as well as mass (e.g. school-based) vaccination programmes. Figure 12 presents vaccination rates across G7 and selected OECD countries for three diseases diphtheria, tetanus and pertussis (DTP) with AMR potential. Vaccination programmes for these three diseases are part of national vaccination plans in many OECD countries. Literature on the effectiveness of vaccines as an effective tool to tackle AMR is only a relatively limited, but rapidly increasingly, area of study. There is however a vast body of evidence on the effectiveness of vaccines in relation to antibiotic sensitive bacteria and lessons can be learned from overarching themes such as the successful uptake of vaccination programmes.

Figure 12. G7 and OECD countries have high vaccination rates for diphtheria, tetanus and pertussis. Children vaccination rates in 2000 and 2013



101. Pneumococcal vaccine presents an example of the potential benefits that existing vaccines (table 5) can have in relation to AMR. Introduction of the this vaccine not only significantly decreased the prevalence of pneumococcal disease amongst vaccinated (82%) and non-vaccinated (39%) individuals within the study-region (Atlanta, United States), but was also linked to a decrease in AMR and antibiotic usage amongst the study population (Ravi et al., 2012).

102. Optimisation of existing vaccination programmes can contribute towards preventing AMR and there is substantial evidence on interventions aiming to improve immunisation rates which can help direct future interventions. A Cochrane review found patient reminder or recall systems in primary care settings to be effective at improving immunisation rates, regardless of patient age and type of vaccination (Szilagyi et al., 2002). Further, all reminder types (postcards, letters, telephone or autodialer calls) were effective, with phone calls being most effective yet also most costly. For programmes targeting children, parents play a key role in uptake of immunisations. It has been found that many children do not receive recommended vaccines, as parents are not aware of the importance of vaccinations, hence particularly educational interventions may be used to target parents (Kaufman et al., 2013). A Cochrane review found that there is limited and low quality evidence on the efficacy of face-to-face educational interventions targeting parents, yet it may be appropriate to include information on vaccination in other healthcare encounters (Kaufman et al., 2013).

103. Vaccines present great potential for limiting AMR, however currently no vaccines exist, which target the most important ARMs, such as MRSA and *C. Difficile*. Further bottlenecks to successful immunisation approaches include lack of uptake and delays in new vaccine market entry. England saw a record high of 2,000 measles cases in 2012, believed to be attributed to lack of MMR vaccination uptake in the wake of a fraudulent and later retracted research paper (Wakefield et al., 1998) claiming a link between autism and bowel disease and vaccine. Since, catch-up vaccination programmes and awareness campaigns have contributed towards achieving highest ever national MMR vaccination levels in England, with 90% of 5-years olds receiving the recommended two MMR doses (PHE, 2013; PHE, 2015).

Table 5. Examples of existing vaccines targeting bacteria with AMR potential and gaps for major AMR causing agents

	Disease	Pathogen
existing vaccines	Cholera	*V. cholerae*
	Diphtheria	*C. diptheria*
	Pneumococcal disease	*S. pneumoniae*
	Meningitis	*N. meningitidis*
	Meninigitis, pneumonia, epiglottis	*H. influenzae*
	Tetanus	*C. tetani*
	Meningitis, bacteremia/sepsis, middle ear infections	*S. pneumoniae*
	Typhoid fever	*S. typhi*
	Whooping cough (pertussis)	*B. pertussis*
no existing vaccines	MRSA	*S. aureus*
	Clostridium difficile	*C. difficile*
	Urinary tract infections (UTI's), gastoenteritis	*E. coli*
	Klebsiella pneumoniae	*K. pneumoniae*

Source: Adapted from Vaccines Europe (Anon n.d.)

4.1.3 Price policies

104. The enforcement of price policies to encourage or discourage consumption of certain goods is widely used as an effective and efficient public health tool (Sassi et al., 2013). More recently, experts and policy makers have started debating on whether the introduction of such approaches may be useful to rationalise the use of AMTs. The introduction, for example, of a targeted co-payment or a user fee on a specific antibiotic (or a class of antibiotics) may contribute to a decrease in consumption of that drug and to a change in the antibiotic mix which may improve the overall efficiency of antibiotic consumption. From an economic perspective, the rationale of applying financial incentives (e.g. taxes, levies, user charges, co-payments, etc.) on AMTs is to incorporate into the final price of the product the marginal cost of the negative externalities for the society caused by the (over)consumption of the antimicrobial itself.

105. The available evidence suggests that price and consumption of antibiotics are closely linked. The introduction in Germany of a new generic version of a fluoroquinolones caused the average price to decrease by about 36% (from EUR 3.85 in 1998 to EUR 2.47 in 2000). This, in turn, increased the demand for that class of fluoroquinolones by 46% (from 2879 defined daily doses in 1998 to 4214 defined daily doses in 2000) (Kaier K, 2013).

106. A number of studies across EU countries and the United States consistently conclude that antibiotics are a necessity good (e.g. as food) and that response to increases in price is generally inelastic. The majority of studies (Baye et al., 1997; Kaier, 2013; Masiero et al., 2010) report values of own-price elasticity ranging between -0.4 to -0.9 (i.e. a 10% increase in the price of antibiotics would decrease consumption by 4% to 9%). The effect of prices seems to be higher in the community compared to the hospital setting (Kaier, 2013). This means that in the community, a price increase produces a higher decrease in consumption. Evidence from Switzerland further suggests that differences across different levels of income are limited (Filippini et al., 2009).

107. If countries decided to introduce price policies to rationalise use of antibiotics, such actions should be carefully designed and should take into account multiple factors. Some of the key issues include:

- The policy should be designed so to specifically target inappropriate use of AMTs as opposed to total use of AMTs. An increase in the cost of AMTs is likely to decrease adherence to a prescribed therapy (Sinnott et al., 2013).

- The policy should maintain a balance between preventing overuse of AMTs and avoiding lack of access for people with lower income. Lack of access to quality medicines at an affordable price may, in fact, lead patients to switch to sub-standard medicines or to stop therapy before full recovery which create an ideal condition to grow ARMs.

- The policy should specifically target patients. In many OECD countries, patients do not directly pay for the drugs they consume. So, simply increasing the price of antimicrobials may merely increase the expenditure of the third-party payer (e.g. health insurances) without any tangible effect on the consumption.

- The policy should consider potential substitution effects. For example, Filippini (et al., 2007) found that an increase in the price of macrolides is likely to induce a higher consumption of newer (and usually more effective) antibiotics.

