Globalisation and antibiotic-resistance epidemiology

Chronicles from the present and impact on a possible future

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Abstract
Globalization has various effects on population health trends and significant implications on public health control. Among the most significant concerns, the rising antimicrobial resistance (AMR) rates and the spread of multi resistant microorganisms are of relevance. An analysis of the factors contributing to the problem is provided to offer an overview and stimulate debate on this key topic.

Running title: Travel and antibiotic resistances

Keywords: migrants, travel, globalization, antibiotic resistances, multidrug resistance, MRD organism, MDRo.

Back in 1962, Hebert Marshall McLuhan first introduced the concept of "global village" into his manuscript "Gutenberg Galaxy": "the world is becoming a global village, a community in which distance and isolation are overcome"[1].

Since then, along with the spreading of globalization we assisted to a reduction on transit time across the world with a quicker mobilization of people and items. This phenomenon, together with the demographic growth and the urbanization on the rise, led to a global spread of pathogens from different areas along with their own carriers. Despite many studies addressed the topic of the spreading antibiotic-resistance on a global scale, at the moment, given their methodological diversity, no conclusive data emerged on the size of the problem and potential factors involved in the spread. However, consistent differences in antibiotic-resistance epidemiology were recorded in different geographical areas according with the "Antimicrobial resistance: global report on surveillance" issued by World Health Organization (WHO)[2].

Multiple factors are involved in the rapid emergence of antibiotic-resistance: over-

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use and misuse of these medications in both infections and prophylaxis, the extensive use in agriculture and the wide deployment as growth supplements in livestock.

Generally speaking, the lack of regulation and monitoring in many countries, together with the impact of globalization, have led not only to the selection but also to the spread of drug-resistant species.

On the grounds of these wide geographical differences in antibiotic-resistance prevalence, other epidemiological factors (such as migration flows, tourism, trade in goods and climate changes) act to amplify the possibility of spread.

1. Migration flows and antibiotic-resistance

There is an increasing body of evidence that human movements facilitate the global spread of resistant bacteria and antimicrobial resistance genes. In particular, the rising antimicrobial resistance (AMR) rates in developing countries, both in healthcare settings and in the community, represent a risk factor for the spread of MDR pathogens especially if these countries are starting points of large migratory flows[3]. Factors facilitating the acquisition and transmission of MDR pathogens among mobile migrants are collapsed housing, hygiene, and healthcare infrastructures in communities of origin as well as poor hygiene conditions during the trip to destination countries[4]. Epidemiological data concerning the relationship among migrant flows and spread of antibiotic-resistance are not conclusive given the methodological diversity of studies carried out till now. However, a recent meta-analysis based on 23 observational studies for a total of 2.319 migrants included from 2000 to 2017 in Europe, showed that the prevalence of any antibiotic-resistance carriage or infection in the given population was 25.4% (CI 95%, 19,1-31,8). This pooled prevalence was higher in refugees and asylum seekers than in other migrants’ groups (33.1%, 11.1-55.1). Regarding methicillin-resistant *Staphylococcus aureus* (MRSA) the prevalence was 7.8% (4.8-10.7) whereas antibiotic-resistant Gram-negative bacteria prevalence was 27.2% (17.6-36.8). Interestingly, no evidence of high rates of transmission of antibiotic-resistance from migrant to host populations was found[5].

2. Role of tourism

International travelers returning from high prevalence AMR destinations to their own countries are possible carriers for resistant microbes acquired through the journey. Moreover, multiple studies showed that the chance of acquiring multi-drug resistant Enterobacteriaceae are related to the local prevalence in the destination area and ranges from 21 to 51% in healthy travels coming from low prevalence area. Trips to Asia or Indian Subcontinent are at major risk for the acquisition of ESBL (extended spectrum beta-lactamase) Enterobacteriaceae or CRE (carbapenem resistant Enterobacteriaceae) with rate of travel-related fecal colonization up to 85%. Lower but still consistent rate of colonization were found for travels to Africa or Middle East countries (13-44%).

