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EDITORIAL

EMERGENT INFECTIONS

What do you call emergent infection? Recognition of an old problem, like human T cell lymphothropic virus infection that has been around for a long time, but only recently was diagnosed? A change in the clinical picture of the disease caused by a recognized pathogen, like severe invasive streptococcal disease - the flesh eating bacteria? A real new and never described before infection, as the encephalitis due to a new paramyxovirus transmitted by horses that appeared in Queensland, Australia, in 1994? The return of cholera to America, after a century? The appearance of Legionnaires disease, probably another old companion of humanity that passed the threshold of detection because of extensive use of air conditioning? The crossing of species specificity like what probably happened with Ebola virus and HIV 1 and HIV 2? All of the above have been called emergent infections, and actually the definition is arbitrary - each paper that addresses the subject has his own criteria... The same holds for books, including books for the lay press, like "Virus X, tracking the new killer plagues out of the present and into the future"[19] or "The coming plague", translated into Portuguese as "A próxima peste"[10].

We would like to point out that emergency is an historical concept, and dynamics of emergence are linkages between microbial variation, vector populations changes induced by economical and biological conditions and expanding and changing human populations. We are in America, and this continent is what it is today, in culture and society, because of what we could call emerging infections that attacked native Americans when they had their first contact with the Spaniards - the real conqueror of Mexico was not Cortez, but smallpox and measles, and the same is true for Peru and Pizarro. It is etimated that 54 millions native Americans died of those introduced diseases - 90% of the original population[3]. The reverse gift of syphilis, in the other direction, was also an emerging infection in Europe and in the invader population - there was a time when one of 13 north Americans had it[26]. The plague emergence in Europe, in 1345, brought by the Mongols, probably from Northern Burma destroyed feudal Europe, chivalry, the power of Church, the landholders place as economic top dogs and is one of the origins of capitalism. There are biblical examples of what could be called emergent diseases and changed history: the first born curse laid on Pharaoh by Moses, or the infectious diarrhea that stopped the Senaquerib's army on the doors of Jerusalem. As physicians we are not used to understand disease in an historical perspective, but we should: after all many factors interact to produce epidemics - urbanization, agriculture, patterns of human behavior, travel, medical practices. Without urbanization and increases in population density, measles could not maintain itself as disease - without a pool of susceptible individuals it would extinguish itself because of long life immunity. The increase in population was made possible by agriculture. We don't need to explain the relationship between human immune deficiency viruses and patterns of human behavior here - they are well known. As for medical practices, Ebola epidemics occurred in great part as hospital related infections because of poor medical conditions and practices in small hospitals in Africa, including the re-use of needles and syringe[2]. Old microbes change and acquire new genetic capacities to do harm - they escape population immunity, develop antibiotic resistance and colonize new ecological niches.

Mathematical models are useful to understand how epidemics run their course, and even to understand what caused them: in themselves, however, they don't prove biological hypothesis. The best example we know of mathematical model running wild is the famous Farr studies of cholera, in 1849. He was one of the first medical practitioners to develop a formula to understand epidemiological dynamics and by studying correlation of cholera mortality with numerous variables he found that elevation of the terrain was a good predictor of cholera mortality - recent statistical tests applied to his data show a very high p, significant of less than 0.05 between cholera mortality at this particular time and height of the place relative to the Thames. Farr believed in miasma as the cause of cholera, a vapor that was inhaled and came from the river, and therefore his formula proved his thesis. John Snow, with his famous action of putting the Broad Street pump out of business, proved that the cause of the disease was contamined water - and elevation is a very nice surrogate marker of exposure to the Thames water, explaining rather well Farr's formula[13]. We suggest that emergent diseases or emergent epidemics should be studied with a broad view and evaluated in many aspects - microbiological, social, economical, behavioral - in order to be best understood. We should not be surprised by emergence or changes in diseases patterns or virulence - actually they should be expected. After all we live in a dynamic world and change is the norm, not the exception in all aspects - why disease should be different? As the mathematical model example rather nicely demonstrates, we should beware of simple, deterministic explanations for very complex and dynamical interactions - those involving emergence of diseases.

