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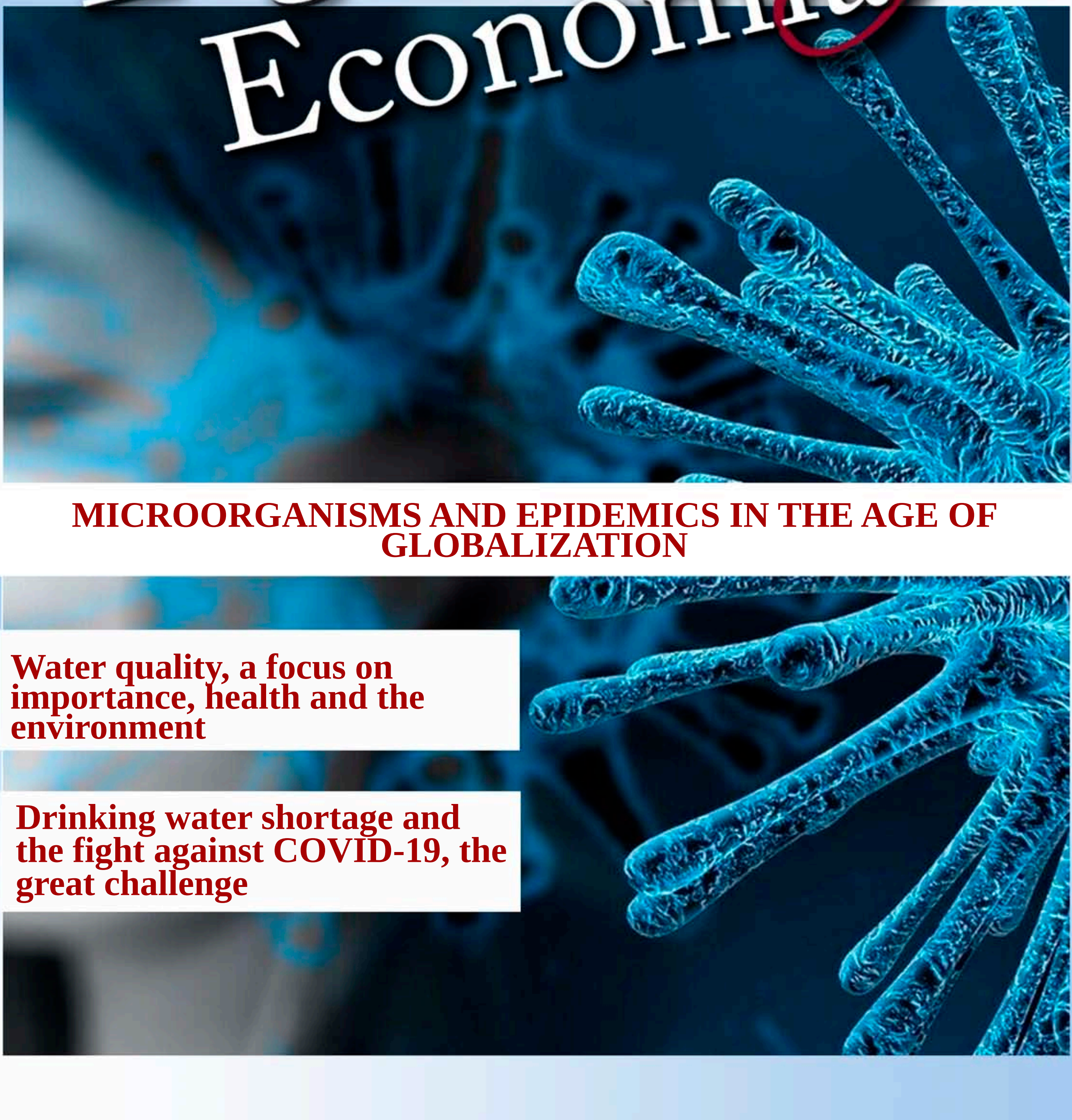

MICROORGANISMS AND EPIDEMICS IN THE AGE OF GLOBALIZATION

Water quality, a focus on importance, health and the environment

Drinking water shortage and the fight against COVID-19, the great challenge

Consejo Editorial

In this edition

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COVID-19

Content

The fight against COVID-19, involves all of us, it is in our hands to contribute to this crisis to pass, please follow the recommendations and stay home. Do not forget to follow us on social networks, to be aware of everything related to this pandemic.

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Invited Writer

MICROORGANISMS AND EPIDEMICS IN THE AGE OF GLOBALIZATION

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Summary:

The increase in outbreaks and epidemics of emerging and reemerging infectious diseases in developing and developed countries invites us to analyze the relationship between humans and nature of which we are also part, since that delicate relationship is being seriously altered by the overexploitation of land and invasion of wild spaces; climate change; accelerated globalization; the growth of the population and the development of megalopolis with its inevitable lúmpenes; forced or uncontrolled migrations, and other elements that facilitate the emergence and transmission of old and new pathogens.

The history of humanity, as well as the result of many wars, as it is summarily exposed, have been, to a certain extent, a consequence of infectious pathology. The outbreaks that are causing the most alarm, especially RNA virus zoonoses, antimicrobial resistance, and the three major pandemics (tuberculosis, HIV / AIDS, and malaria) are reviewed in more detail in this document, which ends by giving an overview of the global activities of different institutions (national, multilateral, public and private) to deal with threats from infectious agents.

"Before the turn of the twentieth century, the health problems of the industrialized world were very different and independent from those that could be found in the colonized territories; in many ways "the West" and the "rest" were just beginning to contact. However, during the twentieth century everything grew in an intertwined way by the transformation of empires, the gigantic migrations, the changes that accompanied capitalism, the revolutions in communications,

[1] PORTER, R. The Greatest Benefit to Mankind: A Medical History of Humanity. New York: Norton & Company 1998, p. 483.

the world wars and the globalization of politics ». Roy Porter, The Greatest Benefit to Mankind.

Globalization can be defined as a process of planetary scope characterized by the flow of people, animals, plants, microorganisms, goods, knowledge, techniques, arts, customs, beliefs, etc. across geographic, political, cultural and ethnic borders. Although it is receiving increasing attention in the last five years due to its magnitude and irrepressible strength, it constitutes a phenomenon that comes from very old. Just think of the expansion of Homo sapiens across our planet that began tens of thousands of years ago. In those days, when that slow and unstoppable exodus began from the African lands, the humans who were hunter-gatherers lived in small communities, made up of just over a hundred individuals ("Dunbar number")..

Given that they were scattered over vast geographical areas, exchange of pathogens between them was improbable and, therefore, risk of epidemics. In contrast, life in cities, more than 50% of humans are already urbanites, has increased incidence and severity of infectious diseases capable of causing pandemics.

The long and rich political, warrior and commercial history of Mesogeios Thalassa ("sea in the middle of the lands"), which was what the Greeks called the Mediterranean Sea; the Silk Road started in the 1st century BC.; the expansion of Viking peoples during the 9th and 10th centuries; the Mongol invasions throughout the 13th century; the "black death" that ravaged Europe in the fourteenth century using commercial routes; the transoceanic routes opened and explored by Portuguese and Spanish since the end of the 15th century and the intense trade that followed between the 16th and 19th centuries, in which the transfer of microbes was also present, constitute historical realities that were joined by others close in time and, therefore, more present in our memory as the misnamed «Spanish flu».

This very brief overview is only intended to remember that globalization and its far-reaching consequences - including the exchange of microorganisms and the appearance of infectious outbreaks - have always existed. It is its geographical breadth, intensity and speed that determine the character of this old phenomenon in each period. Today more than ever the pandemics, epidemics and infectious outbreaks that we have suffered and those that we know may be stalking us emphasize the need to anticipate them or be prepared for when they appear.

Therefore, we have to interpret today's globalization as an old force. Being its enormous strength, scope and magnitude what is really new - it is important to repeat it. It is the result of the very powerful technology that we enjoy, the almost disappearance of borders and tariffs (although it seems that some want to go back to the old days), the general increase of wealth (although there is still a long way to go) and an astonishing increase in population (figure 1) and life expectancy. Changes that have given rise to a much more diverse and accelerated traffic of goods and living beings within a highly urbanized and hyper-communicated world. To the point that for Christakis and Fowler our time is Homo dictyous ("man in a network"). As a sample button of all this, we note that 99.9% of malaria cases registered by

[2] DUNBAR RIM. «Coevolution of neocortical size, group size and language in humans». Behavioral and Brain Sciences 16(4). 1993, pp. 681-735.
[3] CHRISTAKIS, N. A.; FOWLER, J. H. Conectados: El sorprendente poder de las redes sociales y cómo nos afectan. Barcelona: Taurus 2010, p. 233.
[4] EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL. Communicable Disease Threats Report (CDRT) [acceso: 8/5/2018]. Disponible en https://ecdc.europa.eu/sites/portal/files/documents/Malaria%20AER_1.pdf

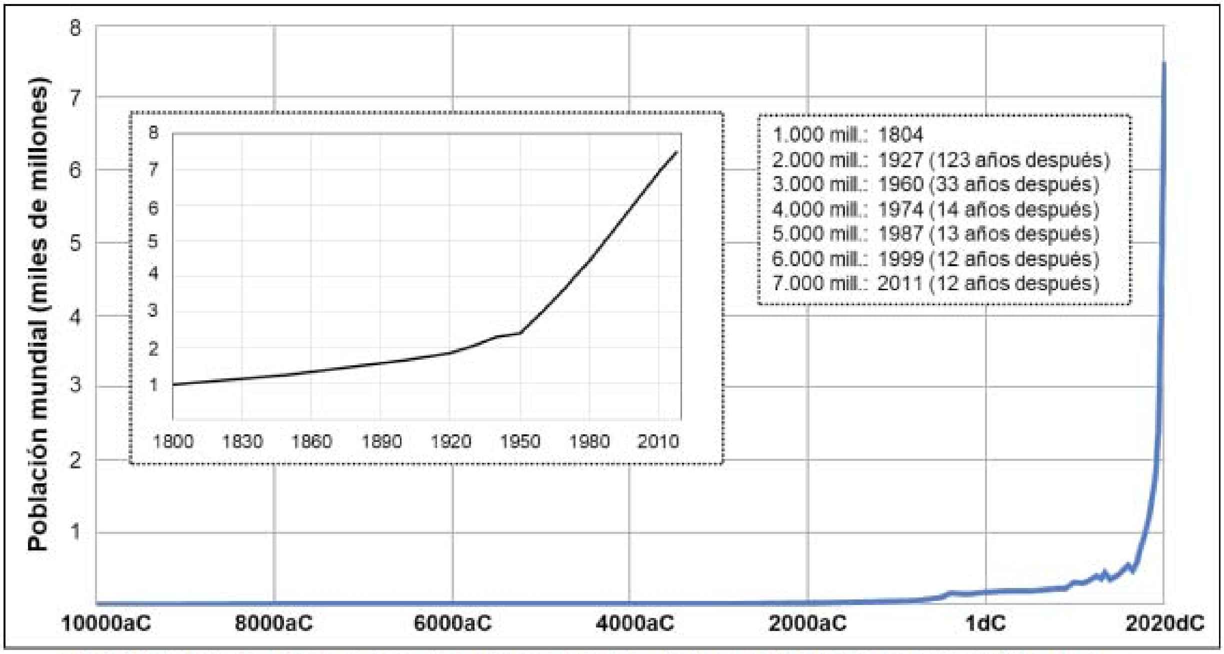


Figura 1. Evolución de la población mundial, desde el Neolítico al año 2018 d. C.
Fuente: Elaboración propia[5 6].

the European Surveillance System (TESSy) in the EU / EEA countries, in 2014, were imported from endemic areas, especially Africa4. At this point, the reader should be warned that this chapter will deal with a set of intricate problems that can hardly be understood from the limits of a single discipline.

Brief history of infectious diseases

Infectious agents must parasitize higher organisms to obtain the nutrients and energy necessary for the functioning of their trophic systems. Most infections are benign and some even beneficial to the host and invader, this is the case of the normal microbiota (or human microbiome). Thus, only a minority of microbial invasions, due to the damage they cause to the host's health, can be labeled as "infectious disease".

From epidemiological point of view, Homo sapiens has undergone profound transformations from its origins due to various causes that we can summarize as follows:

- The long processes of expansion and habitation throughout the planet, known as prehistoric and historical human migrations.

- Exchanges (including genetic) between the dispersed and isolated populations that make up our species (and with Neanderthals until 20,000 or 30,000 years ago).

- The emergence of agriculture and the domestication of certain animals in the Neolithic, developments that were the origin of cities and, therefore, the beginning of human agglomerations and closer contact with desired and unwanted domestic animals (for example, rodents).

[5] UNITED NATIONS. Population Division. The World at Six Billion. New York, 1999, pp. 5 y 8.
[6] WIKIPEDIA. World population [acceso: 6/5/2019]. Disponible en https://en.wikipedia.org/wiki/World_population
[7] KUHLWILM, M.; GRONAU, I.; HUBISZ, M. J. y cols. «Ancient gene flow from early modern humans into Eastern Neanderthals». Nature 530(7591). 2016, pp. 429-433.

- The gradual technological advances that have led to sewerage, running water, better ventilated and healthier homes, food security, antibiotics, vaccines, etc.

All these facts have punctured the great epidemiological patterns exhibited by our species over time. That, although sifted by the civilization process, can still be observed in the different geographical areas. The most pristine pattern, that of H. sapiens hunter-gatherer, persists even in the more than 100 uncontacted tribes that are probably in the world today, located mainly in Amazonian and Papuan lands8 (this author supports the position that it is not necessary to arm expeditions to study this phenomenon).

William H. McNeill (1917-2016), in his canonical work Plagues and People, distinguished five stages in our species' long relationship with microbes.:

- First. The emergence of agriculture and livestock in the Fertile Crescent, some 10,000 years ago, brought about the first major change in these bilateral relations. Today, just as then, the transformation of our habitat puts us in contact with «new» microorganisms that we later infect other congeners - more or less quickly - because of our movements. Thus, childhood infections originated at that time from pathogens that arose from contact with domesticated animals. In the same way that today's emerging infections arise from our approaches, by invasion and fracture of wild spaces, to the horseshoe bat (SARS Severe Acute Respiratory Syndrome), the chimpanzee (HIV) or the Rhesus monkey (Zika). In addition, empirical epidemiological studies on the persistence or disappearance of infections, in isolated human populations of various sizes, have provided estimates of the number of individuals required to maintain a disease within a human group (crowd disease). In the case of measles, rubella, and whooping cough, at least several hundred individuals are required; something that was only achieved with the birth of the proto-cities, that is, when we started to become farmers and herders.

- Second. It would result from encounter between infectious diseases already "civilized" and settled in different regions of Eurasia, in which a balance had been reached between humans and their microorganisms. As it is part of the work of historians to date great phenomena that have marked our course, beginning of this stage - according to McNeill - would be marked by Second Medical War (480-479 BC) started by Xerxes the Great, when he tried to conquer Greece to take over its fertile lands and thus maintain great parasite of society that distinguished his empire.

- Third. It would start at the dawn of the 13th century with the Mongol invasions started in the Far East that reached the easternmost areas of Europe, where the black plague pandemic that arrived in Italy in 1346 began, and from there spread to the rest of the continent. All studies suggest that it was spread by infected rats and fleas traveling on Genoese merchant ships as they fled from Caffa, a city on the Black Sea. Since then, although less virulent, successive outbreaks were not extinguished until the

[8] HOLMES H. «How many uncontacted tribes are left in the world?». New scientist [acceso: 20/3/2019]. Disponible en https://www.newscientist.com/article/dn24090-how-many-uncontacted-tribes-are-left-in-theworld/
[9] MCNEILL, W. H. Plagues and peoples. New York (EE. UU.): Anchor Books Editions 1998, p. 7.
[10] WOLFE N. D.; DUNAVAN, C. P.; DIAMOND, J. «Origins of major human infectious diseases». Nature, 447. 2007, pp. 279-283.
[11] MCNEILL W. H. Plagues and peoples, op. cit., pp. 94-95

beginning of the 18th century. Yersinia pestis (the plague-causing bacteria) was the most conspicuous microbe of this stage. Although it had already debuted much earlier, having caused, among others, the plague of Justinian (541-543 AD), which wreaked great havoc on the Eastern Roman Empire, it disappeared from the domains of Christian Europe in the second half. of the 8th century, since the last mention that exists about it in Christian sources dates back to the year 767. Therefore, it is assumed that, after a series of precarious jumps between cities in the Mediterranean, the microorganism did not find an ecological niche in which perpetuate.

The fourteenth century black plague was lived in apocalyptic terms. He was an unexpected guest of whom nothing was known and his etiology fell prey to all kinds of lucubrations typical of the time, from the wrath of God to an unfortunate crossing of stars and affected all social strata; it caused a very great death, and it was not safe from it neither in the field nor in the city. As the plague was a zoonosis, the contagion was assured because humans, merchandise and rats shared the same habitat (houses, boats, barns or wagons) and traveled on the same sea and river routes, and on roads crowded with pilgrims. The epidemic jumped between the big cities that became, in turn, new dispersal nuclei that ended up reaching the rural environment. Although all this happened very slowly, since in those days a plague started in the southern parts of Europe took more than three years to appear in the northernmost corners. The average speed with which he moved did not exceed five kilometers a day. In contrast, the first SARS case registered in Canada in 2003 only took one day to cover the 12 542 kilometers that separate Hong Kong from Toronto.

- Fourth. It would be the result of the discovery of the New World in the late fifteenth century, and would lead to what the American historian Alfred W. Crosby 16 called the "Columbian Exchange". Thus, from the first lights of the 16th century, there was a notable two-way traffic of agricultural products, animals, knowledge, technological advances and microorganisms between the New and the Old World, a flow that still persists with enormous intensity. Naturally, in this exchange there was no lack of exemplary events. In this category the event that occurred in 1763 during the Pontiac rebellion (1763-1766) can be included - as it was a premeditated action. As the Amerindians in that area of Michigan were hostile to the foreign presence, Sir Geoffrey Amherst (1717-1797), the commander-in-chief of British troops in North America, gave the order to use any means to end the rebels, to what his subordinate, Colonel Henry Bouquet (1719-1765), replied

12 MCNEILL, W. H. Plagues and peoples, op. cit., pp. 170-171.
13 «La peste negra, la epidemia más mortífera». National Geographic (edición en español). 17 de agosto de 2012 [acceso: 9/5/2018]. Disponible en http://www.nationalgeographic.com.es/historia/grandesreportajes/la-peste-negra-la-epidemia-mas-mortifera_6280/1
14 SCOTT, S.; DUNCAN, C. J. Biology of Plagues: Evidence from Historical Populations. Cambridge: Cambridge University Press, 2001. Citado en Christakis, N. A., Fowler, J. H. Conectados, op. cit., p. 157.
15 CENTERS FOR DISEASE CONTROL AND PREVENTION. «Update: Severe Acute Respiratory Syndrome». MMWR 52(23). Toronto, Canada, 2003, pp. 547-550, [acceso: 29/3/2019]. Disponible en https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5223a4.htm
16 CROSBY, A. W. The Columbian Exchange: Biological and Cultural Consequences of 1492. Westport (Conn., EE. UU.): Greenwood Press 1973.
17 BOUQUET, H. Letter, July 13, 1763. MSS 21634:321. British Library. London [acceso: 25/3/2019]. Disponible en http://www.nativeweb.org/pages/legal/amherst/34_40_305_fn.jpeg
18 HENDERSON, D. A. y cols. «Smallpox as a Biological Weapon». Medical and Public Health Management. JAMA 281.1999, pp. 2127-2137.

with a letter in the following terms: "I will try to inoculate the Indians with some blankets that fall into their hands and I will avoid getting infected» 17. This unfortunate event, in the opinion of the director of the smallpox eradication program, Donald Henderson (1928-2016), inaugurated the beginning of the use of the virus that causes it as a "biological weapon».

It is worth remembering that imported communicable diseases had (and can have) devastating consequences for everyone. The plague epidemic that shook Spain between 1596 and 1602, killed more than half a million souls. Its beginning took place in port of Santander where Rodamundo, a ship from Dunkerque (France) and responsible for tragedy, docked. Again, throughout the 17th century, "black death" visited us on several occasions, especially through the port of Malaga, causing more than a million additional deaths. Some authors have considered Y. pestis as an important adjuvant to the economic and political decline of our country.