108. At least in principle, well-designed and implemented price policies may be used as an alternative or, more likely, as a complement to other forms of regulation. A modelling study of the implementation of a 10% tax on antimicrobials used to treat a resistant strain of *S. Aureus* in the United Kingdom (Smith et al., 2006), concluded that such measure would lead to improvements of the major macroeconomic indicators. GDP would increase by 0.04% and total governmental expenditure would fall by 0.075% (0.06% for the healthcare sector alone).

4.2 Preventing the transmission of antimicrobial-resistant microorganisms

109. The scale of the problem and modes of transmission for AMR have been well documented and demonstrated in the literature, hence in the wake of increasingly challenging treatment options, a central aim of policies in G7 countries is to prevent and control the transmission of existing resistance. It has been estimated that one-third of infections are avoidable (The White House, 2015), and hospital outbreaks of ARMs highlight that preventing transmission could help limit outbreaks (FAZ, 2015). Most interventions seeking to achieve this aim are centred on early identification, reducing infectivity, increasing hygiene and reducing susceptibility (table 6). The impact of these interventions could be huge for patients, as the estimated annual AMR incidence lies at 6 million for the United States and EU alone (The White House, 2015; EC, 2011).

110. Early identification features strongly, as being able to rapidly demonstrate the presence of an infection or resistant infection with high sensitivity and specificity will not only avoid unnecessary, prolonged and failing treatment for the patient, but could also reduce hospital and community exposure to the infective agent and save on treatment costs (Bhattacharya, 2013). Interventions on reducing infectivity and increasing hygiene are frequently implemented together as care bundles, particularly in the hospital setting. In the United States, care bundles for the prevention of central line bacteraemia have been estimated to prevent 18,000 lives and USD 1.8 billion per annum (Bartlett et al., 2013; Marschall, 2011). Further measures for preventing transmission include reducing susceptibility of infections, which entails interventions such as the promotion of probiotics, which strengthen the gut flora and prevent infective agents from colonising (Alvarez-Olmos & Oberhelman 2001).

Table 6. Common interventions to avoid the transmission of antimicrobial-resistant microorganisms

Early detection	enhanced provision of testing (lab capacity, point of care testing, eg: TB rapid molecular assay) enhanced infrastructure and new devices screening of patients at risk
Reducing infectivity	isolation of patients (Predominantly in hospital setting) (specialist staff, training) decolonisation
Increasing hygiene	improved cleaning practices (specialist staff, training, peer quality control) alcohol-based hand hygiene contact precautions (gowns, gloves, masks) promote sanitation in schools
Reduce susceptibility	probiotics early removal of catheters health promotion campaigns

4.2.1 Measures to allow an early detection of ARMs

111. Early detection measures aim to enhance provision of information and facilitate rapid response. This includes information provided through diagnostics (eg: point-of-care tests) and surveillance. Measures range from improving existing capacities and infrastructures to the introduction of new technologies in order to save time and cost or to provide new information. Target groups include medical and diagnostic professionals within the community and hospital setting, in addition to executive agencies and surveillance bodies. The introduction of new technology to allow early detection of ARMs would provide benefits to patients, by allowing targeted, evidence-based and rapid treatment, and to the wider society, by facilitating rapid response to emerging trends.

112. Canada, Germany and the United Kingdom have particularly improved their surveillance systems, contributing towards reduction in AMR. Canada successfully responded to gonorrhoea trends observed through surveillance and monitoring systems, by issuing updated guidelines on therapy, which led to a decrease in resistant gonorrhoea isolates from 7.6% to 3.7% between 2011 and 2013 (Government of Canada, 2012). In the past different methods and evaluations were employed for AMR testing, yet since 1997 harmonisation of methods and reference values has been achieved via EUCAST. In Germany, since 2010, almost all ARS laboratories have incorporated EUCAST methods, facilitating international comparisons (BGM et al., 2015). In the United Kingdom, combined data on antibiotic use and resistance published in the ESPAUR report (Public Health England, 2014) has helped identify trends and direct actions for combating resistance.

113. Point-of-care testing and rapid-diagnostics present opportunities for guiding treatment and reducing unnecessary antibiotic use. A Cochrane review found that use of the C-reactive protein point-of-care test for acute respiratory infections (ARI's) could reduce antibiotic use in primary care (Aabenhus et

al., 2014). Despite evidence being of moderate strength and there being no effect on patient outcomes, these and other targeted diagnostic approaches of limited benefit to clinical outcome should also not be underappreciated, as they can reduce antibiotic pressure (Laxminarayan et al., 2013). Stronger evidence as well as cost-benefit analysis will help in establishing guidance on employing these approaches.

114. Bottlenecks to early detection strategies include clear identification of clinical needs, the incorporation of novel technologies into clinical practice and standardisation (consensus on methods and metrics), which can be achieved by fostering dialogue in the medical and diagnostic community. A further challenge includes ensuring sustained financing of early detection information systems. In many cases rapid detection presents cost-saving opportunities, which will need to be determined on an individual basis through deep analysis on cost effectiveness. This particularly applies to diagnostics tests, where many new testing methods are currently being employed supplementary to existing gold-standards.

4.2.2 Measure to reduce infectivity

115. Reducing infectivity aims to prevent spread of AMR by minimising or containing existing disease. Most interventions target infective patients in the hospital setting and include measures such as patient isolation (eg: single room and isolation wards) or decolonisation strategies (e.g. topical AMTs to suppress MRSA). Patient isolation has also been employed in the community for TB control, yet these interventions have been limited to few cases.

116. There is mixed evidence and controversy on the effectiveness of patient isolation. Countries, such as the Netherlands, Ireland, Germany and Denmark, which have seen successes in controlling resistance, have also incorporated patient isolation into their national plans. Germany for example saw a decrease in MRSA rates from 20% in 2011 to 12.8% in 2015 (BGM et al., 2015). Further, a systematic review looking at patient isolation together with other interventions found significant reductions in healthcare associated infections or colonisation rates (Aboelela et al., 2007). A recent review however argues that justification for MRSA screening and isolation is weak and lacks clinical and cost-effective evidence base (Fätkenheuer et al., 2015). As patient isolation practices are implemented together with other measures and tend to vary in practice as well as healthcare worker compliance, clear evidence specifically on the effectiveness of isolation measures is limited. Many studies also focus on specific HAI's and tend to be introduced as bundles of interventions, hence gaps in the evidence base still need to be filled, allowing for the establishment of clear strategies.