We would like to comment a few topics related to emergent infections, using all the definitions of emergence - or re-emergence. Cholera in the Americas is a good example: the disease came again to America in 1991, for the first time in the 20th century[6]. By 1992 cholera had spread to 14 countries in Latin America, with about 400,000 cases and more than 4000 deaths[8]. Contaminated ballast water in ships, lack of water treatment in Lima and the rest of Peru and the popularity of ceviche, raw fish eaten at foodstalls

without due care to hygiene were part of the reasons that caused the epidemic. In Brazil cholera followed the Amazon and then got to the northeast of the country, but never got a hold in the more developed southeast just because water treatment is adequate in this part of the country - some cases happened, and even some deaths, but by no way we could say we had a real cholera epidemic in São Paulo, for instance. Cholera has a pretty good potential of causing epidemics, as proved in the outbreak of cholera from food served in an international flight[9]. In that flight of 194 patients that could be contacted, one hundred had laboratory evidence of contact with cholera, 75 had diarrhea, 10 had to be hospitalized and one died. We should not be surprised, again, because any gypsy and his crystal ball could read in the eighties that cholera could rise again in the Americas: it was the lost decade, military regimens in most of the countries of south America since the seventies, lack of investiments in sanitation, lack of rationality by the rulers, lack of popular housing, increase in shanty towns - favelas and barrios - lack of jobs, putting people selling foods in most of the streets in the region, without any qualms about hygienic handling of said foods, and a very good epidemical potential as proved by this flight were probably there was only one exposure to food contamined with *Vibrio cholerae*. The miracle is that cholera was not here sooner...

Foodborne diseases - cholera is foodborne and waterbone - are changing their patterns according to many factors. Microbial adaptation can lead to human diseases when, for instance, Salmonellae adapted to cattle have contact with humans, like *Salmonella dublin*. Humans get it when they drink raw milk. Other Salmonellae that usually attacks animals can give disease in humans, and the global misuse of antibiotics garantees that those bacteria will be resistant to many antimicrobials. There is evidence that infections with those germs lead to more diseases, and at least to more hospitalization[14]. Global travel is another factor that should be taken in view when we study foodborne epidemics - the cholera flight cited above says it all. Global trate is a part of global travel and there are *Salmonella* epidemics linked to consuption of food brought to the US from southeast Asia and outbreaks of *Shigella sonnei* in UK linked to lettuce brought from southern Europe[1]. The universal trend of Industrial concentration makes easy one small slip in good industrial practice causing a wide ranging epidemic - one episode of contamination in a big milk processor in the US caused 200,000 illnesses by Salmonella in 1985[18]. We could argue that bigger food processors are more careful, and we are seeing bigger epidemics, but less overall disease than before - and this can be true. Immigration and cultural practices can lead to the disease appearance in unexpected places: a 1994 outbreak of Norwalk virus infection in Portuguese immigrants to the US was traced to consumption of raw limpets, a delicacy in the Azores and the immigrants did not realize that limpets extracted from contamined waters could carry pathogens[25]. Cultural practices change also in the natives: all the noise about foods that are good for our health and eating things organic and without preservatives are linked to infantile botulism (giving honey to very young children) and botulism outbreaks caused by food commercially handled without preservatives[12]. Fast food chains cover all the places and all the countries, and the possibilities of contamination in such places are real, and again small errors in food handling can cause epidemics. We have the impression that, again, there is less disease around but when it occurs, it makes a big noise because it will be a real epidemic. The emergence of *Escherichia coli* 0 147:H7 as the cause of hemolytic uremic syndrome besides a bloody diarrhea is a good example, when in 1982 it was described in the US after consumption or raw or undercooked hamburgers[16] - today this is the most common cause of kidney failure in the US and Canada in children, and there have been epidemics of this disease in Japan, UK and other places[23]. By the way, undercooked hamburgers bought from fast food chains are not the only causes of the disease, as it has been around before fast foods chains were invented, only it was not recognized - this is one of the problems in defining emergent infections, as we discussed before. Fast food chains means also that food cooking skills are being lost - more and more people eat away from home today. There is a survey in 1414 US adults that prepared meals at home: one third of them did not wash their hands before putting said hands in the food, neither washed cutting boards after cutting meat or vegetables[1]. Adults older than 30 years old were more likely to wash their hands and having safer food handling procedures than younger people.