- Fifth. It would originate in the eighteenth century and would come from the organization ("stateization") of science, some advances in medicine and the beginning of the Industrial Revolution. This, among other things, meant for cities (especially in those where manufacturing activity was rampant) enormous human agglomerations, unhealthy living conditions and poverty. Well, as Stephen S. Morse has pointed out: «The lúmpenes constitute the highways of microbial traffic». For its part, medicine began to advance hand in hand with science; An exemplary result of this fruitful pairing can be found in the "Royal Philanthropic Vaccine Expedition", begun when the nineteenth century dawned and to which some comments are devoted in another chapter of this monograph.

An equivalent in the nineteenth century of the appalling consequences of plague epidemics in seventeenth-century Spain can be seen in the Irish potato famine (1845-1849), triggered by the emergence of a late blight plague, the agent of which is an oomycete of Andean origin, Phytophthora infestans. Of a population of eight million people who inhabited the island at the time, approximately one million (12.5%) died of hunger and another 1.5 million (19%) were forced to migrate..

Because McNeill's work was published in 1977, I venture to propose a sixth stage that would begin with the eradication of smallpox, at which time the world begins to witness an accelerated and widespread reduction in infant mortality, by time that increased life expectancy to levels never imagined. It can also be verified that the catastrophic theories, so widespread at the end of the 1960s and the beginning of the following, based on the neo-Malthusian idea that the needs derived from the enormous growth of the population could not be met, neither with the existing resources in that moment or with those to come, were not met. Rather, since then we have witnessed three simultaneous and closely related historical revolutions: the

[19] MCNEILL, W. H. Plagues and peoples, op. cit., p. 182.
[20] KOHN, G. C. Encyclopedia of Plague and Pestilence: From Ancient Times to the Present. New York: Facts on File, Inc. 2008, pp. 372-375.
[21] MORSE, S. S. «Global microbial traffic and the interchange of disease». AJPH 82. 1992, pp. 1407-1413.
[22] «Diseases of plants». Encyclopaedia Britannica. 15.ª edición, vol. 17. Chicago (EE. UU.), 1988, p. 359.
[23] «Famine». Encyclopaedia Britannica, op. cit., vol. 4, pp. 674-5.
[24] EHRLICH. P. R. The Population Bomb. New York: Ballantine Books 1971, p. xi.
[25] MCKEOWN, T. El papel de la medicina: ¿sueño, espejismo o némesis? México: Siglo XXI, 1982.

technological-digital, the demographic (characterized, apart from what has already been pointed out, by an estimated decrease in the number and percentage of people living in situations of extreme poverty, and a significant reduction in famines) and that caused by a vigorous globalization. What has transformed the ecosystem and, therefore, the dynamics and scope of epidemic outbreaks that affect all living things.

In summary, throughout history a myriad of factors not only physicians and those who find it difficult to assign their true weight separately (as in any complex, nonlinear system), have governed our species' intricate relationships with the world of microbes and therefore with health and disease.

Let's not forget the basics

The entire history of Homo sapiens –as we are seeing– is not influenced by infections. These can affect a large number of people or animals in a certain geographical area and during a specific period of time, a phenomenon that we call «epidemic» (from the Greek: epí, sobre; and dêmos, pueblo). On other occasions and as a consequence of the civilization process, they afflict a high percentage of individuals or animals in one or several countries and almost simultaneously, so we speak of a "pandemic" (from the Greek: pan, everything; and dêmos, pueblo).

Infectious disease occurs when a microorganism invades a host, multiplies in its tissues, and initiates an immune-inflammatory reaction in order to exterminate the invader or the toxins it produces. Infections can be local or systemic (generalized) and be caused by bacteria, viruses, prions, fungi, protozoa, or helminths.

The term "emerging infection" refers to two phenomena: On the one hand, the appearance of a new infectious disease caused by a microorganism that had not previously infected our species or had not been identified as pathogenic for our species, examples of this are the Rickettsia sibirica mongolitimonae, the SARS coronavirus, the Guanarito virus or Helicobacter pylori and, on the other, to the emergence of a reemerging infection, that is, of a disease whose incidence is increasing, either in its traditional geographical location or outside it. This is what is being observed, especially with arboviruses (ARthropod-Borne virus) or arthropod-borne viruses. A good example of reemerging infection is found in what happened in August 1999: cases recorded at that time of avian and human equine encephalitis announced the appearance in New York of a well-known Old World arbovirus, the West Nile virus (transmitted by A mosquito). Five years later it had become endemic in the United States, southern Canada, the Caribbean, and South America. Phylogenetic studies support the idea that it was introduced to the New World only once,

[26] Diccionario terminológico de ciencias médicas. Barcelona: Elsevier Masson 13.ª ed., 1992; pp. 417 y 921.
[27] YU, X. y cols. «Genotypic and antigenic identification of two new strains of spotted fever group rickettsiae isolated from China». J Clin Microbiol 31. 1993, pp. 83-8.
[28] SALAS, R.; PACHECO, M. E.; RAMOS, B. y cols. «Venezuelan haemorrhagic fever». Lancet 338 (8774). 1991, pp. 1033-1036.
[29] MARSHALL, B. J.; WARREN, J. R. «Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration». The Lancet 323(8390). 1984, pp. 1311-1315.
[30] CRAWFORD, D. H. Viruses: A Very Short Introduction. Oxford: Oxford University Press, 2018, pp. 33-34.
[31] GOULD, E.; PETTERSSON, J.; HIGGS, S. y cols. «Emerging arboviruses: Why today?». One Health 4. 2017, pp. 1-13.
[32] CENTERS FOR DISEASE CONTROL AND PREVENTION. «West Nile virus. Final Cumulative Maps & Data for 1999–2016» [acceso: 3-4-2018]. Disponible en https://www.cdc.gov/westnile/statsmaps/cumMapsData.html

which places us before an episode of anthropogenic origin, in which migratory birds did not mediate, since almost certainly they would have introduced it into more of an occasion. This was not an obstacle so that, once the virus arrived in New York, birds played an important role in its spread and epidemiology. In 1999, only 66 cases had been registered in the USA. USA, all in New York. In 2016 they exceeded 46,000 and were already dispersed in all the states that make up this immense country, with the exception of Alaska.

A little more than 1,400 microorganisms have been identified that are pathogenic for humans, of which about 800 are zoonotic species made up of bacteria, viruses, prions, fungi or parasites. Of the approximately 400 emerging or reemerging pathogens observed in the last 70 years and affecting our species, we know that 60% are zoonotic and that a considerable number of them are RNA viruses. As we will see later, we have limited ability to predict how a new zoonotic pathogen will act. Although they are especially worrying for those that invade us with difficulty, but then they are successfully transmitted between us until producing worldwide pandemics, as has happened, for example, with the HIV or the recombinant porcine H1N1 virus (pH1N1 / 2009) detected in Veracruz (Mexico) On the other hand, because HIV and flu are now spread from person to person without the help of an initiating animal host, the WHO no longer considers them zoonoses.

It is interesting to keep in mind that infectious outbreaks are observed in all living species. Everything that exists in nature coexists and is interdependent, an idea already ingrained in Greek philosophy and also included in the Hippocratic Body (4th century BC). Three examples should serve to underline that there is only «One health» (One Health) and it is very dependent on the environment in which we live (One World):

- White spot syndrome is a disease caused by a very lethal virus (whispovirus) (its mortality reaches 70%) for shrimp and shrimp, especially those raised in aquaculture, so its outbreaks carry considerable economic losses given the high market value of these crustaceans.

- The small ruminant plague (RPP) that sickens these domestic animals, although not our species, is caused by a morbillivirus that belongs to the same family as the measles virus and the rinderpest virus (this has been the second and last fully eradicated infectious disease, after smallpox 36). The producer agent of the PPR can infect up to 90% of the cabins and end up annihilating 70% of its members. As a result, PPR, as it is easily understood, poses a huge threat to the economy and food security of many poor rural households. 80% of the 2.1 billion sheep and goats estimated to inhabit the Earth live in certain regions of

[33] LEVIN, S. y SINGH K. «Zoonosis». En Goldman-Cecil. Tratado de medicina interna, 25.ª Edición. Elsevier España, S. L. U. 2017, pp. 2056-2060.
[34] ONE HEALTH INITIATIVE. Disponible en www.onehealthinitiative.com
[35] «White spot disease overview». Queensland Government. Department of Agriculture and Fisheries [acceso: 21/3/2018]. Disponible en https://www.daf.qld.gov.au/business-priorities/animalindustries/animal-health-and-diseases/a-z-list/white-spot-disease/overview
[36] MCNEIL, D. G. «Rinderpest, Scourge of Cattle, Is Vanquished». The New York Times, 2011 June 27 [acceso: 28/3/2018]. Disponible en https://www.nytimes.com/2011/06/28/health/28rinderpest.html
[37] «Global control and eradication of 'peste des petits ruminants'». Investing in veterinary systems, food security and poverty alleviation. OIE and FAO, 2015 [acceso: 15/4/2018]. Disponible en http://www.fao.org/3/a-i4477e.pdf
[38] SCHEELE, B. C. et al. «Amphibian fungal panzootic causes catastrophic and ongoing loss of biodiversity». Science 363(6434). 2019, pp. 1459-1463.

Africa and Asia haunted by this virosis.

- Chytridiomycosis is an infectious fungal disease caused by Batrachochytrium dendrobatidis (isolated 20 years ago), which has caused massive deaths in recent decades and the extinction on a planetary scale of different species of amphibians. This fungus is responsible for the decline of 501 species of these wet-skinned vertebrates, including the alleged disappearance of 90 of them. According to Scheele y Cols: «Panzootic chytridiomycosis represents the largest recorded loss of biodiversity attributable to a disease." This constitutes a clear example of how the old anthropogenic activity has broken down the barriers to the dispersal of living beings and diseases that threaten biodiversity.

Every time an infectious outbreak appears, something that happens from time to time and unannounced, it causes the population of the area where a more or less serious infectious or communicable disease develops, from which those affected can recover ad integrum, the expected after a common cold; or accompanied by sequelae, which is what is very frequently observed in polio; or lead to death (a large part of the population), which is common in plagues of plague or Ebola.

The fate of each individual when contracting an infectious disease depends essentially on three factors: the virulence of the pathogen that causes it, that is, its ability to cause a disease, which is as much as saying its ability to break all protective barriers; the susceptibility of the host, that is, its resources to neutralize the offending agent, especially by activating its immune system; and the possibility of accessing - if it has already been developed - an adequate therapy.

The susceptibility of the host determines that the type of pathogen causing the infection and its evolution and severity are not the same in a fetus, a newborn, a child, an adult or the elderly. In the same way that they are not comparable in an immunocompetent (healthy) individual or in an immunosuppressed individual, since this is not only more likely to develop an infection by the most common microbes (as is the case of the tubercle bacillus in those diagnosed with AIDS), but that it becomes a propitious victim for the so-called «opportunistic pathogens», which are those microorganisms that are part of the flora of our environment or the microbiota. Thus, C. difficile, which is part of the intestinal flora, in some individuals constitutes the most important cause of pseudomembranous colitis, which can be caused by treatment with certain antibiotics.

It also happens that some viruses, this is the case of herpes simplex and cytomegalovirus, have the ability to infect and immediately remain in the host's cells without interfering with their functions, in a state of latency that is interrupted when they receive signals that the host's immune system is compromised.

The risk of getting sick, either from a microorganism or from another cause, is determined by certain habits and behaviors, diet, environmental degradation (natural or urban), educational and economic level, stress, genetics, operation of health services, etc. In general, it can be stated that diseases, including communicable diseases, do not occur randomly, but when certain circumstances converge. On the other hand, in any conflict such as the one that arises between health and disease there are always at least two points of view. So, according to Jared Diamond 39, From the perspective of the infected human

[39] DIAMOND, J. Guns, Germs, and Steel: The Fates of Human Societies. New York: W. W. Norton 1997,p. 199.

being, genital injuries, diarrhea, cough or sneezing are the symptoms of the disease. While from the invading microorganism, these symptoms constitute shrewd strategies - the result of evolution - with which it tries to ensure their perpetuation. Hence the interest of the microbe in which we become ill.

The pathogens (or their progeny) in order to survive must inevitably invade a host. This can occur through various routes described below:

- Air or respiratory transmission. Some pathogens are airborne suspended in aerosols or droplets (so-called Flügge droplets) that we produce by speaking, coughing, or sneezing, which retain the temperature and humidity they need for survival before invading a new host through their nose , mouth or ocular conjunctiva. Tuberculosis or influenza are transmitted through this route, as is the lethal inhalation anthrax (anthrax) that develops after breathing the spores released by Bacillus anthracis. The prognosis of patients invaded by these spores depends on the early diagnosis and the establishment of adequate antibiotic and support treatment. Even with these measures, inhalation mortality associated with anthrax is likely to exceed 55%. Unique characteristics that make it a prototypical weapon of bioterrorism, although it rarely spreads from one person to another. Anthrax attacks recorded in five US cities. USA Between September 18 and October 9, 2001 they infected 22 people. Of these, 11 were by inhalation, five died; the other 11 were infected through the skin (cutaneous anthrax), and no fatal case was recorded in this group, although before the antibiotic era, their mortality was around 20%. This gram-positive bacillus can also infect digestively.

- Digestive transmission. Some pathogens cause infections because they contaminate food or water. Cholera or the ubiquitous enteric infections are transmitted in this way. Before 1991, there had been no cholera outbreak in South America for a century. But sometimes there are a series of circumstances that inevitably end in an epidemic. That was what happened that year: a ship that docked on the Peruvian central coast pumped its bilge waters contaminated by Vibrio cholerae (specifically by the strain nicknamed El Tor, responsible for the seventh pandemic started in 1961 in Indonesia) and caused a outbreak, the first cases of which appeared in Chancay (a coastal city 60 km north of Lima). From there it spread from suburb to suburb across the continent, leading to a pandemic. It was not the first time that a ship pumped water contaminated by this bacillus on the Peruvian coast or anywhere else in the world. However, at that time the conditions were conducive to the hatching of this diarrheal disease, as the ecological niches that constitute the reservoir of this flagellated bacterium converge with optimal salinity, a rise in environmental temperature and an increase in the level of rivers. 41. Added to this was the fact that the suburbs of South American cities had grown rapidly and their inhabitants suffered in what was known as the "lost decade of Latin America", which began with the financial crisis in Mexico in 1982, which led to deficits. nutritional and a weakening of basic social infrastructure

[40] LANE, H. C. y FAUCCI, A. S. «Bioterrorismo microbiano». En Faucci A. S. et al. Principios de Medicina Interna. 17.ª Ed. Editorial McGraw Hill 2008, pp. 1343-1352.

[41] Experiencia de la epidemia del cólera en el Perú 1991. CRD sobre informes nacionales de Perú. Foro Mundial FAO/OMS de autoridades sobre inocuidad de los alimentos. Marrakech (Marruecos): 28-30 de enero de 2002 [acceso: 2/4/2018]. Disponible en http://www.fao.org/docrep/meeting/004/ab416s.htmu

[42] ALI, M. et al. «Updated global burden of cholera in endemic countries». PLoS Negl Trop Dis 2015; 9(6):e0003832.

and services. It is estimated that each year, worldwide, there are between 1.3 and 4 million cases of cholera that cause between 21,000 and 143,000 deaths.

- Sexual transmission. The contagion occurs during sexual intercourse (vaginal, anal or oral). Among others, syphilis, gonorrhea and HIV are transmitted in this way. Regarding the pandemic that we suffer from this retrovirus, it must be said, even if the political correction feels aggrieved, that "it is not solved solely by technical means. The challenge we face is that of being able to reduce risk, since sexual behaviors can change. Scientific evidence suggests that only a few key interventions are capable of significantly changing the evolution of this pandemic, namely reducing the number of sexual partners and delaying the start of sexual intercourse. Behind this, there is no other recommendation than the one proclaimed since the dawn of this infection: abstinence, fidelity and the use of condoms». After vaginal intercourse, the risk of HIV infection is 4 and 8 per 10,000 exposures for men and women, respectively. In anal sex it rises to 11 for the partner who performs the penetration and to 138 per 10,000 exposures for the recipient (male or female).

- Iatrogenic transmission. It is caused inadvertently when contaminated clinical instruments are used for diagnostic or therapeutic purposes. Or the sanitary personnel don't keep norms of asepsis, verbigracia, hygiene of hands. Or a transfusion contaminated with hepatitis C virus is carried out, or a transplant of a parasitized organ, for example, the protozoan that causes Chagas disease. About 7.74% of the patients admitted to Spanish hospitals in 2017 developed a nosocomial (or in-hospital) infection, which entails a high economic and personal cost that warrants more detailed studies. The use of needles and transfusions contaminated with HIV represent, respectively, a risk of being infected of 63 and 9 250 per 10,000 exposures.

- Vector transmission. A not inconsiderable number of infectious diseases (malaria, dengue, chikungunya or Zika) require a living organism - a vector - that does not cause the disease, but carries the microorganism that causes an infected host to a healthy one. A large number of vectors are blood-sucking insects that ingest pathogens contained in the blood of an infected living being and then inoculate them into a new carrier by aspirating their blood. Almost a fifth of all infections are transmitted by vectors, causing high morbidity and more than 700,000

[43] WHITESIDE A. HIV & AIDS. A Very Short Introduction. Oxford: Oxford University Press 2016, p. 51.
[44] CENTERS FOR DISEASE CONTROL AND PREVENTION. Estimated Per-Act Probability of Acquiring HIV from an Infected Source, by Exposure Act [acceso: 2/4/2018]. Disponible en https://www.cdc.gov/hiv/risk/estimates/riskbehaviors.html
[45] SEMPSPH (Sociedad Española de Medicina Preventiva, Salud Pública e Higiene). Estudio de prevalencia de las infecciones nosocomiales en España (EPINE), 2017 [acceso: 2/4/2018]. Disponible en http://hws.vhebron.net/epine/Global/EPINEEPPS%202017%20Informe%20Global%20de%20Espa%C3%B1a%20Resumen.pdf
[46] CENTERS FOR DISEASE CONTROL AND PREVENTION. Estimated Per-Act Probability of Acquiring HIV from an Infected Source, by Exposure Act, op. cit.
[47] ORGANIZACIÓN MUNDIAL DE LA SALUD. Nota descriptiva. Enfermedades transmitidas por vectores. Organización Mundial de la Salud, octubre de 2017 [acceso: 8/5/2018]. Disponible en http://www.who.int/mediacentre/factsheets/fs387/es/
[48] FORD-JONES, E. L.; KELLNER, J. D. «Cheap torches: An acronym for congenital and perinatal infections». Pediatr Infect Dis J. 14(7). 1995, pp. 638-640.

deaths annually. Because they especially affect the populations of the poorest countries, those located in tropical and subtropical areas, which also have poorly endowed and constantly restless health systems. Many of these conditions are preventable using protective measures that have been shown to be effective. Apart from the mosquitoes that have been the most studied, some flies, ticks, fleas, triatomines and certain water snails also act as vectors..

- Vertical transmission. It occurs when a pathogen passes directly from the mother to the embryo, fetus, or newborn during pregnancy or delivery. What can happen if the mother gets an infection in pregnancy. The acronym "Cheaptorches" is an excellent mnemonic rule about congenital and neonatal infections and refers to the following infectious pictures: C: chickenpox and shingles (chickenpox and herpes zoster). H: hepatitis C, (D), E. E: enterovirus. A: AIDS. P: parvovirus B19. T: toxoplasmosis. Or: others (group B streptococcus, listeria, candida, Lyme disease). A: rubella. C: cytomegalovirus. H: herpes simplex. E: everything else sexually transmitted (any other sexually transmitted disease). S: syphilis. Returning to the risks of HIV infection, it must be said that if the mother is receiving antiretroviral therapy, the newborn will become infected in 10% of cases; if it is not, it will be spread in 25% of cases.

Summarizing what has been developed in the preceding paragraphs, infectious diseases according to their mode of transmission can be classified according to whether they are produced by direct contact from person to person (including aerosols or droplets from nasopharyngeal secretions) or from animal to person; or by indirect contact through a live vector (mosquito or tick) or a physical vehicle (soil, water, food or fomites). They can also be classified according to their natural reservoir, human (anthroponosis) or animal (zoonosis). These distinctions are important from the point of view of the strategy aimed at extinguishing an outbreak, indicating how and where to act. However, the simplicity of this classification should not confuse us, since on many occasions the origin and transmission of a pathogen cannot be established in such a clear way. Let us take an example, although the majority of human cases diagnosed with Middle East respiratory syndrome (MERS) have been attributed to transmission from person to person –especially in healthcare settings–, current scientific knowledge indicates that dromedaries are an important MERS-producing coronavirus reservoir (MERS-CoV) and a source of human infection. The specific role of these desert artiodactyls in the spread of the coronavirus and exact pathways by which microbe is transmitted are still unknown.