117. Despite limited evidence base, decolonisation measures show good efficacy in hospital settings. Many studies focus on MRSA, where short-term studies have found that decolonisation improves health outcomes and reduces costs (Robotham et al., 2011). Randomised trials have further demonstrated that decolonisation resulted in 23-44% lower AMR or bloodstream infections amongst ICU patients over 6 to 18-month intervention period (Climo et al., 2013; Huang et al., 2013). Long-term effects and cost-benefits are yet to be fully demonstrated, yet one randomised trial (Huang et al. 2013) found universal decolonisation of patients to be more effective than screening and isolation measures and a further study (Robotham et al. 2011) found screening coupled with decolonisation to be more cost effective over isolation measures.

118. Apart from increasing the evidence base on measures for reduction of infectivity, bottlenecks include ensuring the employment of trained and dedicated clinical practitioners. Further, contact evasion is an issue that needs to be addressed with regards to isolated patients. Though there is no clear evidence that contact evasion has any impact on clinical outcome, it has been found that in-room contact time of health-care providers is 22% lower amongst isolated patients than other patients in the hospital setting (Fätkenheuer et al., 2015). Further to this, the psychological and ethical implications that patient isolation can have should also be addressed in relation to guidelines and consensus amongst the medical community.

With regards to decolonisation measures, bottlenecks could include emergence of resistance to decolonisation agents. Though this has not been reported, efforts should be made to monitor this closely.

119. A multicentre, cluster-randomised trial showed that use of the AMT chlorhexidine resulted in 23% lower AMR rates amongst ICU over a 6-month period (Climo et al., 2013), and a further randomised trial found that universal decolonisation of patients in ICU to be more effective than patient isolation measures (Huang et al., 2013).

4.2.3 Measures to enhanced hygiene and sanitation in medical facilities

120. The hospital environment favours the development and the spread of infections and resistant microorganisms. For instance, 1.7 million cases of health care-associated infections were documented in the United States in 2002 (Klevens et al., 2007). Patients undergoing a surgical procedure are at a particular high risk and about one patient in 10 develops an infection (Vazquez-Aragon et al., 2003). Medical equipment gets contaminated very easily favouring the contamination of patients, both directly and indirectly through medical personnel. A systematic review came to the conclusion that, before cleaning, almost 87% of medical equipment harbour microorganisms in sufficient numbers to result in nosocomial infections (Schabrun & Chipchase, 2006).

121. A wide range of interventions exist to control environmental contamination and noncompliance with hand hygiene guidelines. Interventions aimed at increasing hygiene and sanitation in the hospital sector are defined as horizontal because they target all the potential pathogens. Conversely, vertical measures as, for example, early detection (see section 4.3.1) or universal screening at hospital admittance target specific agents. Enhanced environmental cleaning practices have been shown to be effectively in decreasing contaminations across patients and in interrupting pathogens transmission (Dancer, 2009). However, insufficient hand washing is unanimously recognized as the most important modifiable cause of hospital-acquired infections. Interventions to increase adherence to guidelines are, therefore, considered at the cornerstone of sanitation policies in the hospital setting.

122. Programmes to increase hand washing adherence rates can significantly limit the spread of ARMs. Hand hygiene compliance rates are currently well below 50% in both Europe and the United States (Boyce & Pittet, 2002; McGuckin et al., 2009; Pittet et al., 2004). WHO has developed the WHO-5 campaign to promote a multimodal strategy aimed at increasing hand washing among hospital personnel. The strategy consists of five components: system change, training and education, observation and feedback, reminders in the hospital, and a hospital safety climate (WHO, 2009). The implementation of this approach has been shown to be very effective in increasing adherence to hand washing guidelines and, in some setting, it has more than doubled the probability of hand hygiene compliance (Kirkland et al., 2012; Lee et al., 2013). In setting where no adequate improvements have been achieved, despite the implementation of the WHO-5 approach, the addition of goal setting, incentives or accountability can further improve results (Luangasanatip et al., 2015).

123. Increasing adherence to hand washing guidelines is a cost-saving intervention. It has been calculated that improving hand hygiene compliance among healthcare workers in a 200-bed hospital by as little as 1% would result in savings due to a decrease in infections of about USD 40,000 per year (Cummings et al., 2010).

5. Tackling antimicrobial resistance: fostering research & development in the pharmaceutical sector

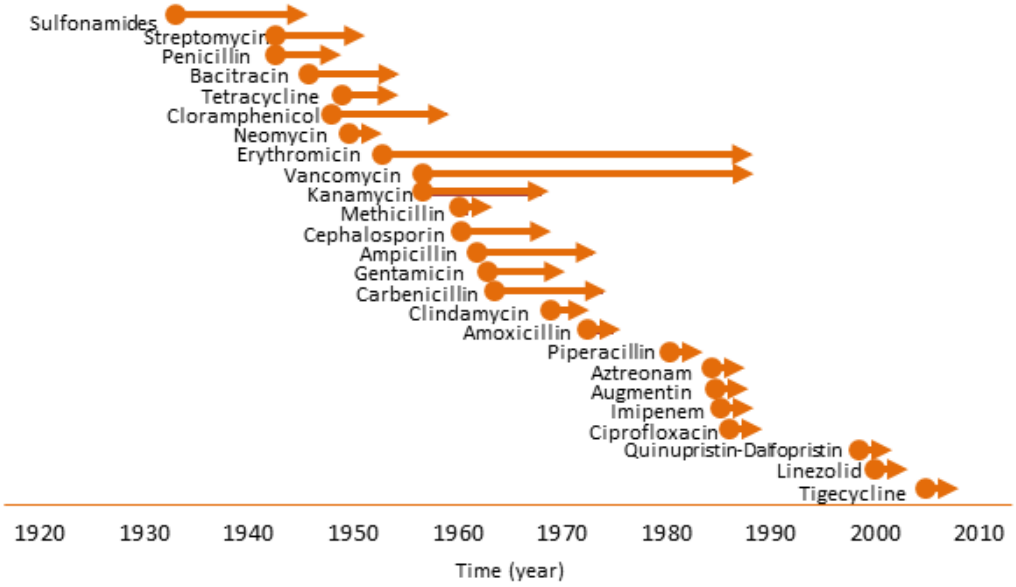
124. The research and development (R&D) pipeline for new antimicrobial therapies (AMTs) is progressively drying up The last major new class of antibiotic was discovered in 1987 and the approval of novel AMTs has fallen 8-fold since then. Investment in this area has become unattractive due to diminishing returns on capital, principally driven by (a) accelerating rates of antimicrobial resistance (AMR) to new AMTs and (b) increased restrictions on their use. Innovative approaches are required to stimulate sufficient R&D activity. Delinking R&D incentives with eventual sales of the product is crucial in fostering investment in this area. Interventions can be divided into two broad categories: push or upstream interventions target the early development phase and aim to lower costs associated with uncertainty surrounding successful development. In isolation, none of these interventions will achieve the desired result and a hybrid approach, combining both push and pull interventions, is needed to ensure development is supported along the entire value chain.

