Stop AMR Global Media Monitor

November 2019

To Do:

- require EU and global transparency on production, distribution, and trade in antibiotics in line with 1999 EC SSC report
- require stricter quality controls on the import of antibiotics which include postproduction environmental criteria
- add requirements prior to market authorisation to assess the risk for AMR development within the environmental risk assessment (ERA) for antimicrobial substances
- create legislation to ensure that last-resort antibiotics and those medically important for human are reserved for human use only
- increase investment in the development of rapid diagnostic tools for use in human and animal health
- develop a publicly accessible database to list all antibiotics used in human medicine and animal husbandry
- enforce that all hospitals take part in surveillance systems and that all have infection control committees in place
- enforce comprehensive data collection for antibiotic-resistant bacteria from animals.
- undertake measures to improve animal welfare, livestock conditions, and animal husbandry practices that take important precautions to secure animal health and reduce the need for medication. This includes the research, development, and authorisation of feed additives to reduce the need for antibiotics as growth promoters
- promote research into environmentally-responsible ways to treat sewage and prevent the release of antibiotic resistant bacteria, as well as responsible waste disposal methods
- facilitate and promote the use of non-antibiotic husbandry products proven to promote animal health and growth
- Work towards international agreement that the Good Manufacturing Practices (GMP) include environmental criteria for all antibiotic active pharmaceutical ingredients (APIs)

Stop:

- allowing prescribers, globally, to sell antibiotics
- allowing regulators and industries to create or refuse to adapt laws that allow antibiotics to continue to be used in preventive roles in husbandry
- allowing hospitals and pharmacies to sell antibiotics without doctor prescription and formal registration
- allowing banks and investors to advertise investing in antibiotics production and start penalizing such behaviour
- export of antibiotics production outside EU avoiding EU oversight and rules
- pharmaceutical waste, one of the leading causes of AMR, by enforcing the development of minimum environmental manufacturing standards.

Antimicrobial resistance (AMR) is the ability of microbes (such as bacteria, viruses, fungi) to counteract the effectiveness of antimicrobial drugs (such as antibiotics, antivirals, antifungals) used against them. Even when used appropriately, antimicrobials can create a selective pressure for resistant microorganisms. However, the development of resistance is accelerated by the misuse and overuse of antimicrobials in human, animal, and plant health along with the pollution of the environment with antimicrobials and antimicrobial resistance genes.

AMR is a serious and urgent threat to global health as antimicrobials have been one of the key pillars of modern medicine since the discovery of penicillin by Fleming in 1928. Any of us could be the next victim of AMR. According to United Nations experts, in the next 30 years 2.4 million people in Europe, North America, and Australia could die from drug-resistant infections (UN IACG, 2019). As life-saving antibiotics stop being effective, AMR could end our capacity to combat infections and halt all surgical procedures. This makes AMR a global health threat that needs international coordination and legislation to be addressed.

Multi and Extensively Drug-Resistant Gonorrhoea

Gonorrhoea is the second most commonly reported bacterial sexually transmitted disease (STI) with 89,239 cases in 2017. If left untreated, the infection can lead to pelvic inflammatory disease, miscarriages, ectopic pregnancies, and infertility. Additionally, *N. gonorrhoeae* infections can facilitate the acquisition and transmission of HIV.

N. gonorrhoeae has developed resistance to several antimicrobial classes such as sulphonamides, penicillins, tetracyclines, macrolides, fluoroquinolones and third-generation cephalosporins. The first treatment failures were reported in Japan in 2000 and subsequently began to spread to neighbouring Asian countries. Within Europe,the first treatment failures using cefixime were recorded in Norway in 2010 and later expanded to England, Austria, France, and Canada. Since the first instances *N. gonorrhoeae* has quickly gained multiple drug resistance with some strains becoming extensively drug resistant (XDR) resisting treatment from even the last remaining monotherapy, ceftriaxone.

The European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) was created to track the threat of resistant gonorrhoea and create treatment guidelines in EU/EEA countries. Since the programme was established it has shown resistance to ciprofloxacin at 46.5% in 2016 and azithromycin at 7.5%.