But before tackling the next section, it should be noted that in general most zoonoses are not transmissible directly or indirectly between people (as they behave as a final host) or, if they are, they are only minimally so as with rabies, Rift Valley fever, or Lyme disease. Only 10% of infections spread almost exclusively from person to person without the mediation of another living being (this is the case of tuberculosis and measles). We also know that once a human has been infected by a non-human host, it can spread to

[49] CENTERS FOR DISEASE CONTROL AND PREVENTION. Estimated Per-Act Probability of Acquiring HIV from an Infected Source, by Exposure Act, op. cit.

[50] ORGANIZACIÓN MUNDIAL DE LA SALUD. Coronavirus causante del síndrome respiratorio de Oriente Medio (MERS-CoV). Datos y cifras [acceso: 16/3/2019]. Disponible en https://www.who.int/es/newsroom/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov)

[51] WOOLHOUSE, M.; GOWTAGE-SEQUERIA, S. «Host Range and Emerging and Reemerging Pathogens». Emerg Infect Dis 11(12). 2005, pp. 1842-1847.

other people, which is what is seen with some strains of influenza A, Y. pestis or the SARS coronavirus. Finally, about 200 species of pathogens, a quarter of zoonoses, have the capacity to transmit from person to person, but this capacity is extinguished if there are no repeated reintroductions from a non-human reservoir, as is the case with E. coli O157, Trypanosoma brucei rhodesiense or the Ebola virus.

The "third army"

We have always been accompanied by three inseparable comrades, wars, communicable diseases and famines, responsible for much of the demographic changes, human suffering and many deaths. Microorganisms mercilessly take advantage of the conditions created by war to infect both the host and the civilian population. Outbreaks of epidemic, even in the best-commanded armies, have been a more lethal factor than enemy action, even during active campaigns. For reasons of space and opportunity, only a few military ephemeris will be exhibited to illustrate what has just been stated.

Herodotus (5th century BC) in his History (L. VIII) relates an epidemic possibly of plague and dysentery that decimated shortly after touching Greek territory to the army of Xerxes the Great, whose contingent has been calculated to have been made up of about 800 000 men. The campaign had to be interrupted and the Persian king returned to Asia with less than half a million of his supporters. Shortly after, in 430 a. C., when the second year of the Peloponnesian War was taking place, a devastating epidemic caused what is known as the plague of Athens. The city lost a third of its inhabitants, including its hero Pericles. The causative agent has not yet been established, although speculation has even been made with the Ebola virus..

Philip III of France (1245-1285) was defeated in his Crusade against the Crown of Aragon, in 1285, by the determination of Roger de Lauria (1245-1305) and a plague of uncertain nature that exterminated a large number of his soldiers. , most of his officers and finally the king himself.

The siege by the Mongolian hosts in 1346 at Caffa (today Feodosia, Ukraine), a Genoese post on the Black Sea coast, offers us a well-known example of the use of corpses to try to stink the besieged population. The Mongols suffered an epidemic of bubonic plague and, as described by a chronicler of the time, Gabriel de Mussis (1280-1356), they transmitted it to the besieged city by catapulting the corpses of the infected. It may be questioned, in the light of current knowledge, whether such an action was the cause of the outbreak of the epidemic within the besieged city. However, we can affirm that the episode was a milestone in the history of what we now call biological warfare.

The ill-fated siege of Metz (France, 1552), which had to be postponed due to the health problems

[52] ZINSSER H. Rats, Lice and History. Londres: George Routledge & Sons 1935, p. 154.
[53] DIXON, B. «Ebola in Greece? ». BMJ 313. 1996, p. 430.
[54] «Felip III de França». L'Enciclopèdia.cat. Barcelona: Grup Enciclopèdia Catalana [acceso: 4/4/2018]. Disponible en http://www.enciclopedia.cat/EC-GEC-0026338.xml
[55] BARRAS, V.; GREUB, G. «History of biological warfare and bioterrorism». Clin Microbiol Infect 20. 2014, pp. 497-502.
[56] GABRIEL, R. A. between Flesh and Steel: A History of Military Medicine from the Middle Ages. Dulles (Virginia, EE. UU.): Potomac Books 2013, pp. 59-60.
[57] ZINSSER H. Rats, Lice and History, op. cit., p. 160.
[58] CONNOLLY, M. A.; HEYMANN, D. L. «Deadly comarades war and infectious diseases». The Lancet (Suppl.) 360. 2002, pp. 23-24

of Carlos I of Spain, was due to dysentery, typhus and scurvy that spread among the members of the imperial army and caused death 20,000 men, a situation that made it impossible to take the place. This, defended by a double wall, was captained by the Duke of Guise (1519-1563) who had at his command 6,000 soldiers, among whom hardly any casualties were registered due to the strict sanitary and food measures that he established. In addition, the doctors who cared for the nobles were made available to the entire garrison for the first time.

In 1792 Frederick William II of Prussia (1744-1797) and his Austrian allies mustered a force of 42,000 men and marched against the armies of the French Revolution. But dysentery decided in favor of those who carried the "Liberté, égalité, fraternité" badge, by annihilating more than a quarter of the Prussian troops, forcing them to retreat across the Rhine.

During the Napoleonic wars (1803-1815) eight times more British soldiers succumbed to disease than to combat injuries. The same happened in the American Civil War (1861-1865), in which more than two thirds of the total casualties were caused by pneumonia, typhoid, dysentery, and malaria.

In the Crimean War (1853-1856) ten times more British soldiers died from dysentery than from Russian gunfire. Half a century later, in the Boer War (1899-1902), British sick leave was five times higher than that inflicted by the enemy. But happily just two years later, during the Russo-Japanese war (1904-1905), the Japanese found that the systematic vaccination of their troops and the rigorous observance of hygienic standards in the campaigns had made their sick leave less than a quarter of that produced by the enemy. To these measures was added another important medical discovery, namely that the louse was the vector for the spread of typhoid fever. Advance that drastically modified the epidemiology of the European armies during the First World War (1914-1919). The delousing and vaccination became part of the ritual to go and, above all, return from the front.

However, such advances in medicine were overshadowed at the end of the Great War by the appearance of an old microorganism that caused a flu pandemic erroneously called "Spanish." Its deadly effects - it did not even respect healthy adults - spread throughout the planet, infecting a very high portion of the world population and striking between 20 and 50 million human beings. This epidemic became known as the "Spanish flu", not because the disease originated in Spain, but because, being a neutral country, it published data on its spread without censorship. Virosis probably came to Spain from France and it is possible that it was the result of the intense rail traffic of Spanish and Portuguese workers to and from France. The number of people who died from the flu in Spain was officially estimated at 147,114 in 1918; 21,235 in 1919, and 17,825 in 1920. It cannot be ruled out that the total sum exceeded 260,000 deaths.

The American Medical Association (AMA) reported in 1919 that during this pandemic, one-third of doctors died from an influenza-related pneumonia. When a pandemic or epidemic appears, health centers and their staff are immediately overburdened and not infrequently collapse. It is not necessary to look for examples in distant and exotic countries, just look at the emergencies of

[59] MCNEILL, W. H. Plagues and peoples, op. cit., pp. 288-292.
[60] Ibid. p. 309.
[61] TRILLA, A.; TRILLA, G.; DAER, C. «The 1918 "Spanish Flu" in Spain». Clin Infect Dis 47(5). 2008, pp. 668-673.
[62] OLDSTONE M. B. A. Viruses, Plagues, and History. Nueva York: Oxford University Press 2010, pp. 307- 308.
[63] ZINSSER H. Rats, Lice and History, op. cit., p. 153.

Figura 2: en la foto puede verse al alférez médico Raimundo Arnet Guach supervisando una campaña de vacunación en el Protectorado español en Marruecos en las primeras décadas del siglo pasado (cortesía de Alejandro Arnet).

our hospitals every year when the flu appears.

All the above means that a group of infectious diseases have received the title of "third army". In this regard, the microbiologist Hans Zinsser (1878-1940), a Harvard professor and medical colonel during the First World War, in his well-known work Rats, Lice and History (1935), wrote, perhaps with some exaggeration seen from reality. current, the following: "Soldiers have rarely won wars. Well, they often end after the flood of epidemics. And typhus - with its brothers and sisters, plague, cholera, typhoid fever, dysentery - have decided more campaigns than Caesar, Hannibal, Napoleon and all the leaders of history. Epidemics bear the blame for defeat, generals with notoriety for victory».

All these experiences have left their mark on an old institution such as the army. What has made it adopt, from the first decades of the last century, a very significant role in vaccination campaigns or lending its help in health crises (a topic that will be addressed in other chapters of this monograph).

Outbreaks don't stop increasing

Each age has had one or more pathogens that have shone above all the rest. Without a doubt, in the last decades HIV has accumulated a huge role. Especially since in the years prior to its emergence the medical and scientific community thought that human-developed technology had almost won the war on microbes. The novel arsenal of antibiotics and vaccines, and the striking improvements in living conditions made the infection, unlike in the past, relatively easy to prevent and cure, at least in the most industrialized countries.

Thus, in this environment of triumph over microorganisms, it was thought that the time had come to "close the chapter on infectious diseases" and focus on the main health problems of the countries that had already made the "epidemiological transition". This mindset made efforts focus on decreasing premature deaths caused by chronic diseases, namely heart disease, neurological conditions, cancer or diabetes. And, also influenced by this vision, President Richard Nixon signed the National Cancer Act on December 23, 1971, to wage "the war on cancer" with an endowment of $ 1.5 billion.

Supporting the idea that we were glimpsing the end of the dark tunnel of infectious pathology would contribute a historical milestone. For the first time and thanks to technology, humans had managed to eradicate an infectious disease, smallpox, a true scourge for our species. In 1979 the last natural case of this disease was declared. However, again nature

[64] PUERTA, J. L. Cooperación al desarrollo dirigida a la sanidad: el papel de los organismos internacionales. Barcelona: Instituto de Salud Global (ISGlobal) 2013, p. 27 [acceso: 17/3/2018]. Disponible en https://www.isglobal.org/publication/-/asset_publisher/ljGAMKTwu9m4/content/cooperacion-al-desarrollo-dirigida-a-la-sanidad-el-papel-de-losorganismos-internacionales

[65] 33.ª ASAMBLEA MUNDIAL DE LA SALUD. Erradicación mundial de la viruela. Organización Mundial de la Salud [acceso: 17/3/2018]. Disponible en http://apps.who.int/iris/bitstream/handle/10665/196590/WHA33_R4_spa.pdf?sequence=1

Tabla 1.- Estimaciones de Salud Global 2015: 20 causas principales de muerte en el mundo (2015 vs. 2000)											
Año	2015						2000				Año
Población	7.344.362.316						6.122.410.060				Población
Tasa de mortalidad (x100.000)	% acumulado de muertes	% sobre muertes totales	N. de muertes	Causa de muerte	Orden	Causa de muerte	Número de muertes	% sobre muertes totales	% acumulado de muertes	Tasa de mortalidad (x100.000)	
768,5	**100,0**	**100,0**	**56.441.320**	**Todas las causas**		**Todas las causas**	**52.134.566**	**100,0**	**100,0**	**851,5**	
119,2	15,5	15,5	8.756.006	Cardiopatía isquémica	1	Cardiopatía isquémica	6.882.843	13,2	13,2	112,4	
85,0	26,6	11,1	6.240.611	Ictus	2	Ictus	5.406.516	10,4	23,6	88,3	
43,4	32,2	5,7	3.190.350	Infecciones vías respiratorias bajas	3	Infecciones vías respiratorias bajas	3.407.854	6,5	30,1	55,7	
43,2	37,8	5,6	3.170.429	Enfermedad pulmonar obstructiva crónica (EPOC)	4	Enfermedad pulmonar obstructiva crónica (EPOC)	2.952.839	5,7	35,8	48,2	
23,1	40,8	3,0	1.694.623	Cáncer de tráquea, bronquios y pulmón	5	Enfermedades diarreicas*	2.177.032	4,2	39,9	35,6	
21,6	43,7	2,8	1.585.530	Diabetes mellitus	6	Tuberculosis	1.666.860	3,2	43,1	27,2	
21,0	46,4	2,7	1.541.880	Enfermedad de Alzheimer y otras demencias	7	VIH/SIDA	1.462.961	2,8	46,0	23,9	
18,9	48,8	2,5	1.388.629	Enfermedades diarreicas*	8	Complicaciones de parto pretérmino	1.340.005	2,6	48,5	21,9	
18,7	51,3	2,4	1.373.159	Tuberculosis	9	Cáncer de tráquea, bronquios y pulmón	1.255.081	2,4	50,9	20,5	
18,3	53,7	2,4	1.342.265	Accidentes de tráfico	10	Anoxia y traumatismos durante el parto	1.120.261	2,1	53,1	18,3	
15,8	55,7	2,1	1.161.914	Cirrosis hepática	11	Accidentes de tráfico	1.118.384	2,1	55,2	18,3	
15,4	57,7	2,0	1.129.246	Enfermedades renales	12	Diabetes mellitus	957.694	1,8	57,1	15,6	
14,4	59,6	1,9	1.059.626	VIH/SIDA	13	Cirrosis hepática	905.418	1,7	58,8	14,8	
14,4	61,5	1,9	1.058.277	Complicaciones de parto pretérmino	14	Malaria	858.896	1,6	60,4	14,0	
12,8	63,1	1,7	942.138	Cardiopatía hipertensiva	15	Autolesiones	748.276	1,4	61,9	12,2	
10,7	64,5	1,4	788.219	Cáncer de hígado	16	Sarampión	739.475	1,4	63,3	12,1	
10,7	65,9	1,4	788.089	Autolesiones	17	Cáncer de estómago	739.363	1,4	64,7	12,1	
10,5	67,3	1,4	774.065	Cáncer de colon y recto	18	Enfermedades renales	708.738	1,4	66,1	11,6	
10,3	68,7	1,3	753.637	Cáncer de estómago	19	Anomalías congénitas	686.583	1,3	67,4	11,2	
9,4	69,9	1,2	691.189	Anoxia y traumatismos durante el parto	20	Cáncer de hígado	661.991	1,3	68,7	10,8	

Tabla 1. Estimaciones de Salud Global 2016: 20 primeras causas de muerte por enfermedades transmisibles en el mundo (2000 vs. 2016). Fuente: Elaboración propia con datos de la OMS[66].

(•) Se han sumado «Enfermedades infecciosas y parasitarias» (I. A.) e «Infecciones respiratorias» (I. B.) (*) Causadas por rotavirus, virus tipo Norwalk, Salmonella, Shigella, E. coli.

Tabla 2.- Estimaciones de Salud Global 2015: 20 causas principales de muerte en España* (2015 vs. 2000)										
Año	2015					2000				Año
Población	46.122.000					40.750.000				Población
Tasa de mortalidad (x100.000)	% acumulado de muertes	% sobre muertes totales	N. de muertes	Causa de muerte	Orden	Causa de muerte	Número de muertes	% sobre muertes totales	% acumulado de muertes	Tasa de mortalidad (x100.000)
859,3	**100**	**100**	**396.340**	**Todas las causas**		**Todas las causas**	**360.528**	**100**	**100**	**884,73**
105,8	11,1	11,1	53.101	Cardiopatía isquémica	1	Cardiopatía isquémica	62.318	17,3	17,3	152,93
79,3	19,4	8,3	34.510	Enfermedad de Alzheimer y otras demencias	2	Ictus	37.696	10,5	27,7	92,51
68,6	26,6	7,2	28.192	Ictus	3	Enfermedad pulmonar obstructiva crónica (EPOC)	20.769	5,8	33,5	50,97
45,7	31,4	4,8	22.047	Cáncer de tráquea, bronquios y pulmón	4	Cáncer de tráquea, bronquios y pulmón	17.677	4,9	38,4	43,38
45,0	36,2	4,7	18.355	Enfermedad pulmonar obstructiva crónica (EPOC)	5	Enfermedad de Alzheimer y otras demencias	16.756	4,7	43,1	41,12
42,7	40,6	4,5	17.271	Cáncer de colon y recto	6	Cáncer de colon y recto	13.065	3,6	46,7	32,06
42,2	45,1	4,4	11.240	Infecciones vías respiratorias bajas	7	Infecciones vías respiratorias bajas	10.074	2,8	49,5	24,72
35,7	48,8	3,8	9.664	Diabetes mellitus	8	Diabetes mellitus	9.507	2,6	52,1	23,33
33,9	52,4	3,6	8.605	Enfermedades renales	9	Cáncer de estómago	6.834	1,9	54,0	16,77
27,4	55,3	2,9	7.052	Cáncer de mama	10	Enfermedades renales	6.577	1,8	55,8	16,14
22,6	57,6	2,4	6.562	Cardiopatía hipertensiva	11	Accidentes de circulación	6.355	1,8	57,6	15,60
22,3	60,0	2,3	6.512	Cáncer de prostata	12	Cáncer de mama	6.346	1,8	59,4	15,57
20,6	62,1	2,2	6.285	Cáncer de páncreas	13	Cáncer de prostata	6.120	1,7	61,1	15,02
19,2	64,1	2,0	6.207	Cáncer de estómago	14	Cirrosis hepática	5.918	1,6	62,7	14,52
18,1	66,0	1,9	5.616	Cáncer de vejiga	15	Linfomas, mieloma múltiple	4.741	1,3	64,0	11,63
18,0	67,9	1,9	5.364	Linfomas, mieloma múltiple	16	Cáncer de vejiga	4.395	1,2	65,2	10,79
16,8	69,7	1,7	5.187	Cáncer de hígado	17	Cáncer de hígado	4.338	1,2	66,4	10,65
10,7	70,8	1,1	5.148	Cirrosis hepática	18	Mocardiopatía, miocarditis, endocarditis	3.932	1,1	67,5	9,65
10,5	71,9	1,1	4.711	Mocardiopatía, miocarditis, endocarditis	19	Autolesiones	3.401	0,9	68,5	8,35
10,3	73,0	1,1	3.917	Autolesiones	20	Leucemia	3.210	0,9	69,4	7,88

Tabla 2.- Estimaciones de Salud Global 2015: 20 causas principales de muerte en España* (2015 vs. 2000). Fuente: Elaboración propia con datos tomados de: World Health Organization. Health statistics and information systems. Disease burden and mortality estimates. Cause-specific mortality, 2000–2015. WHO Member States, 2000 y WHO Member States, 2015; disponible en: http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html

surprised us. The first clinical case of AIDS emerged in 1981, a year after WHO certified65 in its Resolution WHA33.3 of May 14, 1980, the eradication of smallpox. And it took until 1983 for two independent groups of researchers to identify a previously unknown microorganism as the cause of this new infection. It was a virus that had passed from monkey to man. Since then, treatments have been developed that manage to chronify the condition, do not cure it, but allow the infected, in general, to lead a normal life.

[66] WORLD HEALTH ORGANIZATION. Global Health Estimates 2016 summary tables: Global deaths by cause, age and sex, 2000-2016. Abril 2018 [acceso: 8/5/2019]. Disponible en http://www.who.int/healthinfo/global_burden_disease/en/

Thirty-five years after isolating the pathogen, we don't have a vaccine and the pandemic continues to wreak havoc, albeit in a more controlled and localized way.

Not only have we witnessed the HIV/AIDS pandemic, but strains of tuberculosis, malaria and other common pathogens that are resistant to antibiotics have been detected, making this reality one of the most threatening and expensive chapters of the infectious pathology, both in human and economic terms. Likewise, infectious outbreaks do not stop happening, even though their mortality has decreased. There is never a lack of a new or old pathogen, often with the most picturesque name, stalking us that sooner or later it will find a host to invade. And thanks to the current means of transport, it will move easily and quickly from one continent to another, causing a health emergency when the previous one has not yet been extinguished. Communicable diseases were responsible in 2016 for 15% of human deaths (almost 8.5 million) recorded on Earth (Table 1), and 40% of those that occurred in Sub-Saharan Africa.