Among risk factors for colonization, gastrointestinal discomfort, diarrhea, health care assistance in the destination county and misuse of antibiotics emerged as particularly relevant. High-endemic areas as travel destination was also identified as a major risk factor for the acquisition of Enterobacteriaceae multi-drug resistant, including urinary tract infections[6,7].

Particularly interesting is the case of travelers who undergo hospital admission during their journey. One report carried out in Finland and including 1.122 travelers coming back from their destination after having had an occasional hospitalization abroad revealed a rate of multi-drug resistant bacteria colonization of 55% for those coming from tropical areas and 17% from temperate zone. Colonization rates proved highest in those returning from South Asia (77.6%), followed by those having visited Latin America (60%), Africa (60%) and East and Southeast Asia (52.5%). Independent risk factors for colonization were travel destination, time from hospital discharge, young age, surgical surgery and antibiotic administration[8].

3. Medical tourism

Foreigners seeking medical care are another relevant source for the spread of multi-drug resistant bacteria. In 2018, up to 11 million of persons moved abroad for medical purposes. In this particular population, the risk of becoming drug resistant carriers was estimated to be higher in comparison to the local population. In line with this, a recent study carried out in Israel showed that foreign patients seeking advanced medical care had a 6 to 10-fold higher risk to carry multi-drug resistant bacteria than the resident population. Moreover, this risk resulted associated to the microbiological epidemiology of both the local and the origin country[9].

4. Global trade and antibiotic resistance

The development of resistant pathogens has been attributed not only to increased antibiotic use in hospitals and outpatient facilities but also to veterinary applications and as a result of physical processes used in food production and preservation processes[10].

An interesting example, in this sense, is the recent observation of a major increase of colistin resistance (MCR-1) during a routine surveillance project on antimicrobial resistance in commensal *Escherichia coli* from food animals in China[11].

This new resistance was then identified in humans, food-producing animals, pets and food[12]. Nowadays, MCR-1 has been spreading in over 30 countries as a result of colistin use in food-processing industry[13].

Although potentially relevant, the role of global trade in the spread of resistant bacteria and antimicrobial resistance genes has been poorly explored so far. Unlike human use which appears to be better subject to shared regulations, the use of antimicrobials in the area of food production and in the veterinary field, for example for auxological purposes, is often not subject to univocal international rules. The national and international regulation of food/trade linkage is critical in the control of the potential spread of AMR. However currently, regulations on AMR are problematic mostly in settings where political commitment or bureaucratic capacity to regulate is weak[14].

5. Relative impact of the different determinants on spread of drug-resistant species

In recent years, developed countries and in particular Western Europe have experienced significant influx of migrants and refugees owing to ongoing conflicts, political and economic instability, and humanitarian crises in some African and Asian regions. Despite available data suggest that migrants can be the carriers of a significant burden of multidrug-resistant (MDR) organisms, other factors contribute more substantially to the global spread of AMR. In fact, the International Organization for Migration reported that 257.7 million migrants worldwide in 2017; but in the same period the World Tourism Organization reported 1.4 billion tourists worldwide (of which 11 million for medical treatment, as indicated by the Medical Tourism Association) and 7.1 billion passengers used an air flight (ACI Annual World Airport Traffic Report). Finally, the World Bank reported that 750 million cargo shipping containers were shipped in 2016. On the basis of these data, it is evident that the potential contribution of the various determinants to the spread of AMR is profoundly different, relegating the risk associated with migratory flows to an apparently supporting role.

6. Conclusions

Globalization is an irreversible process with serious and poorly controllable implications on health care. In order to prevent and control the spread of antibiotic resistance worldwide, WHO has supported a robust international action plan to tackle the problem, mainly based on:

- Improving surveillance of antibiotic-resistant infections;
- Strengthen policies, programs, and implementation of infection prevention and control measures;
- Regulate and promote the appropriate use and disposal of quality medicines;
- Make information available on the impact of antibiotic resistance.

However, considering the lack of awareness of many nations, in 2019 WHO listed the spread of antibiotic resistances among the top 10 global public health threats facing humanity and advocated the research in new class of antibiotics and diagnostic tools considering the difficulty of all countries involved.

Notes

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