Introduction

In the society which we live in, we develop and we communicate, we are often confronted to challenges and problematic subjects where the public opinion - this force for change, revolution and development - has to be involved. Some subjects are recurring: climate change, animal welfare, hunger in the world, poverty, pollution and so on. These are so many realities that we should try to be the most accurately informed about. The intended goal is then to solve them or to improve their effects.

Overall, we are conscious of these issues and some people feel interested or indifferent but most of them prefer to play a waiting game. A diversity of responses in view of the multitude of solutions that should be brought when confronted to a task that greatly exceeds the capacities of a single man. Despite the actions that we choose to do, any awareness and understanding of a subject starts with an information that must be as complete as possible. In this sense, we must carry out a theoretical and factual reminder about the subject we are discussing: antibioresistance.

Some theoretical revisions:

Antibiotic resistance is no exception compared to the issues previously mentioned. It is more or less familiar to most people in occidental societies that keep using antibiotics as a treatment, either in healthcare or in the food industry. Hence, this antibioresistance is, according to the WHO (World Health Organization), “one of the greatest threat to global health, food safety and development”.

To try and address the reality and the gravity of this judgment, we can use a theory from the naturalist and biologist Charles Darwin. According to him, “species that survive are not necessarily the strongest, neither the smartest but rather those who adapt the best to changes”. Indeed, antibiotic resistance follows the same evolving dynamic described by Darwin. The challenges are nothing more and nothing less than those of our survival and our development.

As a reminder, an antibiotic is a drug used for treating or preventing a bacterial infection. They can “either cause the destruction of bacteria or their growth shutdown”. However, their action is useless in the fight against viruses. Hence, antibiotic resistance is the product of an evolution of the bacteria when exposed to an antibiotic.

The bacteria that become “resistant” to antibiotics consequently become harder to treat than those who are not. Let us point out that antibiotic resistance is a natural defense mechanism of bacteria in response to the antibiotic action. Nevertheless, and this is a crucial point, although it is a natural phenomenon, antibioresistance is increased by a poor use or an overuse of antibiotics. Two factors that cause an acceleration of the antibiotic resistance phenomenon, that has today become global and very concerning. To understand this risk, we need to realize that in the case of a misuse or an overuse of an antibiotic, it will start “selecting” in the sense that, only resistant bacteria will survive and grow in its vicinity. From this point forward, the risk of being contaminated by a resistant bacteria increases, as is the risk of not being cured.

Furthermore, this antibiotic resistance phenomenon is affecting both the bacteria causing infections (pathogenic bacteria) and the other - mainly harmless - bacteria that are naturally present in our body (called “commensal” or “saprophytic” bacteria), in animals (pets or livestock) and in the environment.

(A bit of) historical background:

Historically, antibiotics are a major breakthrough of human History. They allowed the saving of millions. Their discovery and the evidences about their mechanisms of action can be tracked since 1897 with the work of a french medical officer: Ernest Duchesne. However, History has mostly remembered the doctor, biologist and pharmacologist Alexander Flemming as the main discoverer of antibiotics. Indeed, in September 1928, by the accidental contamination of the Staphylococcus bacteria he was working on, by a fungus named Penicillium, he was able to observe that the bacteria present inside the petri dishes had not grown around the Penicillium. He then deduced that the fungi were producing an antimicrobial substance: penicillin had just been discovered. This breakthrough allowed Flemming to be awarded with the Nobel Prize for medicine (1945).

The beginning of a massive use, unprecedented benefits:

This substance called penicillin was broadly used during World War II. Later on, other antibiotics were discovered, extracted and produced, allowing subsequently to greatly reduce the number of death by infectious diseases in Europe and in the rest of the World. As an example, in France “between 1923 and 1960, out of the 15 years of life expectancy gained,

more than 10 were due to the decline in deaths caused by infectious and respiratory diseases". A decline enhanced by the discovery and the use of antibiotics but also by the improvement of hygiene and cleanliness conditions. Antibiotics are undoubtedly the main tool of a gain in life expectancy and the marker of our progress.