The high prevalence of communicable diseases - especially when they become endemic - share a common characteristic with natural disasters, armed conflict and famine: they are always accompanied by other harmful elements that end up creating a vicious circle difficult to break. The potential for an outbreak to spread and spread depends on many and varied factors. But, since it is impossible to analyze each one of them, below, almost all of those who, with more or less force and depending on the infectious agent in question, exert their influence on the vast domain of infectious pathology are listed below.:

- Adaptation and changes experienced by microbes.

- Bioterrorism.

Tabla 3.- Estimaciones de Salud Global 2015: 12 primeras causas de muerte por enfermedades transmisibles en el mundo (2015 vs. 2000)										
Año	2015					2000				Año
Población	7.344.362.316					6.122.410.060				Población
Tasa de mortalidad (x100.000)	%acumulado de muertes	% sobre muertes totales	N. de muertes	Causa de muerte	Orden	Causa de muerte	Número de muertes	% sobre muertes totales	% acumulado de muertes	Tasa de mortalidad (x100.000)
768,5	100,0	100,0	56.441.320	Todas las causas		Todas las causas	52.134.566	100,0	100,0	851,5
121,3	15,8	15,8	8.905.134	Enfermedades transmisibles		Enfermedades transmisibles	11.798.151	22,2	22,2	192,70
43,4	5,7	5,7	3.190.350	Infecciones vías respiratorias bajas	1	Infecciones vías respiratorias bajas	3.407.854	6,5	6,5	55,66
18,9	8,1	2,5	1.388.629	Enfermedades diarreicas*	2	Enfermedades diarreicas*	2.177.032	4,2	10,7	35,56
18,7	10,5	2,4	1.373.159	Tuberculosis	3	Tuberculosis	1.666.860	3,2	13,9	27,23
14,4	12,4	1,9	1.059.626	VIH/SIDA	4	VIH/SIDA	1.462.961	2,8	16,7	23,90
6,0	13,2	0,8	439.026	Malaria	5	Malaria	858.896	1,7	18,4	14,03
4,3	13,8	0,6	315.149	Meningitis	6	Sarampión	739.475	1,4	19,8	12,08
2,3	14,1	0,3	171.435	Otras enfermedades parasitarias y por vectores	7	Meningitis	437.933	0,8	20,6	7,15
2,0	14,3	0,3	145.074	Hepatitis	8	Otras enfermedades parasitarias y por vectores	257.993	0,5	21,1	4,21
1,9	14,6	0,3	139.844	Sarampión	9	Tetanos	217.482	0,4	21,6	3,56
1,3	14,7	0,2	92.272	Sífilis	10	Hepatitis	131.216	0,3	21,8	2,14
1,2	14,9	0,2	89.372	Encefalitis	11	Encefalitis	122.278	0,2	22,0	2,00
0,9	15,0	0,1	66.422	Tos ferina	12	Tos ferina	74.293	0,1	22,2	1,21

Tabla 3: Estimaciones de Salud Global 2015: 12 primeras causas de muerte por enfermedades transmisibles en el mundo (2015 vs. 2000). Fuente: Elaboración propia a partir de datos procedentes de: World Health Organization. Health statistics and information systems. Disease burden and mortality estimates. Cause-specific mortality, 2000–2015. 2000–2015 Global summary estimates; disponible en: http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html
(*) causadas por Rotavirus, virus tipo Norwalk, *Salmonella*, *Shigella*, *E. coli*.

[67] CENTERS FOR DISEASE CONTROL AND PREVENTION. Outbreaks Chronology: Ebola Virus Disease [acceso: 2/4/2018]. Disponible en https://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.html

- Weather.
- International trade (intensity).
- Demography.
- Development of democratic institutions.
- Urban deterioration (growth of lúmpenes).
- Health status of the population.
- Wars and conflicts.
- Human habits (food, hygiene and sexual practices).
- Human development Index.
- Infrastructures and sanitation.
- Environment.
- Organization and effectiveness of the public health and sanitary network.
- Political priorities.
- Technology and industry.
- Susceptibility of the host.
- Land use (invasion of natural areas).
- International trips (intensity).

From West Nile virus to Zika virus, through endless tuberculosis pandemic, everything seems to indicate that number and variety of infectious outbreaks have increased dramatically in recent decades, showing less and less respect for all kinds of borders. natural or political (see table 3). Thus, between 2014 and 2016, we were able to witness a pandemic caused by the Ebola virus that started in Guinea and quickly spilled over to Liberia and Sierra Leone. In addition, 36 cases spread across Italy, Mali, Nigeria, Senegal,

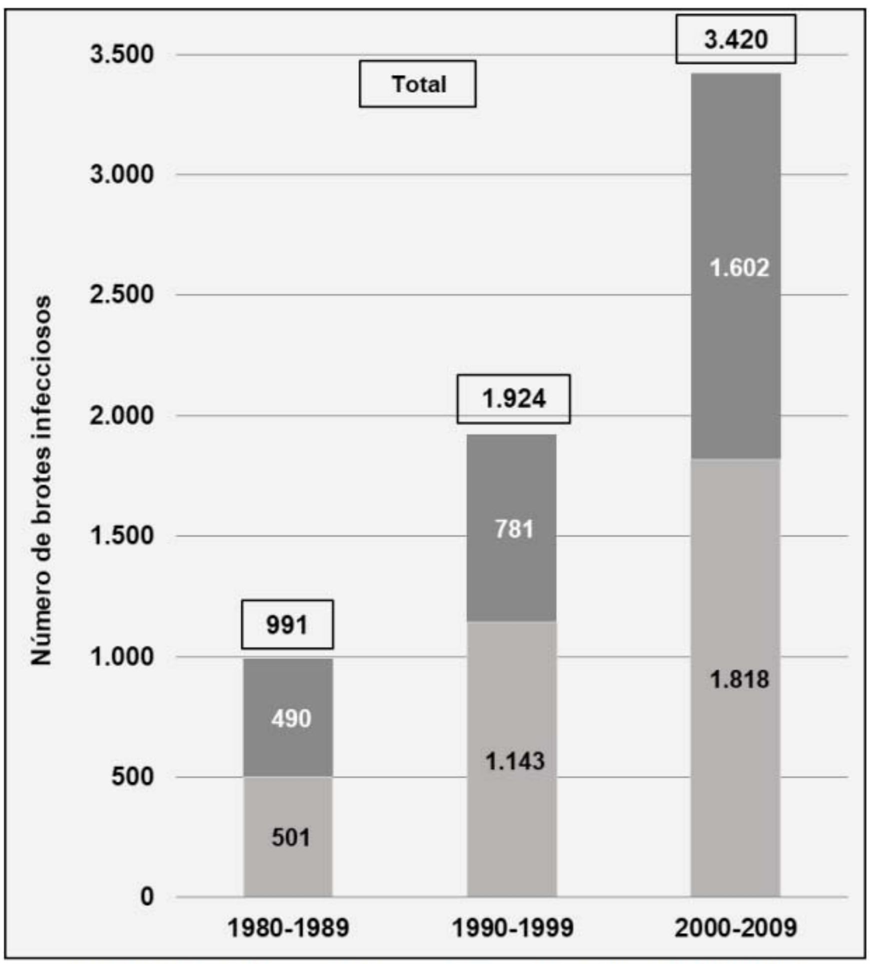


Figura 3: Número de brotes infecciosos registrados en el mundo (1980-2009).
Fuente: Elaboración propia a partir de datos de Smith K. F. y cols[67].

[68] SMITH, K. F.; GOLDBERG, M.; ROSENTHAL, S. y cols. «Global rise in human infectious diseaseout-breaks». J. R. Soc. Interface. 2014, 11:20140950 [acceso: 8/4/2018]. Disponible en http://dx.doi.org/10.1098/rsif.2014.0950

Spain, Great Britain and the USA were reported. USA

In a recent study by Katherine F. Smith et al, data from 12 102 epidemic outbreaks caused by 215 different infectious diseases and that had affected 44 million individuals in 219 nations between 1980 and 2013 have been analyzed. (a period of 33 years). These are some of the conclusions of the study: 56% of outbreaks were classified as zoonoses, in 13% of cases the transmission of pathogen was mediated by vectors. The pathogens responsible for all the outbreaks analyzed were bacteria (48%), viruses (40%), parasites (4%), protozoa (5%) and fungi (2%). Salmonella turned out to be the microorganism that caused the most outbreaks (855). Although viral gastroenteritis –generally caused by norovirus– was responsible for the highest number of registered cases, more than 15 million worldwide.

The probability that a country will suffer, diagnose and then report an outbreak depends on the capacity of its epidemiological surveillance network, its communication infrastructures, its orography and the transparency in the actions of health and political authorities. After controlling for the distortions that these factors produce in any such analysis, study by Katherine F. Smith et al., Alluded to in the preceding paragraph, also revealed that number of outbreaks and the wealth of the diseases that caused them, by country and year, showed a statistically significant increase (p <0.0001), since 1980. In addition, the total number of outbreaks of vector-borne zoonoses was increasing, observing that 80% of them , between 1980 and 1990, were caused by 25% of potential zoonoses, a percentage that decreased to 22%, between 1990 and 2000, and to 21%, between 2000 and 2010.

As already mentioned, around 1,400 species of pathogens capable of producing infectious diseases in humans have been identified, 816 (58%) are zoonoses. Of the total, 177 (13%) are considered emerging or reemerging, with zoonoses being twice as likely to be in this category as non-zoonoses. Emerging and reemerging infections (almost 45% are virosis) are not strongly associated with specific non-human hosts, and are most likely to use a wide range of them. This gives them a great advantage in terms of survival. Of all pathogen species 208 are viruses or prions, of these, 77 (37%) are considered emerging or reemerging. For bacteria figures are 538 and 54 (10%), respectively; for fungi, 317 and 22 (7%), respectively; for protozoa, 57 and 14 (25%) respectively; and for helminths, 287 and 10 (3%) respectively. It easily follows that these numbers vary according to the identification of new microorganisms harmful to our health or how we define an emerging and reemerging infection. Well, not all infectious diseases are known in the same detail as tuberculosis or malaria.

Almost 75% of the emerging infectious diseases in humans are zoonoses, the pathogens that most commonly produce them are RNA viruses, most of which come from non-domestic animals, making the trade around wildlife increasingly relevant. in infectious pathology. SARS (Severe Acute Respiratory Syndrome)

[69] WOOLHOUSE, M.; GOWTAGE-SEQUERIA, S. Host Range and Emerging and Reemerging Pathogens,op. cit.

[70] XU, R. H. y cols. «Epidemiologic clues to SARS origin in China». Emerg Infect Dis 2004 [acceso:4/4/2018]. Disponible en https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3323155/.

[71] RIPPLE, W. J. y cols. Bushmeat hunting and extinction risk to the world's mammals. R Soc Open Sci.2016;3(10):160498.

[72] WOOLHOUSE, M.; GOWTAGE-SEQUERIA, S. Host Range and Emerging and Reemerging Pathogens, op. cit.

[73] CHOMEL, B. B.; SUN, B. «Zoonoses in the bedroom». Emerg Infect Dis 17. 2011, pp. 167-172.

[74] LEVIN, S. y SINGH, K. Zoonosis, op. cit., p. 2056.

emerged as a respiratory and gastrointestinal disease in southwest China and, within months, had spread to 29 countries, causing 8,098 cases and 774 deaths. Civets from masked palms (Paguma larvata), sold in markets in Guangdong, China, were found to be infected with the coronavirus (SARS-CoV). Hence, many of the first cases were restaurant workers who bought them alive and then sacrificed them to prepare various dishes. Hunting and killing wild animals puts us in direct contact with their tissues and body fluids, something that has been crucial in the spread of Ebola, HIV, anthrax, salmonellosis, foamy simian virus (SFV) and other known zoonoses or still to be known.

That RNA viruses are above all the emerging and reemerging microorganisms that have apparently managed to infect our species for the first time in recent decades, may be explained by the fact that in these viruses - unlike DNA viruses - the replacement rates of nucleotides are much higher. This advantage allows them to adapt more quickly to environmental pressures and, therefore, greater possibilities of successfully invading a new host.

Patógeno	**Antibiótico al que es resistente**
Prioridad global	
Tuberculosis	MDR-TB* y XDR-TB**
Prioridad altísima	
Acinetobacter baumannii	Resistente a carbapenem
Pseudomonas aeruginosa	Resistente a carbapenem
Enterobacteriaceae	Resistente a carbapenem, resistente a la 3.ª generación de cefalosporinas
Prioridad alta	
Enterococcus faecium	Resistente a vancomicina
Helicobacter pylori	Resistente a claritromicina
Salmonella (spp.)	Resistente a fluoroquinolonas
Staphylococcus aureus	Resistente a meticilina, resistente a vancomicina
Campylobacter (spp.)	Resistente a fluoroquinolonas
Neisseria gonorrhoeae	Resistente a la 3.ª generación cefalosporinas, resistente a fluoroquinolonas
Prioridad media	
Streptococcus pneumoniae	No susceptible a penicilina
Haemophilus influenzae	Resistente a ampicilina
Shigella (spp.)	Resistente a fluoroquinolonas
*MDR-TB («tuberculosis resistente a múltiples fármacos»): Se define así la TB que no responde al menos a isoniacida y rifampicina, los dos medicamentos antituberculosos de primera línea más potentes. **XDR-TB («tuberculosis extensamente resistente a los medicamentos»): Se define así la MDR-TB que, también, es resistente a fluoroquinolonas y medicamentos inyectables de segunda línea contra la TB.	

Tabla 4. Patógenos prioritarios para los programas de I+D de nuevos antibióticos (OMS)[76]

[75] LAXMINARAYAN, R.; MATSOSO, P.; PANT, S. y cols. «Access to effective antimicrobials: A worldwide challenge». Lancet 387. 2016, pp. 168-175.
[76] WORLD HEALTH ORGANIZATION. Antibacterial agents in clinical development. An analysis of the antibacterial clinical development pipeline, including tuberculosis. Ginebra: World Health Organization 2017, p. 13.

But it is not possible to finish this section without pointing out that some specialists in infectious pathology have called attention - for what has just been explained - to the fact that in the USA. USA 56% of dog owners share a bedroom and even a bed with them, a percentage that rises to 75% in the case of cats. To which is added the growing tendency to live with exotic animals, many of which are important reservoirs of various pathogens (bacterial and viral) for the human species. It is not intended to question the benefits reported to many people by their pets, from psychological support to such healthy habits as exercising, only to point out that because pets can introduce a wide range of zoonotic pathogens into our environment, close coexistence with them it is not without risks.

Antimicrobial resistance: are we heading into a post-antibiotic era?

Antimicrobial resistance (AMR), that is, the ability of microbes to bypass its effects, has been a growing threat to an increasing range of infectious diseases for several decades, making it difficult to treat patients - in especially for the most vulnerable - prolong hospital stays and increase medical costs and mortality75. RAM is a natural phenomenon derived from the evolutionary pressure that any living being experiences, but the inappropriate and intensive use of these compounds, both in humans and animals, is an important catalyst in the process.

An increasing number of (classic) infectious agents such as those causing pneumonia, tuberculosis, gonorrhea, or salmonellosis are becoming strong against antibiotics. The extent of this rebellion is poorly understood by the general population, with its inappropriate use being the main cause of this situation. The relationship between consumption of antibiotics and resistance to them by microorganisms is well documented on spatial and temporal scales in specific hospitals, nursing homes, primary care centers, communities, and countries. Over time, many common pathogens have become resistant, making proper selection of a combined regimen to overcome resistance more problematic..

Recent work published in PNAS, supported by data provided by the IQVIA MIDAS platform and from 76

[77] KLEIN, E. Y.; VAN BOECKEL, T. P.; MARTÍNEZ, E. M. y cols. «Global increase and geographic convergence in antibiotic consumption between 2000 and 2015». PNAS. 2018; 115(15):E3463-E3470.
[78] Ibíd.
[79] BLOMMAERT, A.; MARAIS, C.; HENS, N. y cols. «Determinants of between-country differences in ambulatory antibiotic use and antibiotic resistance in Europe: A longitudinal observational study». J Antimicrob Chemother 69(2). 2014, pp. 535-547.
[80] SPECIAL EUROBAROMETER 445 - April 2016. «Antimicrobial Resistance». European Union, 2016 [acceso: 8-6-2018]. Disponible en http://ec.europa.eu/COMMFrontOffice/publicopinion/index.cfm/Survey/getSurveyDetail/instruments/SPECIAL/surveyKy/2107
[81] O'NEILL, J. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. London:Review on Antimicrobial Resistance 2014, p. 5 [acceso: 5/6/2018]. Disponible en https://amrreview.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf
[82] «When the drugs don't work. How to combat the dangerous rise of antibiotic resistance». The Economist,2016 mar 21 [acceso: 20-3-2018]. Disponible en https://www.economist.com/news/leaders/21699116-howcombat-dangerous-rise-antibiotic-resistance-when-drugs-donu2019t-work
[83] KLEIN, E. Y.; VAN BOECKEL, T. P.; MARTÍNEZ, E. M. y cols. Global increase and geographicconvergence in antibiotic consumption between 2000 and 2015, op. cit.
[84] VAN BOECKEL, T. P.; BROWER, C.; GILBERT, M. y cols. Global trends in antimicrobial use in foodanimals. Op. cit.

countries, has shown that global consumption of antibiotics increased by 65% between 2000 and 2015, from 21 100 to 34 800 million DDD (defined daily doses). It is Spain, in period studied, third country - behind Turkey and Tunisia, and followed by Greece - where DDD grew most by 1,000 inhabitants/day.

In industrialized countries, as is our case, the demand for antibiotics seems to be due mainly to cultural reasons and idiosyncrasies that affect clinical practice. In a Eurobarometer report (2016) on the consumption of antibiotics in the European population, in which citizens were asked if they had consumed these drugs in the last 12 months, 47% of Spaniards answered affirmatively, which positions us in the first place in the EU, followed by Italians. It is estimated that 50,000 people die each year (lower value), due to AMR only in Europe and the USA. USA, and some 700,000 worldwide. In 2050 the figure could reach 10 million individuals.

Spain, England and Ireland, in this order, are countries with highest resistance to colistin, which is widely used in pig herds and poultry farms. Antibiotics are generously administered in livestock farms to maintain the health of animals and promote their growth (through a mechanism not yet well understood), which constitutes an enormous source of resistance, both for the livestock itself and for people.. It has been calculated that in 2010 animals destined for human consumption accounted for at least 63 151 tons of these compounds worldwide. The figure reached, in 2013, 131 109 tons. China, USA The USA, Brazil and India are champions of this particular league, as they spend almost three quarters of world total destined to livestock. This inappropriate use, which in many countries exceeds human consumption, has its reason for being in fact that they are also used as a low-cost substitute for hygiene measures that could also prevent infections in livestock.

There are estimates of the consequences that RAM has for the economy that should not be overlooked. For example, your annual cost to US healthcare system has been calculated. USA It would be between 21,000 and 34,000 million dollars, expense to which must be added more than 8 million additional days of hospitalization. Given that AMR has effects that transcend the health field, it has been calculated that, if everything remains the same, in the year 2050 a cumulative drop in the GDP of OECD countries could be observed between 0.2 and 0.35 trillion dollars.

The discovery of penicillin in 1928 and streptomycin in 1943 was followed in the 1950s and 1960s by a large number of new antibiotics from different classes. However, after that "golden" stage, few new classes have come to the doctor's office. In the 1980s, the total number of new antibiotics began to decrease,

[85] VAN BOECKEL, T. P.; GLENNON, E. E.; CHEN, D. y cols. «Reducing antimicrobial use in food animals». Science 57(6358). 2017, pp. 1350-1352.
[86] WORLD HEALTH ORGANIZATION. «Antimicrobial Resistance». Global Report on Surveillance 2014. Ginebra: World Health Organization 2014, p. XIX [acceso: 5/6/2018]. Disponible en http://www.who.int/drugresistance/documents/surveillancereport/en/.
[87] O'NEILL, J. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations [acceso: 5/6/2018], op. cit., p. 9.
[88] WORLD HEALTH ORGANIZATION. «Antimicrobial Resistance». Global Report on Surveillance 2014 [acceso: 5/6/2018], op. cit., p. 1.
[89] WORLD HEALTH ORGANIZATION. Antibacterial agents in clinical development, op. cit., p. 12.
[90] WORLD HEALTH ORGANIZATION. «Antimicrobial Resistance». Global Report on Surveillance 2014 [acceso: 5/6/2018], op. cit., p. IX.
[91] MCNEILL, W. H. Plagues and peoples, op. cit., pp. 287.

increasing between 2011 and 2016, when some molecule was approved for marketing, which launched a new class. But most of these new agents exert their activity especially against gram-positive bacteria, while the most pressing thing is to find anti-infectives whose main target is gram-negative bacteria, those that the WHO gives preference to in its list of RAM pathogens.