New enteropathogens, like *Clostridium difficile* are being recognized increasingly: this particular germ was first proved to be the cause of diarrhea post antibiotic use and pseudomembranous colitis and now we know that it is the major cause of nosocomial acquired diarrhea in the US - it is an exception to the thesis that hospital infections have very little to do with the physical environment colonization[20]. This disease can be caused not only by antibiotic selection of the intestinal germ population, but by chemotherapy use. This underlines one of the causes of what are being called new infectious diseases - the growing part of the hospital population that has extensive defects in their immune system, by AIDS, chronic diseases, neoplasias, aging. We have a population of people in remission of their primary disease - leukemia, Hodgkin's disease, lymphomas, or in partial control of the disease, but that undergoes frequent series of high dose chemotherapy, has long periods of neutropenia and even in total remission has not normal immunity. HIV infected patients actually did not bring to medical attention infections by totally new pathogens, but in this population they do cause more disease and different aspects of the disease, as happens with *Mycobacterium avium* infection. People with compromised immunity are more frequently infected with *Listeria*, *Campylobacter* or *Salmonellae*.

Of course there are new pathogens, and the finest example is HIV: the leap from monkeys to Humans by the virus can't be more than a century - the disease was unknown before 1981. Probably before this it existed in small villages, in Africa. We have to remember that Africa was very sparsely populated in

the end of last century and the beginning of this one. The population explosion brought AIDS and HIV infection to light, and this happened sooner because of the many wars fought in African soil and the participation of many foreign armies there: Cubans, Belgian mercenaries and believe it or not, Brazilians - our dear departed generals decided by geopolitical reasons to help the marxist regimen in Angola (nobody said they were consistent anyway) and Brazilian planes carried - we don't know this for sure and there isn't any source to cite, but rumors - Cuban troops to Angola, this in the early seventies when to speak of Cuba was a crime against national security in Brazil... Human behavior helped the spreading of HIV - it spread out after the sexual liberation, and the epidemic of recreational drug use. HIV changed the usual features of many diseases that are endemic in the Amercas: Chagas'disease in this type of patient presents as cerebral abscesses and visceral leishmaniasis, kala azar, changes it's clinical picture; South American blastomycosis also interacts with HIV. The interaction between HIV and *Mycobacterium tuberculosis* also should be noted - actually we think the most important of this interaction is the clear increase in viral load and probably as a result in the acceleration of AIDS disease in this patients than the traditional relationship between resistant *Mycobacterium tuberculosis* and HIV patients that did not follow the right treatment. Other viral diseases are, as far as we know, real new diseases: the encephalitis by a novel paramyxovirus, a morbilivirus present in horses and passed to humans described in Queensland, Australia, in 1994[15]. We had in Brazil two examples of new viral diseases: the Sabiá virus, that killed one woman in the outskirts of São Paulo, in Cotia, contamined one scientist in Yale and then was not found anymore and the extensive Rocio epidemic of a flavivirus that caused encephalitis in the coast, very well studied by ROSENBERG[17] and also as far as we know, today, in hiding. This is one very interesting point: those virus have been occasional findings or they will be back? Are new and different virus lurking in the progressively vanishing wild habitats, waiting to get into the blood of the dominant species in this planet? The pulmonary syndrome induced by hantavirus in the four corners region is a good example[7]. The ecological consequences of rain in the winters and abundance of pinon needles caused an explosion in the rat population in this place of the country and soon the navajo population of the region was in panic, with this new disease that caused pulmonary insufficiency and death. There were some cases like those before the epidemic was recognized, but it is not possible to state that it was the same disease. Perhaps one day it should: after all the influenza virus that caused the great pandemic of 1918 and killed more persons than the First World War that just ended was analyzed (at least parts of its DNA) and identified recently. That was another emerging infection at that time...