As a side effect, antibioresistance makes an apparition:

It is precisely because of their great efficiency that antibiotics started to be massively overused, without anybody realising that it could lead to their loss of efficiency in the long run. In that sense, antibiotics are not the universal remedy to definitely get rid of microbes. Indeed, in 1945, Flemming had already brought to light this issue that would jeopardize the whole revolution brought by antibiotics: antibioresistance. Thus " *It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant*. "[1] Regarding penicillin, the first resistant strains appeared only three years after its commercialisation.

As we already discussed, this issue arises in the case of an overconsumption or a misuse of antibiotics. Hence, "initially one-off events, these resistances have become massive and preoccupying. Some strains are multiresistant, meaning that they can survive several antibiotics. Others have even become resistant to almost every existing antibiotics.This phenomenon, still rare in France but constantly increasing, places doctors in a situation where they can't find any new therapeutic option to cure the infection." Overall several level of antibiotic resistance can be distinguished: from lowest to highest, there is natural resistance (systematic), usual resistance, multiresistance (MDR: Multiple-Drugs Resistant), extensive resistance (XDR) and total resistance (TDR).

It is worth recalling that we need to distinguish a "bacterial colonization" that happens whenever a person is a "healthy carrier of a bacteria" from a "bacterial infection", characterized by symptoms caused by a bacteria. The issue of resistant bacteria arises "in law" in the case of a colonisation of the subject by a microorganism, even if the person can live undisturbed and form a peaceful cohabitation with the same microorganisms. In the

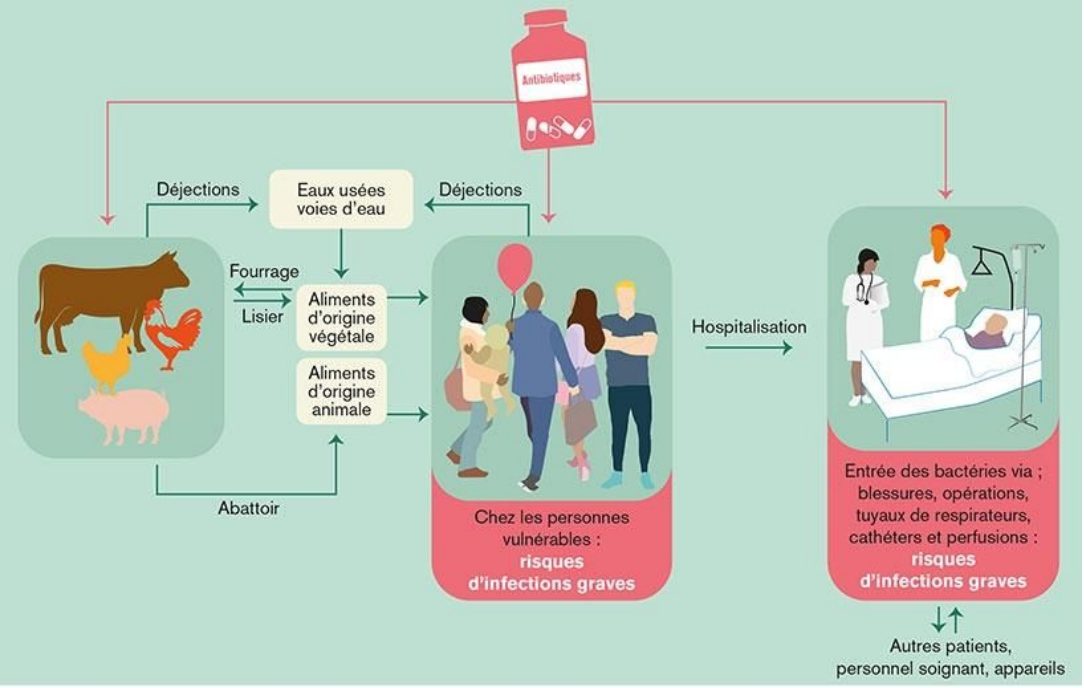
[1] Source ?

contrary, the issue can arise “in fact” and in a more acute way when a person is suffering from an infection and requires an antibiotic treatment.