125. This section provides an overview of the approaches that can be put in place by G7 and OECD countries to foster the necessary R&D activity. Each option presents advantages and disadvantages that are discussed throughout the section. The next section briefly examines the reasons why the current biopharmaceutical development model is failing in this regard. Section two presents a set of policy interventions that, if implemented, may offer the opportunity to correct market failure in the antimicrobial sector. Section three discusses how the different policy interventions may be combined to achieve the desired results.

5.1 A tragedy of the commons that requires a more collaborative research model

126. Since the 1950s the development of pharmaceutical technology has relied on a profit model underpinned by market exclusivity. Under this model, pharmaceutical R&D is financed predominantly by private capital seeking a commensurate return, and is conducted by pharmaceutical companies. Return of investment (ROI) is determined by two factors: drug price and the volume sold. Overall this model has worked delivering innovative therapies (including AMTs) that have improved human health benefitted humanity. However, in seeking to maximise capital returns, AMTs were marketed aggressively resulting in indiscriminate prescribing and distribution. This hastened the rate of resistance. Newer antimicrobials became obsolete sooner (figure 13), extinguishing profits and making investment in this area unattractive.

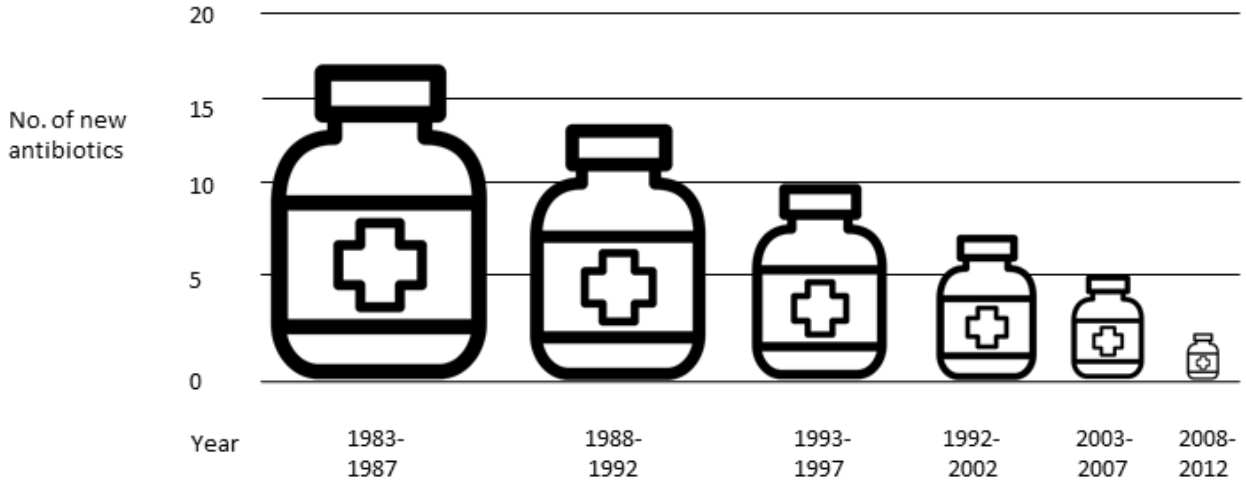
Figure 13. Timeline: antimicrobial discovery to first resistance identified



Source: Adapted from Pray L, 2008

127. The industry has turned away from AMTs, and the majority of large pharmaceutical companies have completely abandoned this area (Bartfai, 2015). The last major new class of antibiotic was discovered in 1987 and the approval of novel AMTs has fallen 8-fold since then (figure 14). Consequently the current AMT pipeline is very limited (WHO, 2015; Infectious Diseases Society of America, 2011; Outterson et al., 2015; Review on Antimicrobial Resistance, 2015).

Figure 14. Number of new antimicrobials approved by the Food and Drug Administration since 1983



Source: Adapted from Infectious Diseases Society of America, 2011

128. This industry response is perfectly rational. Why would companies with an obligation to deliver shareholder returns invest in a product whose use is actively limited and discouraged?

129. When deciding on whether to commence R&D, pharmaceutical investors estimate the net present value (NPV) of the target drug. This calculation considers the (a) time cost of money by discounting future profits to current value, and (b) risk of failure or attrition, not uncommon in pharmaceuticals. The NPV of modern AMTs is estimated to be far below that of other therapeutic categories (Sharma & Towse, 2011; Sertkaya et al., 2014; DiMasi et al., 2004). The lower expected profits are a result of several factors that are unique to AMTs. First, in addition to their shortening lifespan (figure 13), AMTs are deployed in shorter courses than other drugs. Second, the growing attention on limiting antimicrobial places limits on sales. Third, a considerable proportion of need is located in nations with lower ability to pay.

130. There are also technical reasons for market failure in this area. The overall probability of AMT targets being approved is lower than other drug classes (Review on Antimicrobial Resistance, 2015; Renwick et al., 2014). However, this is due to very low success rates in early development phases, as once this hurdle is passed AMTs transition to regulatory review more often than other drugs (DiMasi et al., 2009) suggesting that early R&D may be a suitable policy intervention target.

131. AMTs are a unique medical technology and a diminishing resource. Their scarcity is not related to production limits (marginal costs are negligible) but because of the negative externality of resistance being accelerated by their use. This is the irreducible problem of the profit model. The volume sold, the mechanism that should incentivise the continued replenishment of AMTs is also the very mechanism that makes them become obsolete. To complicate things further, there are also positive externalities associated with their use. An AMT that is deployed appropriately limits the spread of infection and helps prevent the pathogen from developing resistance. AMTs also carry an unusual level of intrinsic value. Similar to military technology, their availability is as valuable as their impact. Unsurprisingly the market valuation of AMTs is considerably lower than societal value. For this reason AMTs are framed as a social good (WHO, 2015).[1]

132. These considerations make AMTs quite a unique commodity, and presents particularly complex problem in terms of finding the right policy interventions to correct the failure of the traditional model of drug development. The literature on this topic emphasises the following key considerations. First, the need for more fundamental science and ambitious research. Pharmaceutical development is heavily reliant on scientific discovery, which usually takes place external to the industry (Kezselheim et al., 2015). Developing new classes of AMTs as well as innovative diagnostic tools and disruptive technology that will depend on ongoing research into the mechanisms of resistance as well as 'blue sky' projects (Ling et al., 2015; Braddington & Piddock, 2011; Head, 2011; So et al., 2012; Outterson et al., 2015). This must include research in livestock and animal health (The White House, 2015).