The shortage of new antimicrobials on the horizon capable of replacing those that are no longer fulfilling their mandate makes the need to protect the efficacy of the existing ones more urgent. Thus, in a recent WHO report it could be read that the advent of "a post-antibiotic era in which common infections and minor injuries can become fatal, far from being an apocalyptic fantasy, constitutes a very real possibility in the century XXI».

Tuberculosis (TB): the white plague that doesn't leave us

In the group of great killers formed by some infectious diseases, TB takes its laurels. Today it is the tenth cause of all deaths in the world and the first among those caused by a single agent. In addition, it has demonstrated enormous tenacity. It reached its maximum incidence in the seventeenth century, to decline in the next and to increase again - to a large extent - as a consequence of the living conditions imposed by the advance of the Industrial Revolution in many cities. Even the wealthy urban classes were not sheltered from their visit. This sad wasting disease has been a source of literary and artistic inspiration.

We still don't know if TB originated independently in both hemispheres or if it was brought by Europeans to the New World92. Its causative agent, Mycobacterium tuberculosis, is a refined, reluctant and resistant bacterium discovered in 1882 by Robert Koch (1843-1910), who would be awarded the Nobel Prize in 1905. Half a century later, in 1921, the corresponding vaccine was available, known as BCG (Bacillus of Calmette and Guérin).

Fortunately, the tubercle bacillus, an old companion of our species for millennia, only causes an active disease in 10% of the immunocompetent people it infects, this means that Homo sapiens has developed immunological mechanisms to control the bacteria and prevent its clinical manifestations. Multiple studies, prior to the appearance of antibiotics, found that latent (asymptomatic) infection with M. tuberculosis conferred high protection against reinfection..

Regarding its epidemiology, the WHO estimates that in 2017 TB among HIV (-) individuals was responsible for 1.3 million deaths (in 2000, 1.7 million) and among HIV (+) people of an additional 300,000. This represents more than a third of the deaths that take place in this last group. Also in 2017, 10 million people with TB became ill (5.8 million men, 3.2 million women and 1.0 million children), that is, there were about 130 cases per 100,000 inhabitants, which is to represent a 37% decrease from 2000. There were fewer than 10 new cases per 100,000 population in most high-income countries, between 150 and 400 in most of the 30 high TB burden countries, and more than 500 in a few countries, including Mozambique, the Philippines, and South Africa. Many of the new

[92] WOLFE, N. D.; DUNAVAN, C. P.; DIAMOND, J. Origins of major human infectious diseases, op. cit., p.282.
[93] ANDREWS, J. R.; NOUBARY, F.; WALENSKY, R. P. y cols. «Risk of progression to active tuberculosisfollowing reinfection with Mycobacterium tuberculosis». Clin Infect Dis 54. 2012, pp. 784-791.
[94] WORLD HEALTH ORGANIZATION. Global tuberculosis report 2018. Gineva: World Health Organization 2018. pp. 1-4 [acceso: 12/4/2019]. Disponible en https://www.who.int/tb/publications/global_report/archive/en/
[95] ORGANIZACIÓN MUNDIAL DE LA SALUD. The End TB Strategy. World Health Organization [acceso:5/4/2018]. Disponible en http://www.who.int/tb/post2015_strategy/en/.

cases are attributable to malnutrition, HIV infection, smoking, alcohol consumption, and diabetes.

TB is present in all countries and age groups. Globally, in 2017, 90% of the patients were adults (≥15 years), 9% people with HIV (72% of them lived in Africa) and two thirds were located in eight countries: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South Africa (3%). These countries plus 22 others made up the WHO list of 30 countries with a high burden of TB, and welcomed 87% of global cases. While the European Region (3%) and the Americas (3%) –according to the WHO classification– house only 6%. The severity of national epidemics varies widely between countries. Every year on the planet the incidence of TB is falling by 2% and its mortality rate by 3%.

Only a relatively small proportion (5-15%) of the individuals with a latent infection by M. Tuberculosis will end up developing disease throughout their lives and of these 16% will die (in 2000, this percentage was 23%) . In 2017 there were about 1.7 billion infected, just over a fifth of world's population. In addition, for that year it was estimated that a million children would have fallen ill with TB, dying 250,000 from this cause (including those associated with AIDS). In TB, as in other conditions that we will see below, differences between the estimated and registered figures are due to a combination of difficulties, among which are access to medical care and the lack of a correct diagnosis (something that should not fail on a well-designed program). End TB Strategy initiative, sponsored by the WHO, has as milestones set for 2020 to achieve that the annual incidence and mortality of TB decrease between 4% and 5%, respectively, and percentage of deaths is 10 %. Furthermore, one of the goals included in "Sustainable Development Goals" for 2030 is to end this epidemic. In 2018, in support of these efforts, initiative known as' FIND. TREAT. ALL. #ENDTB».

Antimicrobial resistant TB is a serious international health problem and a threat to health security. According to the WHO, in 2017 there were some 600,000 new cases of resistance to rifampicin, of which 490,000 were also "multi-drug resistant" (MDR-TB1), a situation defined as resistance, at least, to rifampicin and isoniazid, two first-line drugs for the treatment of this infection. Almost half of these cases were located in India, China and the Russian Federation (listed from highest to lowest incidence).

MDR-TB patients require complex and prolonged treatment with multiple second-line drugs that are expensive, highly toxic, and much less effective. Worldwide, 52% of TB patients successfully complete treatment. On the other hand, half of MDR-TB patients also develop resistance to second-line drugs, known as "extensively drugresistant tuberculosis (XDR-TB2)" and their cure, at best. cases, it is achieved in one out of every three patients. Unflattering data.

As a result of new studies conducted in several countries, the WHO released an updated guide for the treatment of TB in May 2016 (WHO treatment

[96] ORGANIZACIÓN MUNDIAL DE LA SALUD. Joint Initiative «FIND. TREAT. ALL. #ENDTB» [acceso:12/4/2019]. Disponible en https://www.who.int/tb/joint-initiative/en/.
[97] WORLD HEALTH ORGANIZATION. Global tuberculosis report 2018, op. cit., p. 1.
[98] WORLD HEALTH ORGANIZATION. Global tuberculosis report 2017, op. cit., pp. 5 y 40-45.
[99] WORLD HEALTH ORGANIZATION. Global tuberculosis report 2017, op. cit., p. 5.
[100] WORLD HEALTH ORGANIZATION. Antibacterial agents in clinical development, op. cit., p. 13.
[101] CRAWFORD, D. H. «Deadly companions. How microbes shapes our history». Oxford: Oxford UniversityPress 2018, p. 200.

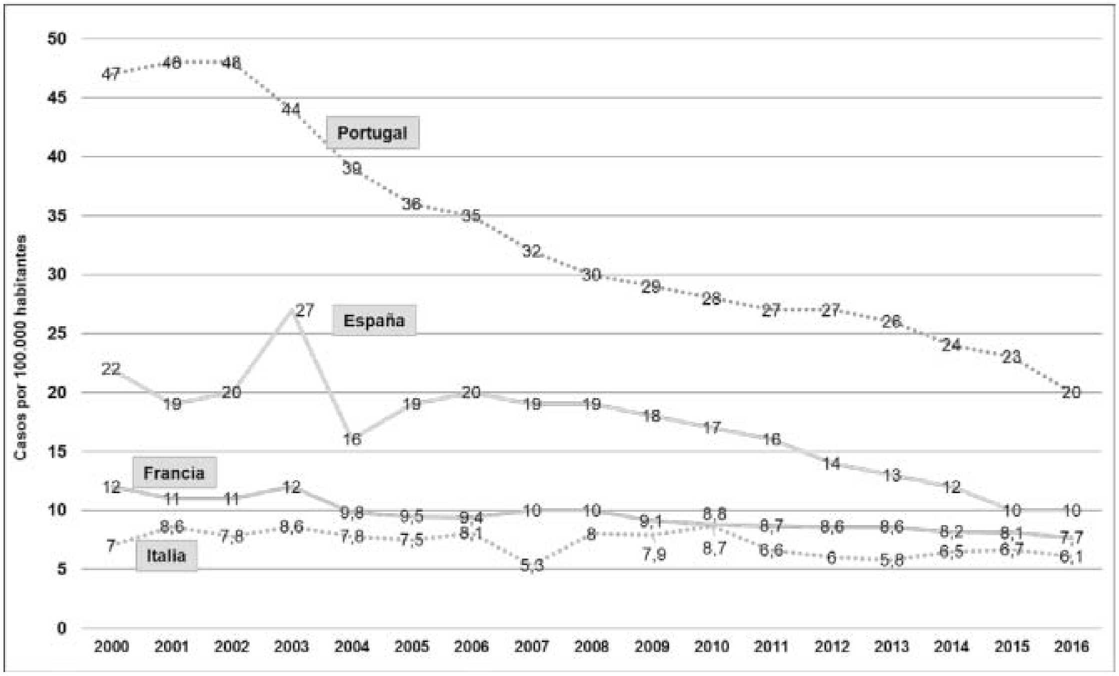


Figura 4: número de casos de tuberculosis en cuatro países europeos (x 100 000 habitantes). Fuente: Elaboración propia a partir de datos del Banco Mundial.

guidelines for drug-resistant tuberculosis, 2016 update). It recommends abbreviated regimens of 9-12 months (except in pregnant women) that until then lasted 20 months, for rifampicin-resistant pulmonary TB or MDR-TB that is not resistant to second-line anti-tuberculosis drugs. The cost of this reduced scheme is about $ 1,000 per person, the previous one varied between $ 2,000 and $ 5,000. Despite this simplification and cheaper treatment, patients face prolonged suffering and more often than not, permanent disability that is aggravated by economic hardships and social stigma, factors that don't favor their recovery.

Currently, MDR-TB is the most common and deadly disease on the planetary scale, among all the RAM infections worldwide, responsible for 250,000 deaths each year. Only two new antibiotics for MDR-TB have been marketed in more than 70 years. And the investment in R&D for this infection doesn't have sufficient funds. In any case, it must be admitted that the situation in which TB is found is largely a consequence of the lack of supervision of patients, the poor observance of therapeutic regimens, interruptions in the supply of medications and the consumption of antituberculous drugs without adequate medical control, which has caused, according to what Fleming predicted, the appearance of mutant chemoresistant strains.

In Spain, a decrease in all forms of TB is observed, currently standing at about 10 cases per 100,000 inhabitants. However, since the WHO does not classify us as a low incidence country, that is, with less than 10 cases per 100,000 inhabitants, a greater effort is necessary to achieve this goal. Furthermore, according to the latest report[102] available from the National Center for Epidemiology in Spain:

- During 2016, the incidence rate was 10.38 cases per 100,000 inhabitants, which represented a 2% reduction compared to 2015. Highest number of cases was recorded in men (62% of the total). The median age was 46 years

[102] CENTRO NACIONAL DE EPIDEMIOLOGÍA. INSTITUTO DE SALUD CARLOS III. Informeepide-miológico sobre la situación de la tuberculosis en España. Año 2016. Madrid, 2019, p. 27 [acceso:22/4/2019]. Disponible en http://www.isciii.es/ISCIII/es/contenidos/fd-servicios-cientifico-tecnicos/fdvigilancias-alertas/fd-enfermedades/pdf_2019/RENAVE_TBC_2016.pdf

for men and 39 years for women.

- The results of the anti-tuberculosis treatment do not reach the goals set internationally, that is, achieve cure in at least 85% of cases.

- The information about whether or not there is HIV coinfection in tuberculosis patients is incomplete, especially in young adults and those over 65 years of age.

- Adults between 25 and 34 years constitute one of the age groups with the highest respiratory TB rates. Given that the highest active transmission occurs at these ages, and that half of the cases in this group come from high tuberculosis endemic countries, it is necessary to intensify the early detection of pulmonary TB in young adults to cut the chains of transmission.

The only commercialized and accepted vaccine against TB is BCG, which leaves a characteristic skin scar. After more than 95 years of use and several billion people vaccinated, it is still up for debate. The duration of the protection it confers is not known exactly, as its effectiveness varies between 0% and 80%. Furthermore, it doesn't prevent post-primary disease, nor does it prevent vaccinate from becoming infected. However, it has demonstrated its ability to protect against evolutionary primary TB, decrease the frequency of early complications, and prevent severe forms of TB in children, which is widely administered in many parts of the world..

We still do not have a vaccine that is effective in adults, either before or after exposure to M. tuberculosis. In Spain BCG is not indicated in the general population. Although it can be recommended to people whose tuberculin test is negative and plan to reside in areas where the disease has a high prevalence.

The fence that hinders the development of a new TB vaccine lies in finding one that has the ability to elicit a response that is more immune than inflammatory. Today we know that the tubercle bacillus, in order to spread and survive among humans, since there is no known animal reservoir, has to cause –as a prerequisite for its transmission– lung damage that alters its morphology. It is not known for sure to what extent this damage is caused by the pathogen or by the host's inflammatory response ("poorly modulated") when trying to defend against aggression.

For the pathologist Willem Hanekom: "The world of discovery and development of new tuberculosis vaccines is in its infancy" Updated information on the development of TB vaccines and antimicrobials can be obtained from the WHO website: Global Observatory on Health R&D (Monitoring R&D activities)

[103] RUIZ MANZANO, J.; GONZÁLEZ MARTÍN, J.; DOMÍNGUEZ BENÍTEZ, J. A. y cols. Tuberculosis yotras infecciones causadas por micobacterias no tuberculosas. En Rozman C., Cardellach F. (eds.).
Farreras-Rozman. Medicina Interna, 18.ª edición. Barcelona: Elsevier España, S. L. U. 2016, p.2152.
[104] KAUFMANN, S. H.; DORHOI, A. «Inflammation in tuberculosis: interactions, imbalances and interventions». Curr Opin Immunol 25. 2013, pp. 441-449.
[105] HANEKOM, W. A. «Tuberculosis Vaccines». En Bloom B. R., Lambert P. H. (eds.). The Vaccine Book. Londres: Academic Press 2016, p. 363.
[106] WORLD HEALTH ORGANIZATION. Global Observatory on Health R&D [acceso: 23-4-2019]. Disponible en https://www.who.int/research-observatory/en/.
[107] MICHAEL, B. A.; OLDSTONE, M. D. Viruses, Plagues, and History: Past, Present and Future. New York: Oxford University Press, Inc. 2010, p. 10.
[108] FAUCCI, A. S.; LANE, H. C. «Enfermedades por el virus de la inmunodeficiencia humana: SIDA y procesos relacionados». En Faucci A. S., et al. Principios de Medicina Interna, op. cit., pp. 1142-1143.

	2000	2005	2010	2012	2013	2014	2015	2016	2017	2000/17
Personas que viven con VIH*	27,4	30,1	32,4	33,7	34,3	35	35,6	36,3	36,9	35 %
Total de nuevas infecciones por VIH*	2,8	2,5	2,2	2,1	2,0	2,0	1,9	1,9	1,8	-36 %
Nuevas infecciones por VIH en personas ≥15 años*	2,4	2,1	1,9	1,8	1,8	1,8	1,7	1,7	1,6	-33 %
Nuevas infecciones por VIH en personas <15 años*	0,420	0,380	0,270	0,230	0,220	0,200	0,190	0,180	0,180	-57 %
Muertes relacionadas con el SIDA*	1,5	1,9	1,4	1,2	1,2	1,1	1,0	0,990	0,940	-37 %
Personas con acceso a terapia antirretroviral*	0,611	2,1	8	11,4	13,2	15,1	17,2	19,4	21,7	3452 %
Dólares disponibles para VIH en países de ingresos bajos y medios	4.800**	9.400**	15.900**	18.800 **	19.500***	19.200 ***	19.000 ***	19.100 ***	21.300 ***	344 %

* Los datos están expresados en millones de personas y referidos al mundo (excepto cuando se indica otra cosa).
** Millones de dólares de EE. UU. Incluye los países de ingresos bajos y medianos según la clasificación de 2012 del Banco Mundial.
*** Millones de dólares de EE. UU. Incluye los países de ingresos bajos y medianos según la clasificación de 2013 del Banco Mundial.

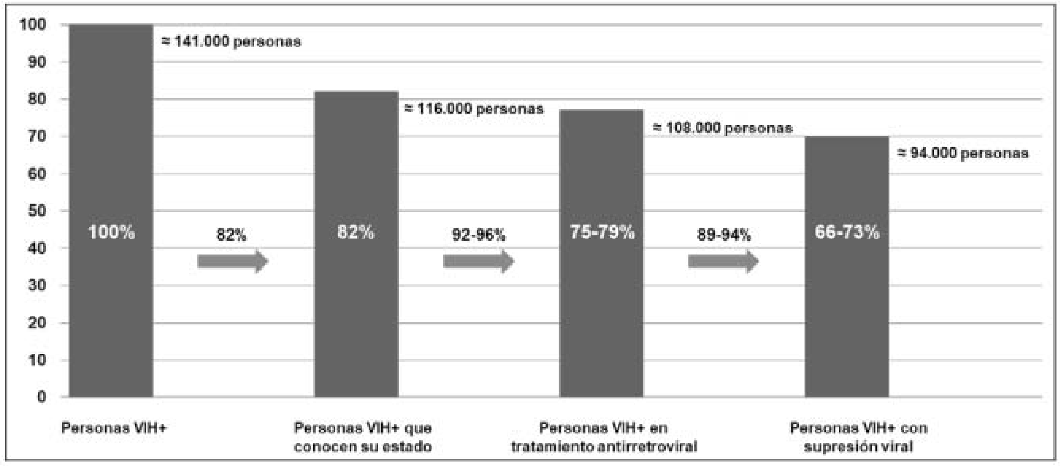
Tabla 5: estadísticas mundiales sobre VIH (ONUSIDA)

HIV: "a piece of nucleic acid surrounded by bad news"

In this lucid way Peter Medawar (1915-1987), the 1960 Nobel Prize in Medicine, defined viruses, and it is difficult to find a more suitable virus for HIV. Protagonist of a pandemic that began almost 40 years ago and that has continued to be one of the great problems facing international health, having already claimed more than 35 million lives. Likewise, he has the sad honor of being the greatest youth murderer on our planet. In 2017, it caused more than a million deaths, infected 1.8 million people and a total of 36.9 million infected were recorded. In sub-Saharan Africa, the region most massacred by the virus, 25.6 million individuals living with HIV were registered, and that was where almost two thirds of new cases that occurred in world occurred.