According to the WHO, it is essential to understand the severity of what is at stake because “if we don’t take emergency measures, we will soon enter a post-antibiotic era where common infections and wounds will be lethal again.”

A global issue:

At last, we need to understand that this problem has become global in the sense that it doesn’t affect only mankind anymore. Actually, we find another important source of antibiotic resistance in livestock. They are fed antibiotics to increase productivity. As a matter of fact, according to the WHO, more than half of the world’s antibiotic production isn’t destined to a human consumption. With this phenomenon of overexposure and overconsumption in the farming industry, the multiresistant strains that are developing as a result, can be transmitted to humans directly to the staff or via the food chain or even via animal excrement that pollute the environment. Thus, we can find resistant bacteria in rivers downstream to cities or farms and even in the water tables. These resistance are “acquired” because they are the product of mutations, consequence from the exposition of an initially antibiotic sensitive bacteria that becomes resistant to the same antibiotic.



What possible answers, what possible understanding of the issue ?

By this phenomenon of antibioresistance, what appears clearly is this close link that is developing between healthcare, activity and consumption spheres. Three worlds that seemed previously hermetical to each other. Hospitals, community medicine, veterinary practices or even the environment management are now linked by bacteria that don't know any frontiers, not unlike a global flow of goods, humans and non-humans. This is why the answer that should be brought is defined as "multi-sectorial", like the WHO "one world, one health" approach.

From now on, our understanding of the problem "applies to the conception and the execution of political, legislations and research work programs where several sectors communicate and collaborate toward better results in the public health field". This is for instance with this aim that "the High-level Meeting on Antimicrobial Resistance" happened, organized by the WHO in Septembre 2016. Similarly, in October 2015, the WHO launched the "Global Antimicrobial Resistance Surveillance System (GLASS)" in close collaboration with existent centers and networks monitoring antimicrobial resistance and based on other existing surveillance programs. The main goal is to index and analyse the emergence and the development of new resistant bacteria strains.

Solutions :

Antibiotic resistance is an unstoppable process because it is "dynamic", in the sense that microorganisms evolve when at the same time, we still need to cure infected people. The solutions and tools used in this fight against against antibiotic resistance are of several kinds.

A first answer would be to chemically modify old molecules to reactivate them against resistant microorganisms.

Another possibility would be to create new molecules but their ex nihilo nature is subjected to secondary effects that we first need to understand and identify. Moreover, their development needs a huge amount of time and money. Another angle of attack that must be considered in a more long-term standpoint would be to change the antibiotic treatment over time. In fact, bacteria are extremely well "optimized" organisms able to survive as efficiently as possible and adapt to the environment, more particularly in an energetic point of view.

Antibiotic resistance is often linked to the modification of a bacteria feature - for instance a shape change of a membrane protein to diminish the affinity to a given antibiotic -. This modification has an energetic cost called “fitness cost”. If we take a population of bacteria subjected to an antibiotic, only bacteria with a mutation allowing then to resist to the antibiotic will survive. During the span of the treatment, every random mutation that would make bacteria sensitive again are a handicap and will not be retained. In the contrary, when we stop the treatment, these mutations are no longer a burden for the carrying bacteria and they can grow again, in a more effective way than resistant bacteria which have to spend energy to express the resistance. Over time, sensitive bacteria, which are advantaged in this precise environment, will become predominant again and the population will lose its ability to resist. Hence, if we prescribe antibiotics that target different part of the bacteria and use them on a cyclical basis (like fallow), with long enough period of time between each use of the same antibiotic so that the bacteria will become sensitive anew, we can theoretically use antibiotherapy indefinitely.

The main reason why this solution is currently impossible to implement is because we over consume every type of antibiotic at the same time. This behaviour led to the emergence of multi-drugs resistant bacteria that we sometimes are unable to cure. Facing this major issue, health authorities have started taking measures to reduce the excessive use of antibiotics and introduce new treatments to prescribe only in extreme cases where classical antibiotics don’t work anymore.