133. Second, the pharmaceutical industry is facing a growing R&D productivity challenge (OECD, 2015). Fundamental problems with the traditional competitive, proprietary model have been suggested, and a transition towards collaborative research encouraged, including greater contribution by SMEs (Munos, 2009; Garnier, 2008; Scannell et al., 2012; McKinsey & Company, 2010). Such an approach is now advocated for AMTs, and a specific intervention is discussed in the next section (Outterson et al., 2015; So et al., 2012; Plahte & Rottingen, 2015; Kieny, 2015; Renwick et al., 2014; WHO 2015).

[1] The literature refers to AMTs as public goods but this is not entirely accurate due to the negative externality (AMTs use by one individual influences their availability to another) resulting in scarcity. True public goods are not influenced by scarcity, and their use by one individual does not influence availability to others.

134. Third, policy interventions in this field will require reconsideration of intellectual property. The broader scientific and research community has realised that traditional copyright laws and patents often discourage collaboration, slow research and hold back innovation. Instead, scientific institutions are increasingly "uploading their research in open-source networks to be shared freely with colleagues in managed Commons." (Rifkin, 2014) p180. An OECD publication examining public private partnerships in dementia research advises that specific consideration of IP in policy frameworks is needed (OECD, 2015). There is similar support for changes in the IP and patent system in the battle against AMR (Plahte & Rottingen, 2015; Outterson et al., 2015; Review on Antimicrobial Resistance, 2015; Kieny, 2015; Renwick et al., 2014).

135. Finally, integrated and accessible information is a critical enabler of collaborative research. Reliable ways are needed to collect, analyse and share data regarding the (a) various strands of research (b) AMR surveillance and epidemiology, and (c) results of clinical trials and other testing.

5.2 Potential policy interventions

136. A considerable literature now exists about potential ways to stimulate sufficient investment in this area. This section provides an overview of the key interventions based on the overarching principles of combatting AMR: (1) access to AMTs based on need, and (b) rational, appropriate deployment of AMTs due to the strong link between use and AMR. Particular emphasis is therefore given to interventions that delink R&D incentives with eventual sales of the product. Delinking is seen as a critical component of effective interventions given the broader goals of AMR (Paccaud, 2012; WHO, 2015; Review on Antimicrobial Resistance, 2015; Morel, 2011). Consideration is also given to participation of SMEs in the research effort,[2] and to stimulate productive scientific collaboration between the range of public institutions and private companies with the potential to contribute to this global effort.

5.2.1 Upstream (push) interventions

137. Interventions can be divided into two broad categories: push and pull. Push interventions target the early phase, the most uncertain part of developing any medical technology. These are designed to lower costs associated with this uncertainty. The advantages of upstream interventions are that they encourage SME participation and represent better value than downstream rewards. Due to discounting, push interventions can be up to 95% cheaper than their downstream equivalents (Spellberg et al., 2012). Given the higher success rate of AMTs in later development phases (DiMasi et al., 2009) early investment may also represent better value.

138. The key disadvantage shared by upstream interventions is that they expose the sponsor to risk. Given the unexpected and stochastic nature of research, investment needs to be seeded over a range of promising technologies. This may dilute the value derived from 'getting in early'. Setting investment priorities is challenging given the multitude of potential targets, stakeholders involved and the unpredictable nature of scientific discovery. The advantages and disadvantages of key push interventions are summarised in table 7.

5.2.1.1. Tax incentives

139. Tax incentives such as credits or deductions can be applied to increase companies' capital to encourage R&D. It is one of the less interventionist options. It is easier to implement and can be structured to favour SMEs. In Canada, biotech SMEs qualify for a 35% tax credit compared to 20% for larger

[2] Seen by many commentators as an important contributor to R&D productivity in medical technology (see Section 5.1)

pharmaceutical companies (OECD, 2003). The disadvantage is the risk to the taxpayer as this option is indirect, less transparent and there are no cost control mechanisms. It also dilutes policy makers' control over targets and priorities. There are no guarantees that the refunded capital will be used for antimicrobial R&D or produce the intended product (Renwick et al., 2014). Many countries already provide tax subsidies to pharmaceutical companies (EY, 2015) without any discernible effect on AMT production. Tax relief does not facilitate collaboration, and does not delink incentives from sales.

5.2.1.2 Product development partnerships

140. Product Development Partnerships (PDPs) enables greater control over priorities and direction of research. Well-designed PDPs can foster collaboration between participants including SMEs, and can include a range of promising targets (Renwick et al., 2014). Risks of this approach concern governance, stakeholder management and sponsor-agent information asymmetry (Morel, 2011; Sharma & Towse, 2011). Despite giving sponsors the greater control over the research agenda, there is still a need to 'pick winners' from a pool of potential targets. This will be challenging if the scope includes ambitious long-term research and diagnostics, which are seen as a critical aspect of the battle against AMR (Jameson & Longo, 2015). This intervention does not delink sales of the product. However, PDPs have led to successful development of a novel drug for Tuberculosis and HIV/AIDS (Bartlett et al., 2013).

5.2.1.3 Direct funding and grants

141. Direct funding and grants subsidise R&D of novel AMTs. Grants can be direct or conditional, for example tied to limited production and supply if the product is successful, or can be used for recruiting skilled personnel (Renwick et al., 2014). This subset of interventions lowers R&D costs to the developer, enables SMEs, and permits focus on specific targets as well as points along the value chain. It does, however, entail considerable risk to the sponsor and requires high levels of transparency and trust. With the exception of conditional grants, these interventions do not explicitly delink sales of the product. No evidence for the effectiveness of this intervention in other disease categories was found. However, this model is frequently used in military procurement where it is often applied using longer term service availability contracts, as opposed to simpler product delivery arrangements. Here the contractor is remunerated on the basis of service performance over time, based on specified key performance indicators, as opposed to selling the product (Jaczynska et al., 2015). This model resonates with the notion of intrinsic value and AMTs as a social good.

5.2.1.4 Corporate bonds

142. Corporate bonds for AMT development have also been proposed, and have been most clearly articulated in the form of an Options Market for Antibiotics (OMA)(Brogan & Mossialos, 2013; Jaczynska et al., 2015). This is based on call options in equity markets, where investors purchase the right to buy a stock for an agreed price in the future. The earlier the agreement, the greater the investor risk but also the higher the potential payoff. With OMA the investors would usually be governments, but can be private sponsors depending on how the market is designed. Sponsors buy options from developers to purchase an agreed quantity of the AMT at a future date. This can be done at any time of the development cycle. Naturally option prices will be higher at later stages when potential AMTs are closer to approval, and vice versa.