In March of 2018, England's public health agency reported cases of gonorrhea resistant to both azithromycin and ceftriaxone – the only treatment still available. Press quickly began to call the infection "super gonorrhea"; in following months two more cases of the super resistant infection had been reported in Australia and spread across European countries.

Unlike other types of bacteria which will gradually lose resistance genes once the selection pressure has been removed, gonorrhea can hoard these genes and continually build up resistance to various antibiotics indefinitely. Additionally, gonorrhea can be insidiously silent with many people unknowingly carrying the disease and spreading it asymptomatically.

According to the CDC, gonorrhea cases rose by 67% from 2013 to 2017 – a jump from 333,000 to 555,608 confirmed cases. In just one year, between 2016 and 2017, reported cases in the UK climbed 22% with the unreported number presumably even higher.

In a 2017 WHO press conference GARDP director Manica Balasegaram told reporters "The situation is, actually, fairly grim,". With AMR on the rise, gonorrhoea is becoming more difficult, and in some cases impossible, to treat. Despite the perpetuated belief that gonorrhoea is a "disease of the past" people continue to die from this multi drug resistant infection. The ECDC 2019 response plans places emphasis on preventing the emergence and spread of *N. gonorrhoeae* to ensure that treatment options remain effective. Their plan aims to strengthen surveillance on AMR and monitor treatment failures to better inform national and international guidelines for treatment. They posit strategies to encourage appropriate management such as an enhanced focus on high risk groups and mandatory reporting of gonorrhoea.

Source: ECDC, CIDRAP

AMR in India

The overuse and poor disposal of antibiotics in India has had catastrophic impacts. For gram-negative bacteria more than 70% of *E. coli*, *Klebsiella pneumoniae* and *Acinetobacter baumannii* isolates and nearly half of *Pseudomonas aeruginosa* have become resistant to fluoroquinolones and third generation cephalosporins. As such, colistin, a last resort antimicrobial, is increasingly used and resistance to it has started to emerge in India. Regarding gram-positive bacteria, 42.6% of *Staphylococcus aureus* showed methicillin-resistance and resistance to vancomycin was observed in 10.5% was of *Enterococcus faecium*. Regarding *Salmonella shigella*, resistance to co-trimoxazole was 80%. This rise in resistance has led to numerous neonatal sepsis deaths with estimates by a Lancet study in 2016 putting that number at 56,524 deaths.

This problem is further exacerbated by two key practices: the poor disposal of unused medicines by states and the overuse of antibiotics in agriculture. Regarding the former, despite the Municipal Solid Waste Management (MSWN) Rules (2016) that give expired drugs the label of domestic hazardous waste, which implies they have to be put in separate bins and incinerated at high temperatures, the Centre for Science and Environment (CSE) concluded that the poor management of such hazardous waste was due to a lax enforcement of the MSWN rules with one senior official at the North Delhi Municipal Corporation, stating: "It's going to take us a few years before we are able to achieve wet and dry waste segregation. Hazardous waste segregation will have to wait." This poor disposal leads to a leaching of active ingredients in the environment where resistance is likely to occur.

The second key practice that increases AMR is the use of antimicrobials in agriculture. This includes both the use in veterinary medicine but also use as plant protection products. Indeed, a study by the CSE has shown that two key antibiotics, streptomycin and tetracycline, are routinely used on crops to prevent them from rotting. This is extremely alarming as streptomycin in particular is a key part of the treatment of tuberculosis in humans, which is still a significant threat to the Indian population health.

Sources: Indian Journal of Medical Research, CSE, DownToEarth, Lancet

AMR in CHINA – Professor Junshi Chen: Chief Adviser of China National Centre for Food Safety Risk Assessment

Professor Junshi Chen is the leading Chinese authority on AMR. He is the Chair of the Chinese National Expert Committee for Food Safety Risk Assessment and the Vice-Chair of the National Food Safety Standard Reviewing Committee. Internationally, he serves as the chairperson of the Codex Committee on Food Additives (CCFA) (2007-2017), UN co-convener of the AMR Inter-Agency Coordination Group (IACG), member of the WHO Food Safety Expert Panel and Director of ILSI (International Life Sciences Institute) Focal Point in China.