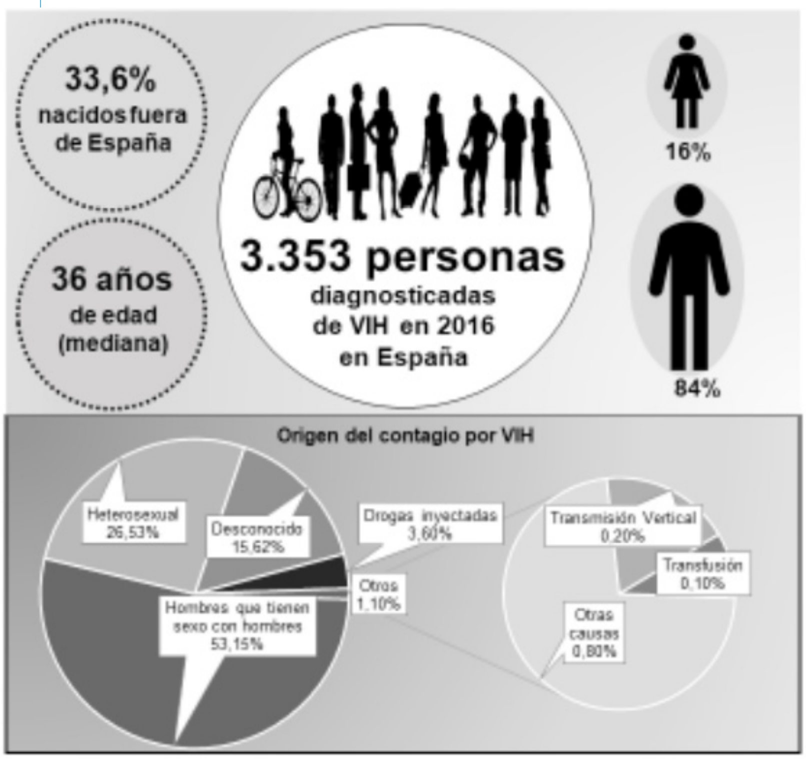
HIV is transmitted through homosexual and heterosexual contacts; by means of blood and blood products, and by transmission of the infected mother to her child during childbirth, the perinatal period or by breastfeeding. After five years of painstaking studies, no evidence has been found that it is transmitted by casual contact, or that insects are able to inoculate it through its bites. We also know that the presence of other sexually transmitted diseases favors or is associated with their spread. Oral sex is a much less efficient way of contagion than anal intercourse as a recipient. Several studies have shown that the incidence of transmission of infection through oral sex between discordant couples (for HIV infection) is very low. However, there are works that have documented transmission solely by intercourse as receiver or cunnilingus as introducer. Therefore, it

[109] WORLD HEALTH ORGANIZATION. HIV/AIDS. Fact sheet [acceso: 3/5/2019]. Disponible en http://www.who.int/mediacentre/factsheets/fs360/en/.
[110] UNAIDS. Fact sheet - Latest statistics on the status of the AIDS epidemic [acceso: 3/5/2019]. Disponible en http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf.
[111] Cascada de diagnóstico y tratamiento de la infección por VIH en España. Ministerio de Sanidad, Servicios Sociales e Igualdad [acceso: 19/4/2018]. Disponible en https://www.mscbs.gob.es/ciudadanos/enfLesiones/enfTransmisibles/sida/publicaciones/profSanitarios/CascadaWEBDxTTOVIH22Novbre17.pdf
[112] EL-SADR, W. M. et al. «AIDS in America - Back in the Headlines at Long Last». N Engl J Med 380(21). 2019, pp. 1985-1987.



Fuente: Plan Nacional sobre el Sida a partir de las estimaciones realizadas por el Centro Nacional de Epidemiología para el año 2013 y datos procedentes de la Encuesta Hospitalaria de pacientes con infección por el VIH, 2016. Disponible en: https://www.mscbs.gob.es/ciudadanos/enfLesiones/enfTransmisibles/sida/publicaciones/profSanitarios/CascadaWEBDxTTOVIH22Novbre17.pdf.

Figura 5: cascada de diagnóstico y tratamiento de la infección por VIH en España.
Fuente: Plan Nacional sobre el Sida[113].



Fuente: Plan Nacional sobre el SIDA. Infografías. Nuevos diagnósticos de infección por VIH en España. 2017. Disponible en: https://www.mssi.gob.es/ciudadanos/enfLesiones/enfTransmisibles/sida/queesSidaVih.htm#tres.

Figura 6: perfil epidemiológico del VIH en España (2016). Fuente: Plan Nacional sobre el Sida[114].

cannot be affirmed - contrary to what is advertised - that oral sex is safe for the purposes of HIV infection.

Among our peers there are groups that deserve special attention because they have a higher risk of contagion, regardless of the prevalence of HIV / AIDS in their environment. The risk of HIV infection is known to be 27 times higher among men who have sex with men; 23 times higher among people who inject drugs; 13 times higher for sex workers, and 13 times higher for transgender women. There are still many countries in which a series of social or legal constraints converge in these groups, which often increase their fragility, as their access to diagnosis and treatment programs is hindered, among other things. In part this explains why, according to the estimates made by the competent international organizations, only 75% [55–92%] of those infected with HIV know their serological status. Or that, in 2017, it was

[113] MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL. Plan Nacional sobre el Sida a partirde las estimaciones realizadas por el Centro Nacional de Epidemiología para el año 2013 y datos procedentes de la Encuesta Hospitalaria de pacientes con infección por el VIH, 2016 [acceso: 6/5/2019]. Disponible enhttps://www.mscbs.gob.es/ciudadanos/enfLesiones/enfTransmisibles/sida/queesSidaVihhtm.
[114] MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL. Plan Nacional sobre el SIDA. Infografías. Nuevos diagnósticos de infección por VIH en España. 2017 [acceso: 6/5/2019]. Disponible en https://www.mscbs.gob.es/ciudadanos/enfLesiones/enfTransmisibles/sida/queesSidaVih.htm.

	INE (1)	Plan Nacional sobre el Sida					Estimación del autor (6)	UNAIDS - AIDSinfo (7) Estimación (valor medio)				IHME (8) Estimación (valor inferior)		
Años	Población española	Nuevos diagnósticos de VIH (2)	Población CCAA participantes (3, 4)	Tasa nuevos diagnósticos de VIH (x 100.000 hab.) (4)	Nuevos diagnósticos de VIH (4)	Fallecidos por VIH/SIDA (5)	Nuevos diagnósticos de VIH	Tasa nuevos diagnósticos de VIH (x 100.000 hab.)	Nuevos diagnósticos de VIH	Total personas diagnosticadas de VIH	Total gasto en tratamiento VIH (mill. dólares)	Nuevos diagnósticos de VIH	Total personas diagnosticadas de VIH	Fallecidos por VIH/SIDA
1981	37.764.458					4								
1982	37.987.108	4				4								
1983	38.160.263	14				11								
1984	38.325.244	52				12								
1985	38.467.025	177				69								
1986	38.571.941	499				189								
1987	38.682.322	1.095				433								
1988	38.704.307	2.274				800								
1989	38.821.377	3.169				1.378								
1990	38.860.627	3.939				2.033		28	11.000	66.000		13.743	84.678	1.907
1991	38.941.622	4.576				2.657		26	10.000	74.000		13.014	96.684	2.521
1992	39.147.940	5.089				3.477		23	8.900	80.000		11.711	106.969	3.288
1993	39.356.082	5.518				4.227		20	7.800	84.000		9.905	115.419	4.009
1994	39.547.353	7.482				5.058		18	7.000	87.000		8.340	121.782	4.672
1995	39.718.895	7.189				5.857		16	6.300	88.000		6.626	126.150	5.341
1996	39.884.246	6.743				5.749		14	5.700	89.000		5.587	130.747	5.146
1997	40.049.974	4.957				3.010		13	5.300	91.000		4.782	131.861	2.910
1998	40.214.066	3.713				1.878		13	5.000	93.000		4.326	133.461	1.884
1999	40.369.867	3.152				1.844		12	4.800	95.000		3.928	135.161	1.852
2000	40.554.387	2.895				1.717		11	4.600	98.000		3.686	136.802	1.690
2001	40.766.049	2.497				1.635		11	4.500	100.000		3.353	138.390	1.599
2002	41.423.520	2.335				1.614		11	4.500	110.000		3.099	142.479	1.589
2003	42.196.231	2.276	14.469.101	10,15	1.466	1.635	4.336	11	4.400	110.000		2.960	147.531	1.584
2004	42.859.172	2.041	17.417.278	9,95	1.733	1.554	4.298	10	4.500	110.000		2.851	151.805	1.501
2005	43.662.613	1.817	17.668.855	9,45	1.670	1.450	4.168	10	4.500	120.000		2.825	155.831	1.408
2006	44.360.521	1.693	17.906.093	10,11	1.810	1.315	4.520	10	4.500	120.000		2.771	159.677	1.292
2007	45.236.004	1.547	24.302.431	11,94	2.902	1.313	5.397	10	4.500	130.000	551	2.751	164.414	1.275
2008	45.983.169	1.349	28.026.013	12,78	3.582	1.215	5.899	10	4.500	130.000	917	2.676	167.902	1.185
2009	46.367.550	1.037	32.732.970	11,34	3.712	1.079	5.301	10	4.600	130.000	947	2.750	169.844	1.053
2010	46.562.483	196	32.843.416	11,69	3.839	1.020	5.497	10	4.600	140.000	981	2.718	171.334	1.002
2011	46.736.257	37	32.853.439	10,99	3.609	953	5.186	10	4.500	140.000	1.080	2.764	173.117	912
2012	46.766.403		37.863.951	10,1	3.824	880	4.774	10	4.500	140.000	978	2.813	173.339	820
2013	46.593.236		46.591.857	9,08	4.229	750	4.279	9	4.400	140.000	919	2.899	172.566	715
2014	46.455.123		46.452.801	9,29	4.315	700	4.345	9	4.300	150.000		3.066	171.871	637
2015	46.407.166		46.407.166	8,66	4.020	633	4.038	9	4.200	150.000		3.245	172.294	679
2016	46.450.439		46.468.116	7,22	3.353	498	3.361	9	4.200	150.000		3.192	173.306	656
2017	46.659.302							9	4.100	150.000				
TOTAL						58.660								53.124

Tabla 6: VIH/SIDA en España (según varias fuentes): nuevos diagnósticos de VIH, total de personas diagnosticadas de VIH y fallecidos por VIH/SIDA.

observed that 47% of new cases appeared in people belonging to these risk groups and their partners.

In Spain, according to data provided by National AIDS Plan under Ministry of Health, of people infected with HIV –about 141,000 throughout Spain–, almost a fifth don't know their serological status; antiretroviral treatment (ART) is received by 75-79% and viral suppression is achieved by 66-73% (in countries such as Namibia and Swaziland, viral suppression among people living with HIV is 75% and 69%, respectively).

Data that indicates that the Spanish health authorities should be more ambitious if they want to achieve the "Objective 90-90-90", that is, that by 2020 90% of individuals infected with HIV know their serological status, 90% of those diagnosed receive continuous antiretroviral treatment (ART) and 90% of those on treatment achieve viral suppression.

The epidemiological profile of people living with HIV in Spain is summarized in Figure 6. While Table 6 shows its incidence and prevalence with data from the National AIDS Plan, UNAIDS and the Institute for Health Metrics and Evaluation (IHME), with this information the reader will be able to get a better idea about the situation of HIV / AIDS in Spain and the level of control –without doubt improvement- that exists over this disease.

Unlike what happens with measles or smallpox, which present with an acute picture followed by immunity for life or death, HIV is limited - in the first instance - to integrate its genetic material in the host cells and to replicate, although the patients are asymptomatic or in a state of clinical "latency". The term is misleading, since it is one thing that there is no appreciable symptomatology and another that the disease does not progress inexorably. Furthermore, clinical "latency" should not be equated with microbiological

[115] FAUCCI, A. S.; LANE, H. C. «Enfermedades por el virus de la inmunodeficiencia humana: SIDA y procesos relacionados». En Faucci, A. S. et al. Principios de Medicina Interna, op. cit., pp. 1152-1153.
[116] OLDSTONE, M. B. A. Viruses, Plagues, and History, op. cit., p. 269.
[117] FAUCCI, A. S.; LANE, H. C. «Enfermedades por el virus de la inmunodeficiencia humana: SIDA yprocesos relacionados». En Faucci A. S. et al. Principios de Medicina Interna, op. cit., pp. 1137-1203.
[118] ORGANIZACIÓN MUNDIAL DE LA SALUD. HIV/AIDS. Data and statistics [acceso: 3/5/2019].Disponible en http://www.who.int/hiv/data/en/

"latency", since there are high levels of plasma viremia during acute HIV infection, which translates into a high risk of transmission115. However, the spread of HIV to members of our species has a slow evolution compared to that observed in viruses that cause hemorrhagic fevers (Ebola, Marburg, Lassa, yellow fever), influenza, measles or polio. This explains why for a long time (years) the infected person can transmit the disease unnoticed. To which it must be added that the lengthening of the life of people with HIV, thanks to antiviral medication, increases the risk of infections.

It has already been pointed out that HIV is poorly transmitted. Just under 5% of exposed people get the infection. While the measles and smallpox viruses infect more than 98%. But there is still more to say about HIV and the measles virus: both attack and invade the cells of the immune system (which are their targets), inducing immunosuppression that leaves the host craving for other pathogens and, therefore, get an opportunistic infection. However, in the case of measles, the host immune system generally overcomes aggression and kills the pathogen.

Human immunodeficiency viruses (HIV type 1 and HIV type 2) are single-stranded RNA viruses of the lentivirus genus and belonging to the family of retroviruses. In H. sapiens infection by these viruses, after a "window period", causes a seroconversion, typically in less than 3-6 weeks, which may be accompanied by an acute condition that mimics that of many viruses. Over time and without treatment the clinical disease arises: the acquired immunodeficiency syndrome (AIDS).

Although there are no medications to eradicate the infection (as is the case with hepatitis C, produced by another RNA virus), antiretroviral treatment (ART) allows keeping HIV under control and lengthening life expectancy in those infected. Today, 59% of adults, 42% of children, and 80% of pregnant or lactating women living with HIV receive ART worldwide. In 2017, there were 21.7 million people in ART programs. If the "Objective 90-90-90" is to be achieved in 2020, it is necessary for another 7.5 million individuals to access diagnostic and follow-up services to control this condition. The next goal is to end HIV / AIDS as a threat to public health by 2030 ("Sustainable Development Goals").

Between 2000 and 2017, the number of new cases fell by 36%, deaths associated with HIV decreased by more than a third, and 11.4 million lives were saved thanks to ART. Table 5 shows, worldwide, the evolution that some parameters related to the HIV / AIDS pandemic have undergone between 2000 and 2015, the period in which the "Millennium Goals" have been in force. It is worth noting that the number of people with access to ART multiplied by 24 in that period of time. This achievement is the result of the enormous efforts made by the national programs to fight AIDS, to which have been added the help of civil society and a group of entities (public, private and multilateral) that have

[119] ORGANIZACIÓN MUNDIAL DE LA SALUD. Estrategia mundial del sector de la salud contra el VIH,2016-2021. Hacia el fin del SIDA. 2016 [acceso: 19/4/2018]. Disponible en http://apps.who.int/iris/bitstream/handle/10665/250574/WHO-HIV-2016.05-spa.pdf?sequence=1

[120] UNAIDS. 90–90–90: An ambitious treatment target to help end the AIDS epidemic. Geneva: UNAIDS 2014 [acceso: 19/4/2018]. Disponible en http://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf)

[121] President's Emergency Plan for AIDS Relief (PEPFAR). Disponible en https://www.pepfar.gov.

[122]WEBSTER, P. «PEPFAR at 15 years». Lancet, 2018; 392(10143):200.

[123] UNAIDS. 90-90-90: An ambitious treatment target to help end the AIDS epidemic, op. cit., p. X.

[124] U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. Aidsinfo [acceso: 20/4/2018]. Disponible en https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/19/58/fda-approved-hiv-medicines

their sights set on promoting the development of individuals and countries. All these efforts will have to be redoubled until 2030. It is fair to mention, at least, the PEPFAR program (President's Emergency Plan for AIDS Relief), promoted in 2003 by President George W. Bush and, happily, maintained by his successors in the White House 121. Since in its three decades of existence it has dedicated more than 80 billion dollars to the global fight against HIV / AIDS. Part of them have gone to subsidize the activities of the Global Fund against AIDS, Malaria and Tuberculosis and the twin institution focused on vaccines, Gavi (Global Alliance for Vaccines and Immunization).

The extraordinary ability of HIV to mutate and reproduce in the presence of antiretroviral drugs (FAR) leads to the emergence of resistance, which ends up rendering ART ineffective. Also contributing to this phenomenon are the side effects of antivirals, which, when superimposed on the symptoms of the disease, especially in the final stages, produce enormous discomfort for the patient, which results in little follow-up of the treatment. The same can happen if ART is associated with other medications for concomitant pathologies, or for other reasons. The chemoresistance of HIV, like that of any other microorganism, involves: a) an increase in health costs for the administration of second-line drugs, generally more expensive and not always available in lower-income countries; b) one more burden for the patient and his family; c) the spread of resistant strains, and d) the need to develop new drugs, a company that requires resources (which detract from other priorities), time (measured in years) and, not infrequently, facing failures. The degree of resistance to FAR as a result of the progressive generalization of its use (see Table 5), is not well known due to the lack of reliable data in many countries..

Currently, there are seven groups of FAR that act on different molecular targets (until a few years ago there were only four) and a pharmacokinetic enhancer. When all this arsenal is available and a 'highly active antiretroviral therapy' (HAART) can be instituted or, more intelligibly, very potent combinations of FAR, it is possible to maintain borders almost all situations on HIV.

Before starting treatment, it is essential to carry out a genotypic study of resistance to FAR. According to the GeSida / PNS Consensus Document on ART (January

[125] GeSIDA. Documento de consenso de Gesida/Plan Nacional sobre el Sida respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana (actualización enero 2018). 2018, p. 23. Disponible en http://gesida-seimc.org/category/guias-clinicas/antirretroviral-vigentes/

[126] U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. «What is a Preventive HIV Vaccine?». Aidsinfo. [acceso: 20/4/2018]. Disponible en https://aidsinfo.nih.gov/understanding-hiv-aids/factsheets/19/96/what-is-a-preventive-hiv-vaccine

[127] PAVLAKIS, G. N.; FELBER, B. K. «A new step towards an HIV/AIDS vaccine». Lancet 392(10143).2018, pp. 192-194.

[128] WALKER, B. D. «AIDS Vaccines». En Bloom B. R., Lambert P. H. (eds.). The Vaccine Book. Londres:Academic Press 2016, pp. 401-422.

[129] MOIR, S.; CONNORS, M.; FAUCCI, A. S. «Inmunología de la infección por el virus de la inmunodeficiencia humana». En Mandell, Douglas y Bennett. Enfermedades infecciosas. Principios y práctica. Elsevier España 2015, pp. 1599-1614.

[130] GIRARD, M. P; KOFF, W. C. «Human Immunodeficiency Virus Vaccines». En Plotkin S. A. et al.Plotkin's Vaccines. Elsevier, Inc. 2018, pp. 400-429.

2018), this should be started in all patients with HIV-1 infection, whether or not they have symptoms.

We don't yet have approved HIV vaccines, either preventive or therapeutic, but research continues in several directions. Since the objectives of a therapeutic vaccine may be, for example, aimed at slowing down the progression of the infection; eliminate the need for ART by maintaining undetectable levels of HIV, or be part of a broader strategy to completely kill HIV from the infected organism. In Pavlakis and Felber's opinion: "Although the search for an AIDS vaccine has led to many scientific advances, its achievement remains beyond our reach". In essence, the three major obstacles to developing an HIV vaccine can be summarized as follows:

- First. As already indicated, HIV belongs to the family of retroviruses (RNA viruses), which are characterized by having the unique ability to hide from the immune system and infect the host cells for life. Retroviruses contain an enzyme, reverse transcriptase (or retrotranscriptase that gives its name to this family of viruses), thanks to which, once they have invaded a cell using its RNA, they generate double-stranded DNA. This viral DNA can be integrated into cellular DNA using another enzyme, also carried by the virus, integrase. Once the viral material forms part of the host's cellular genome, it is called a provirus, and it is confined there (indefinitely) to be copied –as a "part" of cellular DNA– when cell division occurs. The provirus will therefore be inherited by the two daughter cells (after division). In this way, HIV creates a reservoir within the cells (basically lymphocytes) of the infected individual. And at any time with the right stimulus, for example, a malaria, tuberculosis, or other infection, the provirus uses retrotranscriptase to make a strand of RNA to generate new viruses that sprout from the surface of the host cell, which supposes the destruction of this. Unlike the rest of human retroviruses, HIV has a marked cytolytic power. As in animal models it has been found that the formation of the latent viral reservoir occurs a few days after exposure to the virus, if the infection is to be prevented for life, the immune response - promoted by the vaccine - would have very little time to act.

- Second. HIV exhibits extreme genetic variety due to its high replication kinetics and the errors that reverse transcriptase generates in process of producing DNA from RNA (reverse transcription). Even within same infected individual, diversity observed exceeds that which can be observed during a flu pandemic of planetary dimensions. These properties of the virus make it very easy to adapt to rapidly changing environments and cope with selective immunological or pharmacological pressures.