Given this impasse, there is a fourth possible way, and this solution is closely connected to our project: the use of bacteriophages and phage therapy. Roughly speaking, this therapy is already used in Eastern Europe countries since the XIXth century. It involves the administration of phages in an entity: they are viruses naturally found in the environment that infect and kill bacteria very specifically. The main advantage of this specificity is that it allows the removal of pathogenic bacteria without affecting other bacteria (for instance bacteria helping for digestion), unlike broad-spectrum antibiotics. Moreover, phage therapy, thanks to its specificity to target one bacteria specie, is a harmless way to treat a patient.

At last, event though bacteria are capable of developing a resistance toward phages in the same way than for antibiotics, phages possess the advantage of being organisms and not molecules, hence they can co-evolve with the bacteria they target. This technique could be a starting place to answer the alarming progression of antibiotic resistance.

Among all these attempts to find a solution, none claims to beat antibiotic resistance all by itself but only to control its process. Indeed, after every discovery of a new mean to fight resistant bacteria, they will try to evolve and to counter it. This is why, as Darwin envisioned it in his theory, we can say that microorganisms are such a powerful specie, capable of surviving everything, and also a formidable opponent. Hence, our fight should be part of a chronology, a race forward to adapt and innovate before the other party does.

To sum up, we have to find new way to fight, use them wisely and effectively (a bacteria that we know is resistant but can be killed by old ways shouldn't be eliminated with newly found tools). If we add to this equation a good prevention and education to ideally use antibiotics (Public health campaigns: "Les antibiotiques c'est pas automatique" in France or "Become an antibiotic Guardian" in England). And lastly, everything should be articulated around a public health system that prevents the diffusion of resistant microorganisms.

It's the association of these different tools (technological research, good use of existing antibiotics, public awareness, hygiene) that can surely guarantee a sufficient lead in the race for antibiotics. This attempt to solve and wholly understand the problem can also be found through governmental and international programs that were implemented. For example, in May 2015, the WHO, the FAO (*Food and Agriculture organization)*, the UNO (United Nations Organization) and the OIE (World Organization for Animal Health) have adopted an global action plan to fight resistance to antibiotics. It is composed of five axis: sensitize the public health staff, reinforce research and supervision, take measures for sanitization, hygiene and infection prevention, optimize the use of antimicrobials substances for human and animal health, support sustainable investments in finding new treatments, diagnosis and vaccines.

Already engaged in the fight, the EU has launched action plans in 2001 and 2011. The very last one, dating back from June 2017 takes into account the global aspect of the issue and aspires at making Europe a leading region. It includes, among other things, the « *Joint Action on Antimicrobial Resistance & Healthcare - Associated Infections* », coordinated by the Inserm. It gathers 44 institutional partners - Health ministry, research institutes, public health institutes - and aims at moving to the concrete, more particularly by taking inspiration from what is already in place in other countries. Concerning France, a European plan (announced in 2016) was put in action via an interministerial roadmap.

Today, the world has understood that antibiotic resistance is a major challenge for public health. In 2014, for the first time ever, the WHO released an alarming report on the situation and the reality about antibiotic resistance. In the world, 700 000 people are dying every year because of antibiotic resistance and 25 000 of them in Europe.

A number that doesn't cease to increase. Indeed, according to a report from the economist and Financial Secretary to the UK Treasury, Jim O'Neil - an analysis from an economist perspective - if nothing is done, the number of death in the world caused by antibiotic resistance could reach 10 millions in 2050. A reality that depends greatly from the number of resistant bacteria "imported" from other places, from the antibiotic consumption and also from the decisions in public health policy. (Example of the Nigeria: in 2002, more than 95% of the hospitalized patients were systematically treated with two or three different antibiotics when only 5% had been tested to see if the antibiotic was adequate".[8])