Table 7. Advantages and disadvantages of key upstream interventions

Mechanism	**Advantages**	**Disadvantages**
Tax incentives (credits, deductions, vouchers)	Relatively easy to implement ; Minimal governance and information asymmetry risks; Can be designed to favour SMEs	Risk to tax payers - no cost control mechanisms; Dilutes sponsor's ability to set agenda & priorities; no guarantee that capital will be spent on AMR; Does not facilitate collaboration ; Does not delink incentives from sales
Product development partnerships (PDPs)	Sponsor can set targets and priorities; Can be structured to incorporate collaboration; Spreads sponsor risk over a number of projects; Lowers costs to enable SMEs; Reduces financial risk on developers	Risk to sponsor; Challenging governance (multiple stakeholders) and information asymmetry; Requires high levels of trust ; Basic model does not delink incentives from sales
Direct funding & grants	Lowers costs to enable SMEs; Sponsor can set targets and priorities; Can be targeted along value chain; Conservation component can be added to direct funding (conditional grants); Lowers competition for human capital (personnel grants); Can complement other interventions	Risk to sponsor; Requires high levels of transparency and trust ; Entails information asymmetry; Can entail complex contractual requirements
Long term availability contracts	Delinks incentives from sales; Ensures product completion and availability	Risk to sponsor; Requires high levels of transparency and trust ; Entails information asymmetry; Can entail complex contractual requirements; Can stifle innovation
Corporate bonds / options market	Can enable SMEs; Permits seeding and spreading risk across a range of targets and along value chain	Requires accurate information and transparency; Susceptible to gaming ; Does not delink incentives from sales; Potential conflict of interest; Market solution to market problem; Does not facilitate collaboration
Global collaboration platform	Lowers marginal cost of information; Lowers duplication and waste; Promotes innovation, creativity and agility; Enables early identification & exploitation of promising targets; Better productivity, technical and allocative efficiency; Involves SMEs; More transparent; Spreads risk for sponsors and participants (no need for *ex ante* commitment to any particular target)	Challenging to initiate and administer; Needs well designed architecture and state of the art IT; Needs long term commitment and political will including recurrent funding; IP and patenting implications

143. Like other push interventions, the advantages are that this can encourage SME participation (if purchased early) and potentially deliver considerable discounts compared to downstream equivalents. It permits hedging of risk by seeding across numerous early projects, perhaps to a greater extent than PDPs or grants. The downside is that this model depends on exchange of accurate and realistic information regarding the probability of success. This can be challenging particularly as corporations may be hesitant to disclose sensitive data. Also, the potential of a project may be exaggerated by companies that want to attract the payment but are ill-equipped to carry the development through (Brogan & Mossialos, 2013). Conflict of interest may arise if purchasers of options are also responsible for a drug's approval. There is no delinking between incentives and sales, and the proposal doesn't promote collaboration.

5.2.1.4 Global collaboration platform

144. Enabling collaborative R&D through an open source platform, briefly discussed earlier, is one of the broader upstream interventions. Given that the history of scientific discovery is one of fortune, cooperation and iterative innovation, this may be a useful foundation to meet the scientific challenge of AMR. The key advantages concern reduced duplication, sharing resources, cutting marginal cost of information and enabling innovation and agility. Projects can be initiated and terminated without losing the knowledge derived from failure. Participants can contribute knowledge and insights, and examine existing intelligence and previous research (that may have been discarded) in new and innovative ways (Munos, 2009). The cumulative learning enables new discoveries that may otherwise have been dormant. The leveraging effect results in better productivity, and technical and allocative efficiency. An additional benefit would be a better integrated supply chain and improved regulatory transparency (Renwick et al., 2014).

145. Creating the open source platform makes information and ideas freely available, lowers barriers to entry for all actors and enables entrepreneurial innovation to flourish. A major advantage is that sponsors need not 'pick winners' or make *ex ante* commitments to single lines of scientific enquiry. This reduces the risk associated with several other push interventions.

146. In practice this would involve linkage of research data across a range of disciplines and sectors, molecule libraries, clinical trial data and surveillance data into one freely accessible global repository, and would require considerable investment. The approach would also rely on strong governance and administration and political buy-in from a range of stakeholders. It would also need to be coupled with changes to IP and patenting at international level - a considerable challenge but one that is not entirely new or ground breaking (Plahte & Rottingen, 2015; Kieny, 2015). The United Kingdom AMR review, chaired by a former investment banker, considers such a model to 'oil the gears' of R&D, and agrees that R&D *"undertaken amidst great secrecy… can lead to wasteful and avoidable duplication of effort, for instance where two companies research very similar areas unsuccessfully, with neither company aware of the other's activities and failures."* (Review on Antimicrobial Resistance, 2015) p27.

147. There are several examples of this approach being applied in other areas. These include re-annotation of the *Myobacterium tuberculosis* genome, the African Network for Drugs and Diagnosis (ANDI), the *Medicines for Malaria Venture* and the *Coalition Against Major Diseases* (So et al., 2012). The latter has developed common data standards and a pooled repository of multiple companies' clinical trial data and has resulted in advances in treating neurodegenerative disorders such as Alzheimer's and Parkinson's disease (Coalition Against Major Diseases, n.d.). An open source platform forms the basis of the WHO AMR strategy (Kieny, 2015; Renwick et al., 2014).

5.2.2 Downstream (pull) interventions

148. Downstream mechanisms aim to boost the reward at the end of the development process. These levers reduce the risk to sponsors but, due to the time cost of money, also inflate the size of the intervention. Risk is transferred to the developer thus limiting the involvement of less capitalised SMEs. An advantage is that they incentivise finished products and enable developers to act without outside interference, which can be said to enhance efficiency (Renwick et al., 2014). Establishing the size of the reward and the criteria to qualify for it can be challenging. Another drawback is the high level of trust required by developers in the sponsor remaining dedicated to the commitment, which due to the long lead-time, can span political and business cycles. Key interventions are summarised in table 8.

5.2.2.1 Monetary prizes

149. Monetary prizes for successful development of a product are the most commonly proposed pull intervention (Kieny, 2015; Renwick et al., 2014; So et al., 2012; Outterson et al., 2015). The advantage of prizes is their simplicity. There is little additional infrastructure or legislation required, and they can be offered by NGOs as well as governments **Invalid source specified.**. In addition, prizes can be awarded for a specific, under-prioritised field of enquiry, such as diagnostic technology (Plahte & Rottingen, 2015; Kieny, 2015). An alternative are advance purchase commitments (APCs) where the sponsor commits to purchasing an agreed amount of the AMT thereby guaranteeing revenue (Renwick et al., 2014). These are a downstream version of OMAs discussed above. The advantage of APCs is that they may do more to promote conservation (delinking) if a volume clause is added. Prizes have been used in research for HIV/AIDS, genomics and TB with mixed success (Morel, 2011).