China has one of the highest consumption rates of antimicrobials in the world making AMR is a key concern for its authorities. For Prof. Junshi Chen, the Chinese AMR situation faces several problems and challenges regarding both human and animal medicines. Regarding the former, first, there is no official surveillance network with data not being shared between various institutes, except in large hospitals. Second, in middle and small hospitals, antimicrobials are managed poorly with this being subject to large geographical variation. Third, management of outbreaks at the hospital level is not optimised and this can lead to epidemics caused by highly virulent antimicrobial-resistant microbial strains.

For veterinary medicine, there is a massive overuse of antimicrobials (23% of global veterinary antimicrobial consumption, (Wu, C. and Shen, J., Chin J Prev Med 52, (4): 340-343, 2018. Chinese Academy of Engineering Report, 2015) with 50% of the total Chinese antimicrobial production used in this sector, including as growth promoters. Surveillance programs have low coverage do not cover sufficient sample sizes and are only focused on animals in farms but omit the rest of the food chain. This is of major concern as antimicrobial-resistant pathogens are often found in foods (*Salmonella, Campylobacter, Listeria etc.*, in meats, poultry and aquaculture species). These resistant pathogens in food are one of the most common ways for humans to contract resistant infections.

Despite these serious concerns, China has achieved some results. These include the introduction of regulations on antimicrobial use and the development of a National Action Plan. Furthermore, the use of antimicrobials in

hospitals has fallen from 67.3% in 2010 to 39.1% in 2015. In animals, four fluoroquinolones antimicrobial drugs have been banned and colistin was banned as a growth promoter. In 2018, the Chinese government announced it would aim to eliminate the use of antibiotics in feed by 2020, with 100 pilot livestock farms designated for the program.

Sources: Presentation by Professor Chen Junshi; National Action Plan; Rabobank

Global trends in antimicrobial resistance in animals in low and middle-income countries

Human consumption of antimicrobials is just the tip of the iceberg. Scientists say that more than 73% of all antimicrobials sold in the world are used in animals (Th. V. Boeckel et al., Science, 2017). The reason for this is that in animals antimicrobials are given regularly in small doses to prevent infections, and, in some countries as growth promoters to increase productivity. The EU has introduced legislation to curtail this practice, the 2006 ban on antibiotics as growth promoters for example, however a recent study found many lower and middle-income countries (LMICs) have far fewer regulations for meat production and fuel the proliferation of antimicrobial resistance.

Study co-author Thomas Van Boeckel, PhD. reports that "India and China are by far the biggest hot spots of antimicrobial resistance in animals, probably fueled by the fact that antibiotics are so cheap and easily available". He estimates that by 2030 antibiotic use in could grow by 59% in China if the livestock sector remains unaddressed.

Since 2000, meat production has grown by 68% in Asia, 64% in Africa, and 40% in South America. The study found that from 2000 to 2018 the proportion of antimicrobial compounds with resistance higher than 50% (P50) increased from 0.15 to 0.41 in chickens and from 0.13 to 0.34 in pigs and plateaued between 0.12 and 0.23 in cattle. Aside from India and China, resistance hotspots also include Pakistan, Iran, Eastern Turkey, Egypt, and Southern Brazil.

Aside from the negative impacts to human health from the practice, Van Boeckel also points out that if animals become resistant to first line antibiotics farmers may turn to more expensive second-line drugs which could drive up the price of meat. He adds that wealthier nations should support farming practices that decrease antibiotics use and export models such as those used in pig production in Denmark and the Netherlands which have reduced antibiotic usage without decreasing overall production.

Source: CIDRAP

Multi drug resistant tuberculosis

Cases of tuberculosis (TB) have fallen over the years due to global efforts from organisations like The Global Fund; however, those that do become infected are finding their treatment options increasingly limited. Multi drug resistant (MDR) strains of TB are resistant to at least two of the most effective antibiotics, isoniazid and rifampicin. TB strains can also be extensively drug resistant (XDR), meaning in addition to the aforementioned antibiotics, the strain is also resistant to any fluoroquinolone and any second-line injectable drugs such as amikacin, capreomycin and kanamycin.