One aspect of the emergent infections are changes in the virulence and behavior of old known enemies, like staphylococci and streptococci. The staphylococcus in the last 50 years had many surprises for us: first of all his quickly acquired resistance to penicillin, the methicillin resistance, then the toxic shock syndrome, linked to the use of tampons by women and the absorption of a toxin[22]. We postulate that there is another surprise that Staphylococci can bring us soon, the resistance to glycopeptide antibiotics - we hope it won't be soon, but we predict it will come. After all, enterococci have this capacity and enterococci with multiresistance are infections that probably have no adequate treatment[4].

Streptococcal diseases are also changing. We are having again rheumatic fever, after many years of decline: streptococcal toxic shock came into being recently and even more recently the emergence of necrotizing facilities, the flesh eating bacteria, showed us that germs that have been around for decades, even without the capacity of getting resistance to penicillin, can and do change their clinical pattern[5]. Scarlet fever, on the other hand, is vanishing - as by now... The emergence of a highly virulent clone in the decade of 1980 probably has something to do with the expression of a potent superantigen by streptococci and increased virulence[21]. Another old companion of humanity is changing: the pneumococcus, that changed his pattern of resistance and today can lead to therapeutic dilemas - what is the best option to treat penicillin resistant pneumococcal meningitis[11]?

We could write a lot about the emergence of multiresistant bacteria induced by many factors - antibiotic use in raising poultry, antibiotic prophylaxis and mostly antibiotic misuse. Many mechanisms of bacterial resistance to antibiotics may occur and are being more and more studied and known, but this knowledge does not directly helps patients infected by those germs. Progress in antibiotic discovery are, and probably always will be behind antibiotic resistance. The genetic variability of most microbes, the facts that we cultivate at most 1 to 2% of all microbes and can study only those strains and the fact that antibiotics and microbes are companions for millions and millions of years guarantee that all antibiotics will found germs that are resistant to them - the question is when and what importance it will have in the clinical setting. Classic measures to contain the proliferation of what is called by medical residents "those superbugs" are not effective. Isolation in particular is much used, but probably not very effective, if efficient at all. Misuse, the major cause of antibiotic resistant bacteria, is linked to medical practices and probably someday it will be determined that not every physician can prescribe any antibiotic - it is what is happening with blood transfusion - in most American hospitals and in some Brazilian ones there is a committee on blood transfusion that supervises and even suspends transfusions given outside written protocols[24]. We don't think it is appropriate calling infections by multiresistant bacteria "emerging infections" - after all they are all known pathogenical agents, that are showing new characteristics and resistance.

This review did not cover all emerging diseases - that is too much. We did not dwell on Lyme disease, Erlichiae and all the "Cold zone" disease linked to thicks, as they appear to be not

very important, as by now, in South America - we can be proved wrong in the next few years. We would like to imagine a strategy for the future - what to do to prevent emergence of new disease? Actually we can't prevent - what we can, and should do, is to understand better the relationship between human modifications in ecology and diseases, to investigate before doing things that change this relationship and them doing them - just the opposite of what was done when our generals decided to colonize the Amazon and increased malaria in Brazil from 100,000 cases to one million cases a year, in a few years... We have to have a global surveillance system, capable of an early warning of the emergence of new diseases. We have to have collaboration between countries, between the WHO and PAHO and between sentinel laboratories. We need a global Center for Disease Control, worldwide. And we need to understand that microbes were here before us, will be here long after humanity is gone and will change. The most we can do is to discover how they change and devise tricks of containing the bugs, before they spread.

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