5.2.2.2 Milestone prizes

150. A major drawback of prizes and AMCs is that they disadvantage SMEs. Milestone prizes can circumvent this by rewarding pre-determined advances in R&D earlier in the development process. However, in a field where fortune and unexpected breakthroughs are common, it can be challenging to agree, *ex ante,* on what exactly would qualify for a milestone prize. Nevertheless, milestone prizes can complement other interventions (Renwick et al., 2014).

5.2.2.3 Patent buyouts

151. Patent buyouts are similar to prizes except that the purchaser buys the manufacturing rights thereby taking control of production and supply. A key advantage is that this delinks incentives from sales. However, if targeted at the end product this intervention will exclude most SMEs. It may also be difficult to stimulate sequential innovation on public IP, and implementation is likely to be a challenge (Renwick et al., 2014).

5.2.2.4 Advance market commitments

152. Instead of a lump-sum monetary reward, Advance Market Commitments (AMCs) promise an agreed market share to developers. In addition to technical challenges, the obvious disadvantages are that this does nothing to delink incentives from sales, and that the power of this as an incentive is undermined by policy to reduce the use of the product. It is therefore considered an inferior pull intervention to prizes (Renwick et al., 2014). AMCs have been used in the development of pneumococcal vaccines in the developing world, but there were criticisms that these were more akin to procurement contracts to meet demand in poorer countries as opposed to levers stimulating the actual development of the vaccine (Oxfam, 2008).

Table 8. Advantages and disadvantages of key downstream interventions

Mechanism	Advantages	Disadvantages
End prizes & APCs	Simple; Rewards successful development; Principal-agent problems avoided; Sponsor can be NGO or government; Can be aimed at specific category (e.g. diagnostics)	No impact on SMEs; All risk on developer; Does not delink incentives from sales ; Requires trust if a long lead time exists; Setting success criteria can be challenging
Milestone prizes	Permits sponsor to control development path and value chain; Enables SMEs to participate	Setting milestones *ex ante* can be challenging
Patent buy-out	Sponsor gets control over production and supply ; Delinks incentives from sales; Rewards successful development; Avoids principal-agent problems	Risk to developer; No impact on SMEs; May stifle subsequent innovation
Advanced Market Commitment	Rewards successful development; Does not require changes to regulation or establishment of new entities	*Ex ante* specification difficult; May maintain artificially high prices; Uncertain size of markets and conservation policies may undermine incentive; Does not delink incentives from sales; No impact on SMEs; No effect on collaboration
Patent extension / exclusivity	Higher prices prolonged, increases NPV of drug better ROI for developer; higher lifetime prices may limit no. of doses sold	Does not delink incentives from sales; Delay of generic entry and competition; No impact on SMEs; High prices impact on access; Reduced incentive to develop newer AMTs; Time cost of money diminishes incentive; No impact on SMEs; No effect on collaboration
Transferrable IP rights; 'wildcard' patent extensions	Flexible mechanism; Includes SMEs	Does not delink incentives from sales; Rent transfer to consumers if rights applied to 'blockbuster' AMTs
Harmonised approval & clinical trials	Lowers development costs; More rapid and efficient ; Faster global access	Potentially challenging administration and governance; No impact on SMEs; Does not delink incentives from sales
Priority review	Lowers development costs; Faster access	Safety potentially compromised; No guarantee of effectiveness or novelty; Affects approval times for non-AMTs; No impact on SMEs; Does not delink incentives from sales
Value-based pricing	Incentivises R&D in truly novel AMTs (disincentive for low-value R&D); Higher prices may limit use; Can be revised periodically based on fresh data	Higher prices affect access; Time cost of money diminishes value / sets unreasonably high prices; Does not delink incentives from sales ; Disagreements of effectiveness and value likely

5.2.2.5 Patent extensions and exclusivity

153. Patent extensions and exclusivity are based on the notion that increased revenue from an extended market monopoly will incentivise R&D. Like AMCs, the interventions do not promote prudent use of AMTs and do little to incentivise SMEs. Given the heightened regulation of antimicrobial prescribing, patent extensions may be a seen as an insufficient incentive by developers (Review on Antimicrobial Resistance, 2015). Prolonged higher prices may limit the use of the product but this entails equity concerns. Moreover, such arrangements may dampen competition and innovation, as companies may exploit exclusivity and delay further development of new products (Renwick et al., 2014). The Generating Antibiotic Incentives Now (GAIN) Act in the United States is an example of this approach but there is little evidence of its effectiveness to date (Paccaud, 2012; So et al., 2012; Bartlett et al., 2013; Review on Antimicrobial Resistance, 2015).

5.2.2.6 Priority review

154. Given the considerable barrier of approvals, priority review for AMTs is often proposed as a mechanism. An alternative are vouchers that can be redeemed for any product. Again, this does little to encourage preservation of AMTs and could be challenging from a regulatory perspective (Review on Antimicrobial Resistance, 2015). This is also the case for lowering regulatory requirements for antimicrobial products. There is little evidence that this approach promotes development of novel AMTs. It may actually raise concerns regarding effectiveness, safety and result in waste (Doshi, 2015). Nevertheless, given the objective of ensuring access based on need, harmonising approvals globally could be a helpful mechanism particularly if deployed alongside other interventions (Review on Antimicrobial Resistance, 2015). Funding and/or coordinating clinical trials for products that have passed early development phases has also been suggested, as this is one of the most costly parts of the development process (Outterson et al., 2015; Review on Antimicrobial Resistance, 2015). Downsides include risk to the sponsor but, in combination with other interventions particularly a central data platform, this may be a more efficient way to conduct trials and approvals.

5.2.2.7 Value based pricing

155. The societal value of AMTs differs from their market valuation. Value based pricing of AMTs aims to overcome this discrepancy, considered a key contributor to market failure. This intervention simply sets prices for AMTs at higher level to increase the reward for developers, and is effectively a disaggregated end prize. This may dampen demand and reduce inappropriate use, but could also affect access based on need (Renwick et al., 2014). This mechanism does not delink sales volume and does not facilitate SME participation. Agreement on prices can be challenging and, due to discounting, prices would need to be very high to sufficiently incentivise development.