- Third. Another major stumbling block to vaccine development lies in the fact that the HIV envelope glycoproteins (which act as antigens), which are the main target of host-produced antibodies, are not easily accessible. For these glycoproteins bind to the receptors that are present on the surface of the infected T lymphocytes, this binding being the point by which the genetic

[131] RERKS-NGARM, S.; PITISUTTITHUM, P.; NITAYAPHAN, S. et al. «Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand». N Engl J Med 361. 2009, pp. 2209-2220.
[132] WORLD HEALTH ORGANIZATION. Global Observatory on Health R&D, op. cit.
[133] ASHLEY, E. A.; PHYO, A. P.; WOODROW, C. J. «Malaria». Lancet 391. 2018, pp. 1608-1621.
[134] BASSAT, Q.; ALONSO, P. L. «Malaria y babesiosis». En Rozman C., Cardellach F. (eds.). FarrerasRozman. Medicina Interna, 18.ª Edición. Barcelona: Elsevier España, S. L. U. 2016, pp. 2261-2262.

material of the virus penetrates into the cells. On the other hand, neutralizing antibodies are not only difficult to generate from the host, but require years of exposure to glycoproteins for a mutation to take place that is capable of acting effectively against HIV, something that only happens in one minority of individuals. Furthermore, most of the immunogens used in vaccines tested to date are composed of monomeric forms of the glycoprotein gp120 (one of those present on the surface of HIV), and not by the native trimer that is the one exhibited by infecting viruses, the only one capable of generating effective humoral immunity.

Data from the first trial of an HIV vaccine was published in 2009 and showed some degree of protection. The trial, called "RV 144", was carried out in Thailand and showed a 31.2% lower infection rate in the vaccinated group than in the placebo group. Although the result was not good enough to obtain marketing authorization, it did provide valuable clues in designing the strategies with which to achieve an effective vaccine. Up-to-date information on the development of HIV / AIDS vaccines and antimicrobials can be obtained from the WHO website: Global Observatory on Health R&D (Monitoring R&D activities).

Malaria: the "mother of fevers"

Malaria or malaria are terms that come, respectively, from medieval Italian (mala aria) and from Latin (palus -udis, which means swamp) and give name to a life-threatening disease caused by a plasmodium (Plasmodium). It parasites red blood cells and is transmitted to people by the bite of infected female mosquitoes of the genus Anopheles that act as vectors, there are about 40 species of anopheline that perform this function..

There are more than 120 species of plasmodia that can infect mammals, birds and reptiles, but only six cause malaria in man: Plasmodium falciparum, P. vivax, P. ovale curtisi, P. ovale wallikeri, P. malariae and P. knowlesi, the latter is responsible for a mainly zoonotic infection (macaques are its natural host), located in Malaysia and capable of causing serious clinical conditions. Of these parasites, two are the most relevant for our species:

- P. falciparum. It is the most virulent parasite and the most prevalent cause of malaria in the African continent, the Indian subcontinent and Southeast Asia, as well as in some areas of the Pacific and wide regions of the Amazon. It is also responsible for the majority of malaria deaths worldwide.

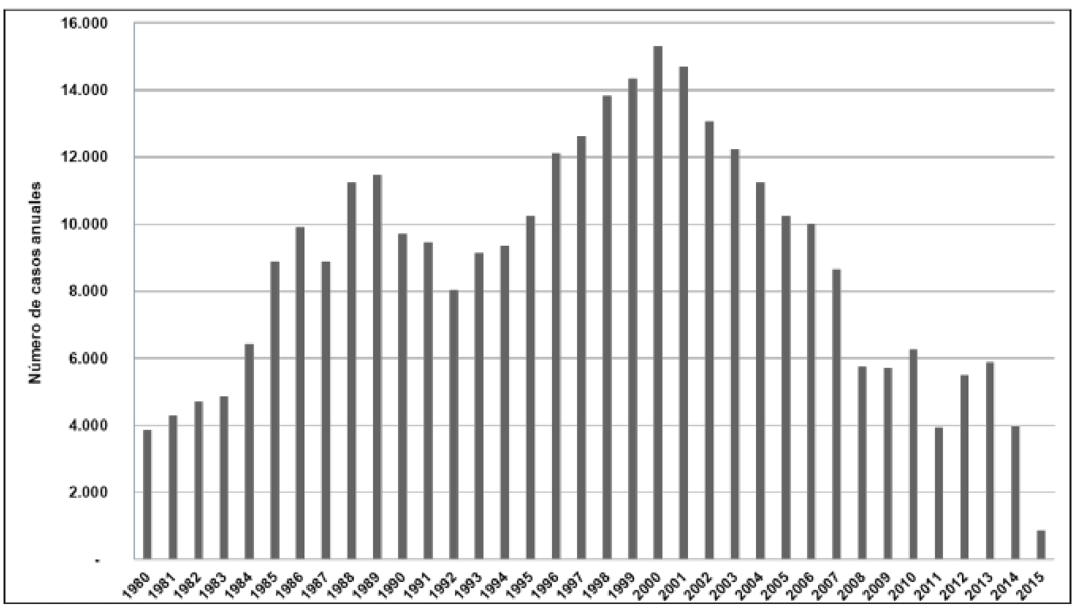
- P. vivax. It is the dominant parasite in most countries that are not located in sub-Saharan Africa. It is the most geographically widespread species and is transmitted mainly in Asia, Oceania, Central America, South America and some residual foci in the Middle East.

[135] HARPER, K.; ARMELAGOS. G. «The Changing Disease-Scape in the Third Epidemiological Transition». Int J Environ Res Public Health 2010; 7(2):683.
[136] PUERTA, J. L. El Canon de Medicina Interna del Emperador Amarillo. Dendra Méd Rev Human 8(1).2009, pp. 100-106. Disponible en www.dendramedica.es137 HOFF, B.; SMITH, C.; CALISHER, C. H. Mapping Epidemics: A Historical Atlas of Disease. Franklin Watts 2000, p. 57.
[138] ASHLEY, E. A.; PHYO, A. P.; WOODROW, C. J. Malaria, op. cit., p. 1608.
[139]WORLD HEALTH ORGANIZATION. World malaria report 2018. World Health Organization 2018, p. XIIXV [acceso: 3/5/2019]. Disponible en https://www.who.int/malaria/publications/world-malaria-report2018/en/

Although it is possible that we have hosted these harmful parasites at least 50,000 or 100,000 years ago, various studies have shown that they began to be relevant to man as pathogens about 10,000 years ago, coinciding with the development of agriculture and the first human settlements. Since then, they have played - and continue to play - a prominent role in history due to its undeniable imprint on our health and demography, to which must be added its effects on the economy, military conflicts and even the future of nations. Literature, both ancient and modern, contains numerous allusions to "intermittent" fevers that we now identify with malarial pictures. The first document written on this pathology is found in the classic book of Chinese medicine, the Canon of Internal Medicine of the Yellow Emperor or Nei Jing Su Wen, whose first composition is attributed to Emperor Huang-Ti or Yellow Emperor (a. 2700 a. C.). This text describes some of the symptoms of malaria, a morbid condition that the author refers to as the "mother of fevers." The history of malaria gives a lot to write, in fact, there is an important cast of books, monographs and articles on the subject.

Malaria, although a preventable and curable disease, is still one of the main problems facing international health. The incidence of the disease depends, on the one hand, on the control measures and the suitability of the habitat for the development of the vectors; and on the other, the level of wealth and education, the frequency with which natural disasters occur and the existence of armed conflicts. The least common routes of transmission are from mother to child and by blood transfusion (thanks to screening done by donors, but they are still a not insignificant risk in countries with scarce resources).

It is estimated that in 2017 there were 219 million clinical episodes of malaria worldwide, compared to 239 million in 2010 and 217 million in 2016. Despite



Fuente: Elaboración propia con datos tomados de Centralized information system for infectious diseases (CISID). WHO Regional Office for Europe. Disponible en: http://data.euro.who.int/cisid/.

Figura 7: número de casos de malaria importada en la región Europa de la OMS. Fuente: Elaboración propia con datos de Centralized information system for infectious diseases (CISID)[143].

[140] BASSAT, Q.; ALONSO, P. L. Malaria y babesiosis, op. cit., p. 2263.

[141]WORLD HEALTH ORGANIZATION. World malaria report 2018, op. cit., p. IV [acceso: 3/5/2019].

[142] WORLD HEALTH ORGANIZATION. History of malaria elimination in the European Region. Copenhagen, 20 April 2016 [acceso: 30/4/2018]. Disponible en http://www.euro.who.int/__data/assets/pdf_file/0003/307272/Facsheet-malaria-elimination.pdf?ua=1

[143] WHO REGIONAL OFFICE FOR EUROPE. Centralized information system for infectious diseases (CISID) [acceso: 6/5/2019]. Disponible en http://data.euro.who.int/cisid/

this difference of 20 million clinical episodes between 2017 and 2010, the calculations for the 2015-2017 period revealed the lack of significant progress in reducing it. Thus, while its incidence rate worldwide decreased between 2010 and 2017, going from 72 to 59 clinical episodes for every 1,000 people at risk. During triennium 2015-2017 it has been maintained at 59 clinical episodes for every 1,000 people at risk.

The majority of malaria cases in 2017 occurred in following WHO regions: Africa (200 million; 92%), South-East Asia (5%), and Eastern Mediterranean (2%). Fifteen sub-Saharan countries and India supported almost 80% of global burden of malaria. Concentrating in five countries, almost half of clinical malaria episodes worldwide: Nigeria (25%), DR Congo (11%), Mozambique (5%), India (4%) and Uganda (4%).

The 10 countries in Africa with the highest burden reported increases in malaria cases in 2017 compared to 2016. Nigeria, Madagascar and DR Congo were the countries where the highest increases were estimated, with more than half a million clinical episodes. In contrast, India reported 3 million fewer cases in the same period, a decrease of 24% compared to 2016.

Worldwide, deaths from malaria were estimated at 435,000 in 2017; 451,000 in 2016 and 607,000 in 2010. More than 90% of deaths from this disease are recorded in the WHO African region.

Some age groups are at much greater risk than others of contracting parasitaemia and presenting severe clinical conditions, namely infants, children under five years of age, pregnant women, and patients with HIV / AIDS. In addition, tourists and migrants from non-endemic areas must be added because they lack partial acquired natural immunity (INA) against the parasite, which develops with age in individuals living in endemic areas, and which is the result of the repeated infections that they suffer throughout their lives. It is easily understood that in endemic areas it is children (who are acquiring their INA) and pregnant women (due to a temporary decrease in their INA) who exhibit more flowery and deadly clinical pictures, as also happens to those who have never been infected . Globally, two thirds of deaths from this parasitemia are concentrated in children under five years of age. In

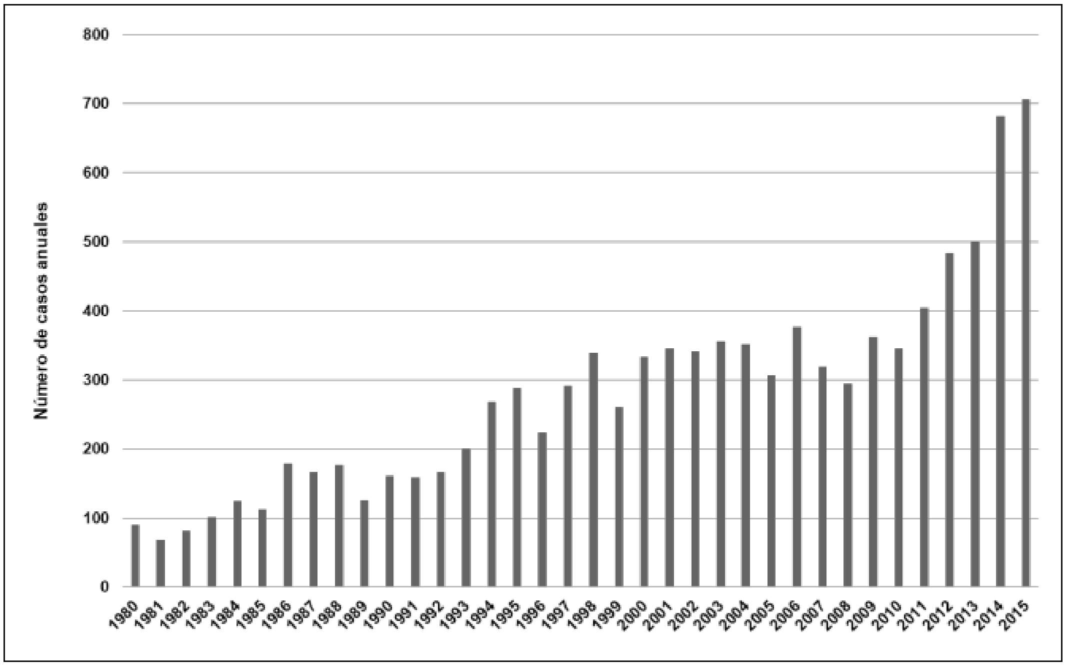


Figura 8: número de casos de malaria importada en España. Fuente: Elaboración propia con datos tomados de Centralized information system for infectious diseases (CISID) [142].

[144] GIBBS, L. M.; CREECH, D. A. «Malaria». En Kellerman R. D., Bope E. T. Conn's Current Therapy. Philadelphia: Elsevier 2018, p. 570.

[145]WORLD HEALTH ORGANIZATION. World malaria report 2017, op. cit.

[146] KYROU, K.; HAMMOND, A. M.; GALIZI, R. y cols. «CRISPR–Cas9 gene drive targeting doublesex-causes complete population suppression in caged Anopheles gambiae mosquitoes». Nature Biotechnology36. 2018, pp.1062-1066.

highly endemic regions, along with the high mortality rate, malaria also places a heavy burden on children due to the effects it has on their development, since it prevents them from adequate schooling and entry into the world of work. This is what happens to the poorest citizens of the least developed countries in the world.

Until the end of World War II, malaria was endemic in much of southern Europe (including Spain). The Balkans, Italy, Greece and Portugal were particularly affected. It was in 2015 when for the first time in the entire WHO European Region (comprising countries such as Armenia, Azerbaijan or Georgia) not a single case of indigenous malaria was registered. The evolution of the incidence of imported malaria in the WHO European Region and in Spain..

The treatment of malaria, particularly that caused by P. falciparum, underwent a major revolution in the past decade of the 1990s with the introduction of artemisinins, compounds derived from a plant of ancient use in China, Artemisia annua (sweet wormwood). The antimalarial treatment regimen is determined by the availability of medications, the place where the infection occurred, the type of parasite, the severity of the symptoms, and the patterns of drug resistance (which is also increasing). Chloroquine remains the drug of choice for all susceptible Plasmodium strains. However, the appearance of resistance limits its use worldwide, especially in those places where malaria is endemic.

In many regions, resistance to antimalarials has been linked to resistance to insecticides used to control anopheline mosquitoes and pyrethroids. This is the only class of insecticide currently used to impregnate mosquito nets, although its use is still very useful. In addition, new molecules capable of filling these deficiencies are being developed. On the other hand, the technique known as gene drive, with which a genetic mutation can be provoked that sterilizes the females of the transmitting mosquitoes, could become, if the results are confirmed outside the laboratory, a strategy to eradicate malaria.

A vaccine against malaria is not yet available on the market. The complexity of the disease-causing parasites makes their development an arduous task. The most advanced candidate vaccine is RTS, S / AS01. In fact, in April 2019, a pilot vaccination program with this preparation was launched in the Republic of Malawi. Up-to-date information on the development of vaccines and antimalarials can be obtained from the WHO website, Global Observatory on Health R&D (Monitoring R&D activities).

Is it possible to anticipate ?: priority pathogens and vaccines

The Ebola pandemic in West Africa in 2014 mobilized numerous and varied institutions worldwide that participated in the joint undertaking to research treatments for this deadly virus. The effort, apart from containing the pandemic, resulted in the rVSV-EBOV (Recombinant vesicular stomatitis virus – Zaire Ebola virus) vaccine, which to date has been shown to be effective. But a certain lack of coordination was also revealed within the scientific community and in global R&D programs. These chiaroscuros caused the WHO, at the request of its 194 member states, in May 2015 to gather a wide network of experts to launch the initiative called R&D Blueprint. Its objective is to develop a strategic plan capable of expeditiously mobilizing and coordinating the different R&D

[147] «RTS, S Clinical Trials Partnership. Efficacy and safety of RTS, S/AS01 malaria vaccine with or withouta booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlledtrial». Lancet 386(9988). 2015, pp. 31-45.

[148] WORLD HEALTH ORGANIZATION. «Malaria vaccine pilot launched in Malawi» [acceso: 4/5/2019].Disponible en https://www.who.int/news-room/detail/23-04-2019-malaria-vaccine-pilot-launched-in-malawi

[149] ORGANIZACIÓN MUNDIAL DE LA SALUD. Global Observatory on Health R&D, op. cit.

[150] WORLD HEALTH ORGANIZATION. «About the R&D Blueprint». World Health Organization [acceso:20/3/2018]. Disponible en: http://www.who.int/blueprint/about/en/#.

[151] NUKI, P.; SHAIKH, A. «Scientists put on alert for deadly new pathogen - 'Disease X'». The Telegraph. 10/3/2018 [acceso: 20/3/2018]. Disponible en https://www.telegraph.co.uk/news/2018/03/09/world-healthorganization-issues-alert-disease-x/

[152] Coalition for Epidemic Preparedness Innovations. Disponible en http://cepi.net

[153] PREDICT [acceso: 21/3/2018]. Disponible en http://www.vetmed.ucdavis.edu/ohi/predict/index.cfm

[154] Global Research Collaboration for Infectious Disease Preparedness. Disponible en https://www.glopidr.org

initiatives when an epidemic is detected or even before its appearance. So that, where appropriate, diagnostic tests, medications and vaccines are available that are useful in dealing with the crisis. All this is summarized, as John-Arne Rottingen, scientific adviser to the WHO committee, has clarified in the development of «plug and play platforms that work for a large number of [communicable] diseases or for all of them; that is, systems capable of generating a rapid [diagnostic and therapeutic] response".

The so-called 'Scientific Advisory Group' is responsible for guiding and reviewing the work carried out by the WHO expert teams involved in the R&D Blueprint. In addition, this multilateral organization carries out a series of consultations and activities on different aspects of this initiative with various institutions such as, for example, the Coalition for Epidemic Preparedness Innovations (CEPI); Global Research Collaboration for Infectious Disease Preparedness (GloPID-R), and PREDICT (Prevent, Identify, and Respond). The latter is part of the USAID (United States Agency for International Development) Emerging Pandemic Threats program, which began its activity in 2009 with the objective of strengthening the global capacity for detection and discovery of zoonotic viruses with pandemic potential154. From this collaboration, work methods and instruments have emerged that have allowed R&D Blueprint to prepare a list of priority pathogens that are periodically reviewed by the "Scientific Advisory Group". But, above all other considerations, the important thing is that the idea that the early stages of the development of certain vaccines must be advanced, although the details of the next epidemic are not known, since the work carried out will result in a shortening of the time necessary to dispose of them or a diagnostic test when the crisis appears.

Virology, bacteriologists, vaccinologists, public health experts and infectious diseases meet at the work sessions organized by the R&D Blueprint. The list of priority infectious diseases - all viral, not a single bacterial! - established at the second meeting held in January 2018, was as follows:

- Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome (SARS).
- Ebola virus disease and Marburg virus disease.
- "Disease X".
- Lassa fever.
- Rift Valley fever.
- Crimea-Congo hemorrhagic fever.
- Nipah and henipavirus diseases.
- Zika.

The mysterious "disease X" is nothing more than a warning to remind us, thanks to the existing heritage, that a serious human pandemic - and of planetary dimensions - could be caused by an unknown pathogen ("X") to date. Reason why R&D Blueprint is working on the implementation of a transversal R&D plan that, in case this happens, the best conditions are given to face this threat called "X".

At this point, it should be noted that advances in genome editing technology make it possible to manipulate or create entirely new viruses. Hence "disease X" may also be the product of deliberate action or, simply, a laboratory accident. Unfortunately, there is already a history of the latter, since it was what caused, for example, an influenza pandemic in the former USSR in 1977; and the death from smallpox recorded in 1978, in the department of medical microbiology at the University of Birmingham (GB). However, most likely, if we face something new, it is a zoonosis, which spreads within our species, becoming an epidemic or pandemic, in the same way that the flu virus does..