In the EU/EEA region the average number of cases reported has remained relatively stagnant at 1,300 cases annually. Of those, at least 20% will be extensively drug resistant. For MDR TB more than half of patients will die of their infection. In these cases, the infection may not respond to the treatment or the patient may stop treatment due to significant adverse effects from the seven-drug regimen necessary. For patients with XDR TB successful treatment rates are even lower, with only a 25% success rate, far below the 75% success target set in the Tuberculosis action plan for the WHO European Region 2016–2020.

Tuberculosis continues to pose a grave risk in the EU as well as globally due to increasingly resistant strains severely curtailing our ability to treat the infection. If antimicrobial resistance continues to spread at its current rate, tuberculosis may become impossible to treat with our current pool of antibiotics.

Source: ECDC, ECDC

ECA audit on AMR

The latest report from the European Court of Auditors (ECA) found that there is little evidence that EU efforts

against AMR have had any significant impact. The activities of the European Commission (EC) and other EU agencies have led to some progress, mostly regarding veterinary and food related issues, however, the overall EU health AMR burden has not decreased. National governments rather than the EC have proposed a new research partnership on AMR funded through Horizon Europe.

Most policies against AMR are the responsibility of Member States (MS) as it is MS' mandate to deal with human health. As such, the EC and the European Centre for Disease Prevention and Control (ECDC) have acted as facilitators to the National Action Plans of MS. This has been through joint visits (EC & ECDC) to MS. These were found to be very useful by the MS in question, however, these are done at the request of MS and only 6 have occurred so far.

99% of the EU budget for AMR, €1.5 billion since 2004, goes to research. Because of the cost and complexity of collecting information, pan-European surveillance of superbug infections has been deficient despite efforts by the European Centre for Disease Prevention and Control. The auditor's report that the Joint Action on Antimicrobial Resistance (JAMARI) has been successful in the short term, however the long-term impact is still unknown.

A strong focus of the ECA audit was on the New Drugs for Bad Bugs Programme (ND4BB), which was one of the "flagship initiatives" of the EC's AMR funding. Out of its 7 projects, 4 incurred significant delays in using the available funding due, partly, to the volatility of the drug discovery field. One particular project, ENABLE, had significant success and at the time of the audit it has 5 potential drug candidates in the pipeline. However, there is the possibility that these will never reach the market as the platform established in this project is scheduled to end in 2020 and there is currently no market to sell antibiotics due to stewardship efforts at reducing consumption.

The ECA audit found that, while there are various monitoring strategies, the EC and MS did not consistently use the outcome indicators jointly developed by the EU agencies. Furthermore, the surveillance data on healthcare associated infections (the primary source of resistant microbial infections in humans in Europe) is still lacking. Finally, the EC's One Health Commission Plan assigned addressing the role of the environment in AMR as a specific objective. However, the ECA audit found that there is still little data and insufficient knowledge on how AMR spreads in the environment. The auditors recommend that EU support of national action plans and policy coordination efforts be strengthened. Additionally, there is a need for better surveillance and further research into new antibiotics.

Source: ECA

Antimicrobial consumption in the EU/EEA 2018

Overall in the EU/EEA region there was no statistically significant change in antibacterial usage between 2009 and 2018; however, for 9 countries (Austria, Belgium, Denmark, Finland, Italy, Luxembourg, the Netherlands, Portugal and Sweden) there was a reduction in usage. Bulgaria, Ireland, Latvia, and Poland saw a statistically significant increase in usage over the same period. All EU MS with the exception of Cyprus and the Czech Republic as well as Iceland and Norway reported data for this report.

Roughly 33,000 deaths each year are attributed to AMR in Europe; antimicrobial consumption is one of the key contributors to the development of resistance. The report finds that because consumption of antimicrobials can vary wildly between countries, monitoring of consumption and resistance patterns must be strengthened so that they may provide reliable data with which to base legislation on.

Source: ECDC

Euro Health Workers Spotty on Antibiotic Knowledge

A survey from the ECDC indicates that European healthcare workers, for the most part, have a high level of knowledge about appropriate antibiotic use and the role that inappropriate prescribing plays in antibiotic resistance. However, an important knowledge gap remains. The survey responses suggested some divergence between knowledge and practice. The author said these can be used when developing locally adapted interventions to ensure prudent use of antibiotics, focused on changing behaviour and practice among healthcare workers.

Sources: ECDC ECDC