5.3 Combining interventions into a comprehensive approach

156. In isolation, none of these interventions will achieve the desired result and a hybrid approach is universally recommended (Bartlett et al., 2013; Head, 2011; Morel, 2011; Kieny, 2015; Outterson et al., 2015; Review on Antimicrobial Resistance, 2015; So et al., 2012; WHO, 2015; Sharma & Towse, 2011). However this is difficult to design because the various elements are complementary and negating depending on the specific permutation in which they are applied. Unsurprisingly there is little agreement on what a package should include.

157. The ideal approach needs to encourage and harness global innovation and entrepreneurial thinking balanced against the notion of AMTs as social goods and the concerns of preservation and need-based access. A mix of upstream and downstream interventions is needed to ensure development is supported along the entire value chain, from concept to approval, production and distribution. Based on what discussed in this literature review, other elements of the global AMR challenge, the broader context of R&D, and practicality, a comprehensive approach may be based on the following elements:

1. A global collaborative research platform**.** Using an open source approach to engage the 'global brain' in developing new AMTs and conducting other complementary research is one of the more effective and efficient methods at our disposal. The additional benefit of an integrated data repository is its enhancement of other strands of research and other elements of the global AMR project (e.g. surveillance, drug approval and trials).

2. Other push levers such as milestone prizes and grants should be deployed to enable SMEs and academia to participate and contribute this global collaborative. This should include a set of incentives aimed at diagnostics and other neglected research areas.

3. Patent buyouts for successfully developed products. These pull levers incentivise completion of development, are attractive to larger stakeholders and, most importantly, sever links between sales and development costs. Licensing, supply, pricing and distribution would be in the control of the sponsor, ensuring that other AMR objectives are met.

4. Funding of clinical trials and a single global approval process would round out the package. The clinical trial process is a considerable disincentive for developers to engage in AMT research and should be incorporated into the package. This would not only lower this barrier but would also increase the depth and richness of the integrated data repository, access to which would, in turn, make the clinical trial process more efficient. Harmonised approval would expedite access to AMTs for populations in need regardless of ability to pay.

158. This package is similar to the approach proposed by the WHO (Kieny, 2015; Plahte & Rottingen, 2015; Renwick et al., 2014). It will require considerable financial investment. However, the need for public money as and the creation of a dedicated public institution are unanimously endorsed in the literature. The most commonly proposed approach is an international consortium to finance the package and to provide arbitration and oversight on matters regarding IP, approval and administration (Review on Antimicrobial Resistance, 2015; Renwick et al., 2014; Kieny, 2015; Outterson et al., 2015; So et al., 2012). Modelling the one-off and recurrent costs of financing such an approach is beyond the scope of this paper, but it should always be considered against the cost of inaction as well as the cost of inappropriate prescribing.

6. Conclusion

159. Antimicrobial resistance is a natural phenomenon that arises when an antimicrobial therapy decreases its effectiveness up to becoming completely ineffective. Inappropriate prescription and use of AMTs, poor adherence to the prescribed therapy, insufficient hygiene practices are among the factors that play a crucial role in helping antimicrobial-resistant microorganisms (ARMs) grow. In addition, the recent trends in globalisation, trade liberalisation, the rising number of travellers and growing interdependence all contribute to the increasing risk of the spread of existing infections. At the same time, the development pipeline of new AMTs has progressively dried up and the number of available AMTs is now only a fraction of what it was decades ago.

160. AMR is a global health and economic threat. The death toll in the United States and EU countries is estimated in about 50,000 lives a year (0.7 million globally). Hospitals spend on average an additional USD 10,000 to 40,000 to treat patients infected by antimicrobial-resistant infection and this figure is likely to double once that lost economic outputs are taken into account. However, if no effective actions are put in place, it has been estimated that up to 10 million deaths per year may occur globally between 2015 and 2050. In the same period, OECD countries may experience cumulative losses in GDP of about USD 2.9 trillion.

161. This document has reviewed and analysed the available evidence on the current and future health and economic burden caused by antimicrobial resistance (AMR), the policies currently in place in G7 countries and beyond to address AMR and, finally, the potential effectiveness of innovative actions that countries around the world can put in place to fight against AMR. Based on a review of the literature and current practices in G7 and OECD countries, this paper has identified area in which a commitment from G7 countries would help move forward actions to address AMR and its associated health and economic burden. In particular:

1. Ongoing efforts to improve surveillance and monitoring systems should be further strengthened. Further areas of improvements include: i) surveillance of AMR in the community (as opposed to AMR in hospital setting); ii) number of microorganisms that are covered by surveillance programmes; iii) better monitoring of antimicrobial prescribing practices.

2. The adoption of a comprehensive set of measurable targets related to the incidence of ARMs and that can help gauge the effectiveness of policies should be encouraged. Measurement of these targets should be integral part of the continuous evaluation processes that G7 countries have already in place.

3. The upscaling, at the national level, of effective and efficient interventions to rationalise the use of antimicrobials (e.g. stewardship programmes) and to prevent the spread of ARMs (e.g. better sanitation and early detection) would provide a significant contribution to containing the health and economic burden cause from AMR.

4. Internationally concerted approaches to foster innovation as well as basic research would lower barriers that currently hinder R&D in the antimicrobial sector and would increase the and productivity of research at the global level.

5. G7 countries would benefit from the development and implementation of comprehensive action plans in partner economies. Such plans should be designed to reflect international standards and, as far as possible, to adopt a ‘one-health’ approach. Coordinating efforts with other partner economies in the G20 may offer an excellent opportunity to upscale efforts.

6. OECD, with its distinctive cross-sectoral expertise, is placed in a unique position to help G7 countries and their G20 partners in tackling AMR. The OECD can provide a forum where governments can discuss, develop and coordinate new strategies for prudent antimicrobials use in human medicine and agriculture. OECD can evaluate the detrimental economic impact caused by AMR. Finally, OECD can review and assess the most promising innovative actions to tackle inappropriate use of antimicrobials and to overcome barriers to innovation.

162. In conclusion, this document shows that there is a strong case for G7 action in the area of AMR. For more than a decade the G7 has consistently committed to tackling global health challenges, including the fight against infectious diseases, and efforts to reach health-related MDGs. The strong political will of G7 countries would help move forward efforts to achieve the goals stated both in the recent resolutions issued by the World Health Assembly (WHA67.25, WHA68.19 and WHA68.20) and in the EC road map against AMR (EC, 2015). G7 countries, in particular, can create significant added value and change the architecture of the international response to AMR in the areas of rationalising use of antimicrobials in animals and human, incentivizing research and development of new AMTs, and addressing the potential economic consequences of AMR.

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