Without wishing to be exhaustive, a list of communicable diseases for which there is already an internationally marketed vaccine and also a list

[155] 2018 Annual review of diseases prioritized under the Research and Development Blueprint. Informalconsultation. Ginebra: World Health Organization, 6-7 February 2018 [acceso: 26/3/2018]. Disponible en http://www.who.int/emergencies/diseases/2018prioritization-report.pdf?ua=1156 ROZO, M.; GRONVALL, G. K. «The Reemergent 1977 H1N1 Strain and the Gain-of-Function Debate».
mBio 6(4). 2015, pp. 1-6.
[157] HAWKES, N. «Smallpox death in Britain challenges presumption of laboratory safety». Science 203(4383). 1979, pp. 855-856.
[158] WORLD HEALTH ORGANIZATION. WHO vaccine pipeline tracker, op. cit

Tabla 7. Ejemplos de vacunas disponibles y en investigación para enfermedades transmisibles (OMS) [159]

Vacunas disponibles	Tipo de agente	Vacunas en desarrollo	Tipo de agente
Cólera	Bacteria	Anquilostoma humano	Nematodo
Dengue	Virus	*Campylobacter jejuni*	Bacteria
Difteria	Bacteria	Chagas	Protozoo
Encefalitis japonesa	Virus	Chikungunya	Virus
Encefalitis transmitida por garrapatas	Virus	Dengue	Virus
Enfermedad neumocócica	Bacteria	Enterovirus 71 (EV71)	Virus
Fiebre amarilla	Virus	*Escherichia coli* enterotoxigénica	Bacteria
Fiebre tifoidea	Bacteria	Esquistosomiasis	Trematodo
Haemophilus influenzae tipo b (Hib)	Bacteria	Fiebre paratifoidea	Bacteria
Hepatitis A	Virus	Herpes simplex	Virus
Hepatitis B	Virus	Leishmaniasis	Protozoo
Hepatitis E	Virus	Malaria	Protozoo
Influenza	Virus	Norovirus	Virus
Malaria	Protozoo	*Salmonella* no tifoidea	Bacteria
Paperas	Virus	*Staphylococcus aureus*	Bacteria
Papiloma humano	Virus	*Streptococcus agalactiae* (estreptococo del grupo B)	Bacteria
Poliomielitis	Virus	*Streptococcus pneumoniae*	Bacteria
Rabia	Virus	*Streptococcus pyrogenes*	Bacteria
Rotavirus	Virus	Tuberculosis	Bacteria
Rubéola	Virus	Vacuna universal contra la influenza	Virus
Sarampión	Virus	Virus inmunodeficiencia humana (VIH-1)	Virus
Tétanos	Bacteria	Virus Nipah	Virus
Tos ferina	Bacteria	Virus sincitial respiratorio	Virus
Tuberculosis	Bacteria		
Varicela	Virus		

Tabla 7. Ejemplos de vacunas disponibles y en investigación para enfermedades transmisibles (OMS) [160]

of "vaccines in development" (Pipeline vaccines). The latter lists those communicable diseases for which a vaccine is being investigated under the supervision of the WHO Product Development for Vaccines Advisory Committee (PDVAC). There is no point in describing the phase in which each one is, since on WHO website, Global Observatory on Health R&D (Monitoring R&D activities) 158, more detailed and, above all, updated information can be obtained from the state of development in which they are.

Final considerations and recommendations

[159] WORLD HEALTH ORGANIZATION. «Immunization, Vaccines and Biologicals. Vaccines and diseases» [acceso: 16/5/2018]. Disponible en http://www.who.int/immunization/diseases/en/

[160] WORLD HEALTH ORGANIZATION. «Immunization, Vaccines and Biologicals. Vaccines and diseases» [acceso: 16/5/2018]. Disponible en http://www.who.int/immunization/diseases/en/

The great threats from the microbial kingdom must be seen in the current pandemics caused by the tuberculosis bacillus, HIV and Plasmodium; the challenge of "superbugs" due to the effect of RAM; the heyday - in the last five years - of emerging infections caused by new zoonotic viruses, or the possibility of new crises by microorganisms unknown to date ("disease X"). What makes the integration of medicine, veterinary medicine and biomedical research inescapable. To achieve this objective, the concept of One World, One Health, to which we have already referred, cannot make more sense, since major health problems affect us all.

Unfortunately, efforts to combat communicable diseases, although to a lesser extent than in the past, remain fragmented. There is still no mechanism that guarantees the viability of the projects and guides them towards the main global epidemic risks. Furthermore, countries where health emergencies almost always occur have very limited research and investment capacity and weak health systems. Reality that requires greater supranational collaboration that ensures the suitability and continuity of the programs underway.

In the event of a new pandemic, medicine should be in a position to provide some protection. However, it will most likely surprise us without a vaccine to prevent it or a medication capable of counteracting its effects. This is what has been happening even with already known diseases. Ebola outbreak of 2014-2015 produced almost 30,000 patients and more than 11,000 deaths, its causal agent was not unknown, it was identified in 1976. And, although more than 25 outbreaks had been counted since then, there was no therapeutic to combat it. In this order of things, it is worth remembering that Spain receives around 80 million people annually, which has put us on the podium of the tourism champions. To this must be added that around 200 million air passengers (almost 1 billion the EU), legal immigrants (more than 650,000 in 2018) or irregular (more than 56,800 in 2018) who move within our borders We welcome and the 17 million Spaniards who visit abroad every year, some of them traveling to more or less exotic countries. Data that should lead the Spanish health authorities to substantiate plans and measures more in line with this vulnerability.

Pharmaceutical companies do not seem to find the necessary incentives to tackle projects aimed at fighting certain pathogens, especially emerging zoonoses or tuberculosis, alone. However, they are the only institutions with sufficient assets to obtain permits for the marketing of medicines and vaccines. Given that successfully developing a vaccine against certain pathogens generally requires years of work and an investment of several hundred million dollars of dubious recovery, the pharmaceutical companies were moving further and further away from this therapeutic niche. The only way to overcome the stumbling block has been through the creation of consortia within the framework of "public-private alliances" (PPP, public-private partnership), in which laboratories share objectives, knowledge and risks with academic institutions, organizations multilateral, cooperation agencies and philanthropic entities. In promoting this new vision and form of collaboration, much is owed to the Bill & Melinda Gates Foundation, something that cannot be neglected..

[161] WORLD HEALTH ORGANIZATION. «Ebola outbreak 2014-2015» [acceso: 4/5/2019]. Disponible en https://www.who.int/csr/disease/ebola/en/

[162] CENTERS FOR DISEASE CONTROL AND PREVENTION. Outbreaks Chronology: Ebola Virus Disease, op.cit.

[163] INSTITUTO NACIONAL DE ESTADÍSTICA. «España en cifras 2018», pp. 51-52 [acceso: 21/3/2019]. Disponible en http://www.ine.es/prodyser/espa_cifras/2018/

[164] INSTITUTO DE TURISMO DE ESPAÑA (TURESPAÑA). «Ficha de coyuntura, acumulado 2017». [acceso: 21/3/2019]. Disponible en http://estadisticas.tourspain.es/eses/estadisticas/fichadecoyuntura/paginas/default.aspx

On the other hand, the deadly effects of RAM are already evident worldwide. Superbugs claim no less than 50,000 lives annually in Europe and the USA. USA in addition to many hundreds of thousands in other areas of the planet. Having been estimated to cause, in the EU alone, losses of € 1.5 billion per year due to additional healthcare costs and added productivity losses. Furthermore, according to some estimates, 300 million people worldwide are expected to die prematurely from RAM in the next 35 years. The speed and volume of international travel make it possible, as with other infectious diseases, for these pathogens to spread everywhere. Such a mixture of different microorganisms, particularly bacteria, from so many different locations, constitutes a great opportunity for them to exchange their genetic material, thus emerging new resistant strains at a rate never seen before.

It is also worth recalling here that vaccination programs constitute one of the most impressive success stories in the union of science with public health. Such has been its success in the prevention of communicable diseases that, paradoxically, in the most developed countries, our invulnerability to infections that affected previous generations is taken for granted. This unscientific interpretation of events has caused vaccination coverage to decrease in recent years and as a result we are witnessing outbreaks of diseases that are preventable through vaccination and that in many places on the planet have disappeared from newspaper headlines. Which should lead us to remember, again, that we continue and will continue to face the threats posed by infections and epidemics, whether old or new, and that we cannot throw away what we have learned from our past experiences of so painful way.

In short, for all that has been exposed throughout these pages, an effective intersectoral, international and multilateral coordination is required. In order for this to be achieved, the cooperation between the different agents must not be questioned - for the sake of outdated ideologies - it must be assumed that microorganisms do not need visas to cross borders, that resources (of all kinds) are limited and that the union makes the force. Well, hardly, without observing these premises, it will be possible to establish priorities for the implementation of R&D programs that make vaccines (or other therapeutics) available at the right time and also finance them adequately, both in rich countries and in other countries. Poor countries. Because when epidemic crises arise, the drawbacks of atomized actions and lack of funds manifest themselves painfully and clearly. As Ronald A. Klain, named Ebola response coordinator by Barack Obama in 2014, has explained, it took nearly nine months for the US Congress to enable $ 1.1 billion to fight Zika, a disease that had already spread throughout the United States. USA Amount that had to be withdrawn from the funds destined to fight the Ebola epidemic unleashed in Africa, so in his own words: «Literally, it was necessary to undress one saint to dress another».*L&E*

[165] O'NEILl, J. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations, op. cit. pp. 3-4.
[166] EPFIA. Annual Report 2017. Unlocking tomorrow's cures. 2018 [acceso: 4/5/2019]. Disponible en https://www.efpia.eu/media/219734/efpia_annual-report_2017_interactive.pdf
[167]WALSH, B. «The World Is Not Ready for the Next Pandemic». Time magazine. 15/5/2017, pp. 24-30.

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WATER QUALITY A FOCUS ON IMPORTANCE, HEALTH AND THE ENVIRONMENT

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Globally, the problems related to this resource are increasingly serious. Where the most vulnerable are the physically, geographically and economically limited human groups of opportunities to access water with the primary objective of meeting basic needs. A study carried out over a period of 25 years by (Ritchie & Roser, 2019) shows that globally for the year 1990, 42% of people without access to water were located in East Asia and the Pacific. Instead, for 2015, this percentage fell by 20%. In contrast, sub-Saharan Africa represented 22% of people without access to water by 1990, by 2015, this increased to approximately half of the total registered worldwide. In fact, the absolute number of people without access has decreased in all regions during this 25-year period, with the exception of sub-Saharan Africa. The number of people in sub-Saharan Africa without access to a reliable and dignified water source increased from 271 million to 326 million in 2015.

Historically, man has been linked to water and its benefits from its genesis to its development as a social being, in its evolution, the main settlements cited by history made their way depending on a water course. Water is life, it supplies, refreshes, calms and regenerates. But its access and supply sometimes faces barriers, more than environmental; economic, political and social. According to the World Health Organization, more than 5.3 billion people had access to drinking water in 2017, while the rest had access to basic quality water, depending on long-distance water sources walking and carrying containers, while other groups met their needs from the water collected in streams, ponds, rivers or lakes without previous studies.

How is water quality defined? The quality of the water can be defined from previous studies, where a reference limit is followed for maximum concentrations that the water can contain according to biological, physical, chemical and radiological parameters. These reference limits are established by each country following the recommendations of the World Health Organization. Therefore, the importance of water quality is imperative for the management of health and life of people. By consuming water of suitable quality, drinking water, innumerable diseases and complications are prevented, most of them of biological origin.

The consumption of stagnant and polluted water due to poor soil and waste management due to the lack of sanitary plans, causes diarrhea, dysentery and cholera, and is one of the fundamental reasons that explains the high infant mortality rates in the regions. most disadvantaged. In the same way, the consumption of water from wells without having been analyzed following the health regulations, can be a source of various diseases in the early or long term, especially related to minerals and heavy metals, which accumulate in the different organs of the human body, triggering serious complications over time.

Similarly, it must be kept in mind that living beings need minerals and some heavy metals for the proper functioning of the body, but in low concentrations. When the limit is exceeded it generates intoxications. Heavy metals such as arsenic (As), cadmium (Cd), cobalt (Co), mercury (Hg), nickel (Ni), lead (Pb), among others, cause serious diseases when their concentrations exceed the maximum limit. long-term consumption. For example, Alzheimer's is related to the intake of aluminum (Al), hematological alterations to arsenic (As), paralysis of the central nervous system to barium (Ba), kidney damage to cadmium (Cd), disorders of the gastrointestinal tract, liver and kidneys to molybdenum (Mo), heart and liver problems to nickel (Ni), neurological damage to lead (Pb), stomach cramps to zinc (Zn), this just to mention some of the many health effects.

The scarcity of water and its poor quality not only brings diseases, but poverty persists in its quality. Poverty and social instability as a result of the reflection of a broken society with divided interests and resources generates forced migrations, people who are forced to move and seek a new scenario to reside, one where they can have water resources in quantity and quality. However, this option is only one way for part of this percentage, not all people have the option of mobilization. The relationship between water and poverty has deep spatial roots; that is, the place where people with the least resources generally live tend to have difficulties in accessing drinking water.

Although the distribution of drinking water in large cities is complex, carrying with it complicated logistics; The most vulnerable areas are rural communities, whose inhabitants depend mostly on agriculture and the direct use of natural resources. In these areas, public health supervision and information assistance to populations is little or nil, exposing residents to problems in water quality as a product sometimes from the summation of environmental deterioration on a generation scale.

The degradation of water quality contributes to the scarcity of this resource. This is an important aspect in the management of water resources related to the care and protection of hydrographic basins, which consist of the limit or contour within which the water drains to a common point. Human-caused pollution is the greatest threat to watersheds, be it from point sources from industrial plants, factories or other facilities; or non-point sources of contamination, the ones that really worry, since they involve everything that can drag or dilute the water. Within a hydrographic basin, the negative impact not only affects the water resource, but everything that converges there: such as continuous deforestation, soil erosion, contamination of the surface water, whether by sediments, agrochemicals, fertilizers and after that, groundwater pollution and loss of fauna.

The use of land, excessive paving, exploitation models, a climate of increasing instability with droughts, floods and extreme events, suggest that it is necessary to implement integrated, coordinated and oriented actions to direct the diagnosis of the reality of the watersheds. The perspectives and measures should be directed to the sustainable use and conservation of the biophysical environment based on changes in social, political, economic and cultural dynamics. The correct management of a hydrographic basin must be focused on maintaining the internal balance, not on the overexploitation of natural resources and not on their degradation, ensuring the right to water for populations, but to achieve this or direct these actions, each person who is a member of society must be aware of their own actions and measure the footprint of contamination left by their transit.

Water as a resource is imperative for the development and balance of societies, and despite the progress made in the Millennium Development Goals, there is still a lot of work to do in managing surface and underground water resources. Their access goes beyond a human right, it is an environmental problem, an animal welfare, a matter of sustainability on a global scale. Therefore, its health depends on the quality of the environment, it is important to be aware of the role that different forest cover plays on water quality as an element and the consequences of excessive deforestation. Maintaining the quality of the water that every person drinks daily involves us all.

As reasonable and visionary beings, intensification of use of water in the near future due to increased demand for water resources for agriculture, energy production and products in relation to the increase must be taken into account very closely. of the population, injecting more gases and pollutants into the atmosphere, accelerating the effects of climate change on the various geographical scenarios, which further aggravates the situation. Greater exploitation of natural resources, greater vulnerability of different water bodies. To conclude, surveillance of water quality must be applied, as established by the Health Organization since 1976, from the quality, quantity, accessibility, coverage, affordability and continuity of the resource to populations in acceptable condition. and meeting the goals of health protection. *L&E*

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Environmental CAPSULE

DRINKING WATER SHORTAGE AND THE FIGHT AGAINST COVID-19, THE GREAT CHALLENGE

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On March 22, World Water Day was celebrated and its main objective is to create awareness in man of the importance of caring for the vital liquid for the life of humans and species on Earth.

Just at this time when we are facing a worldwide fight against COVID-19 and in which washing hands with soap and water is vital to control this pandemic and preserve life, millions of people do not have access to the service of drinking water.

This pandemic reminds all of us who have the availability to wash our hands at any time, that we are immensely privileged and that we must take care of water, a vital liquid as it is a limited resource without which we cannot live.

Likewise, so that all the governments of the world become aware of the global water crisis and the need to seek urgent measures to achieve Sustainable Development Goal No. 6: Clean water and sanitation for all by 2030.

The lack of drinking water has long led to an unbalanced health system in many places, increased costs for the consumption of this vital liquid and in the face of this pandemic, the need for it has increased and this has forced to people who have to invest in the purchase of bottled water in order to comply with the sanitary measures that the authorities have recommended to avoid the spread of COVID-19.

COVID-19 is the most brutal teaching we have ever received on the need for awareness of the use and conservation of water. The water sector must face challenges in the immediate future, among which we can mention:

1. Guarantee water in quantity and quality for the world's population.

2. To develop a solid culture of management, use and care of water, as well as of all natural resources, both in homes, workplaces, schools and in general, among all the people and cultures of the world.

3. Establish public policies for basin sanitation in both wastewater and solid waste to achieve clean rivers and beaches.

4. Promote the reuse of treated water and the recycling of garbage.

5. Implement more effective reforestation policies to recover the vegetation of the basins and the natural recharge of springs and aquifers, which regulate flooding in the lower parts for the benefit of population centers.

6. Create a financial policy for the water sector.

When to wash your hands?

• Before eating or cooking.

• After going to the bathroom.

• After handling raw food or trash.

• After touching pets, money, handrails, doorknobs, etc.

• When returning from the street.

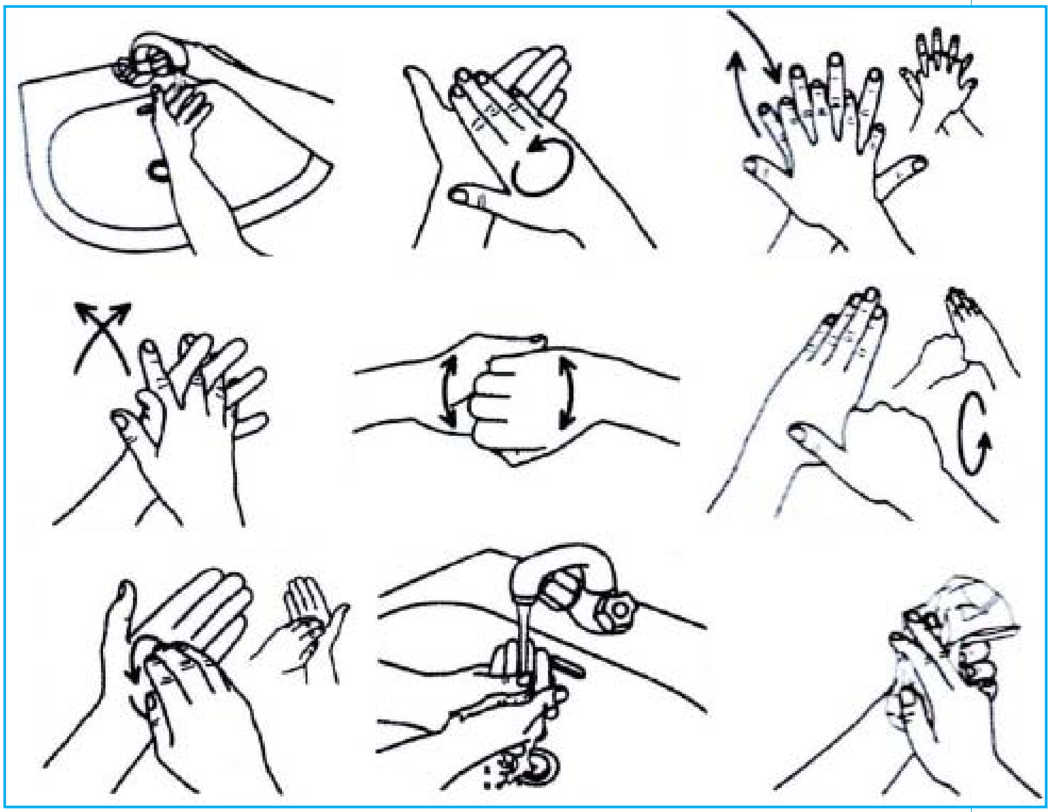
• And now for COVID19, permanently, but without wasting water.

How to wash your hands to fight COVID 19?

• Wet your hands under running water.

• Apply enough soap to cover your hands.

• Rub all surfaces of the hands, including the back, between the fingers and under the nails, for at least 20 seconds.



• Rinse well under running water.

• Dry your hands with a clean cloth or single-use towel.

COVID 19 has caused worst pandemic in recent times, but the hope is that the times to come will be better for our planet and for those who manage to overcome it.

Water is the basis of life and the economy. Let's take care of it! L&E

Alianzas alrededor del Mundo

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