To conclude, antibiotic resistance is nowadays a serious global public health issue that is progressing very rapidly. Indeed, despite the WHO mobilization, the number of victims doesn't cease to increase, wirth more and more pessimistic previsions. In view of the urgency to find new therapies, to preserve already existing antibiotics and to limit the resistance progression in the environment, every single project is much welcome.ence, all the research programs whose developing and innovative perspectives could lead to alternative or complementary strategies are needed in the approach that the world should have. Fundamental research in antibiotic resistance is thus the base to therapeutic and diagnostic innovations. This is why our project is a perfect fit to the strategy developed by the "French ministry of health and welfare" when they wrote the "report from the special working group for antibiotic protection" organized in June 2015 ("Together, let's save antibiotics"). Hence, in a global and holistic approach, a priority (first out of nine) that has to be established for 2015-2020 is "the improvement of known antibiotics and the optimal use in treatments, the creation of new antibiotics and alternative therapies (targeted immunotherapy, adjuvants to antibiotic therapy, vaccination, phage therapy etc…)." Concerning our project, we choose to deal with the human aspect of antibiotic resistance, although we are very conscious that a unique and unidirectional answer is in no way a solution. Corollary, it is adds up to the numerous solutions that regularly come up.

Sources:

BRUN-BUISSON, Christian, « Du rapport O'Neill aux données relatives à l'usage des antibiotiques en France et à la stratégie Française », *Colloque : Quelle communication sur l'antibiorésistance ?*, November 2017.

The Centers for Disease Control and Prevention (CDC), « The report, *Antibiotic Resistance Threats in the United States* », 2013.

The Centers for Disease Control and Prevention (CDC), *National action plan for combating antibiotic-resistant bacteria*, March 2015, URL link : https://www.cdc.gov/drugresistance/pdf/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf

European Centre for Disease prevention and Control (ECDC) /European Medicine Agency (EMEA) Joint Technical Report, « *The bacterial challenge: time to react A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents* », September 2009.

Institut National de la Santé et de la Recherche Médicale (Inserm), « Resistance aux antibiotiques, un phénomène massif et préoccupant », URL link : https://www.inserm.fr/information-en-sante/dossiers-information/resistance-antibiotiques, 22/03/2018.

Ministère de l'agriculture, « C'est quoi l'antibioresistance ? », URL link : http://agriculture.gouv.fr/cest-quoi-lantibioresistance, 29/10/2013.

Ministère des Solidarités et de la Santé, « L'antibiorésistance, pourquoi est-ce si grave ? », URL link : http://solidarites-sante.gouv.fr/prevention-en-sante/les-antibiotiques-des-medicaments-essentiels-a-preserver/des-antibiotiques-a-l-antibioresistance/article/l-antibioresistance-pourquoi-est-ce-si-grave, 14/06/2018.

Ministère des Solidarités et de la Santé, « Propositions du groupe de travail spécial pour la préservation des antibiotiques », Rapporteurs Dr Jean CARLET et Pierre LE COZ, Juin 2015, URL link : http://solidarites-sante.gouv.fr/IMG/pdf/rapport_antibiotiques.pdf, Consulté le 11/07/18.

MESLE, France, Institut national d 'études démographiques (JNED), « L'évolution de la mortalité par cause : les différentes facettes de la transition épidémiologique », *médecine/sciences*, Volume 13, n°8-9, pp. 1008-1017, 1997, Lien URL : http://www.ipubli.inserm.fr/bitstream/handle/10608/499/1997_8-9_1008.pdf?sequence=10, Consulté le 11/07/18.

Organisation Mondiale de la Santé, « Resistance aux antibiotiques », Lien URL : http://www.who.int/fr/news-room/fact-sheets/detail/r%C3%A9sistance-aux-antibiotiques, 5/02/2018.

Organisation Mondiale de la Santé, « L'approche multisectorielle de l'OMS «Un monde, une santé» », Septembre 2017, Lien URL : http://www.who.int/features/qa/one-health/fr/, Consulté le 11/07/2018.