Epidemics on a Global Scale and in Brazil

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Disease classification and its impact: neglected transmissible diseases are discriminatorily called 'tropical'

The international Classification of Diseases (ICD/WHO) is a century and a half-long effort to standardize the way in which we refer to diseases and causes of death. In its 1989 version, the ICD 10 is highly complex and less a single classification of diseases than a family of classifications with distinct objectives. In addition to processes of health and illness, it also finds room to address health interventions and external causes of illnesses/injuries as opposed to their nature alone. The family flagship is the "International Statistical Classification of Diseases and Related Health Problems" (Laurenti et al., 2005). This is the standard form of referring to diseases today, covered in thousands of three or more digit codes that span the whole universe of disorders. However, there are other ways of referring to diseases.

One often employed classification considers only three groups, characterized by "origin": (1) transmissible diseases; (2) chronic, non-transmissible diseases (including mother/child diseases, as well as malnutrition); and (3) external causes or "injuries" (violence and trauma). The logic of this classification expresses the epidemiological situation of the world today, in which an "epidemiological transition" has seen a marked reduction in transmissible diseases in developed nations and a sharp rise in chronic non-transmissible illnesses, especially cardiovascular disease and cancer. Most developing countries still face a double challenge of continued high frequency of transmissible diseases and a fast growth in chronic, non-transmissible ailments. For different social reasons, violence and trauma are on the rise on either side of the North/South divide.

Another classification often used to account for maladies on a global scale is the following: Groups I, II and III (used by some organs of the WHO), referring, respectively, to global diseases, neglected diseases and highly neglected diseases (as used by Doctors Without Borders (MSF)). The latter is impregnated with a confusingly humanitarian sense mixed with the strong presence of an economically-tinged analysis. The traditional health indicators have been gradually substituted by a new concept: Burden of Disease (BoD), weighed in disability-adjusted life years (DALYs). Today, the most common way of indicating

the gravity of a health event is by measuring these losses, and, implicitly, associating them with degree of development. Table 1, adapted from a recent WHO publication, gives us an idea of what we are talking about here. Based on statistical data from 2002, it shows that DALYs due to transmissible diseases top the list of "causes" worldwide, though with obvious emphasis on less developed nations. The reverse occurs with non-transmissible diseases, with external causes distributed more or less homogeneously.

Table 1 – Distribution (in %) of disability-adjusted life years per cause (2002)

Causes	Country Incomes				
	Low	Low to medium	Medium to high	- High	Total
Transmissible diseases	70	34	30	- 8	54
Non-transmissible diseases	20	48	51	- 77	33
Injuries	10	18	19	- 15	13

Source: WHO (World Health Statistics), 2008

Such is the global importance of transmissible diseases that the Millennium Development Goals (Box 1) include the combat of mortality among women and children alongside HIV/Aids and malaria in the eight core development goals, eighteen targets and the forty-eight indicators used to track them. These considerations are necessary in order to present a general panorama of the relevance of transmissible diseases. They can be considered neglected insofar as they do not receive the attention they deserve from Big Pharma, with its tendentious manner of looking at human health necessities through profit and market-tinted lenses. In this sense, the definition of "orphan drugs" can be extended from those developed to treat rare diseases (fewer than 200 thousand cases) to include remedies for high incidence diseases in excluded populations living in the underdeveloped world or in pockets of poverty in developed nations (Angell, 2005; Badiaga et al., 2008).

If we consider neglected diseases in general and in the Americas in particular, we encounter numerous cases of maladies long-since eradicated in developed countries. In terms of parasitic and bacterial diseases identified as neglected worldwide, Hotez et al. (2007) count thirteen, including three soil-transmitted forms of verminosis (ascaridiasis, ancilostomosis and trichurisis), filariosis, oncocercosis, dracunculosis, schistosomiasis, Chagas disease, sleeping sickness, leishmaniasis, Buruli ulcer disease, leprosy and trachoma. An expanded list also includes: dengue, treponematosis, leptospirosis, strongiloidosis, trematoids transmitted by food, neurocisticercosis, the mange and "other tropical infections". This mention of the tropics, clearly prejudiced and unscientific, is complemented by the affirmation that neglected diseases are "among the most

common infections affecting the estimated 2.7 billion people who live on less than US$2 a day".

Box 1 – The Millennium Development Goals – MDG (1990-2015)

Goal 1	Eradicate poverty and extreme hunger
Goal 2	Achieve universal primary education
Goal 3	Promote gender equality and empower women
Goal 4	Reduce child mortality
Goal 5	Improve maternal health
Goal 6	Combat HIV/Aids, malaria and other diseases
Goal 7	Ensure environmental sustainability
Goal 8	Develop a global partnership for development

Source: UN General Assembly, Report of the Secretary-General, Roadmap towards the implementation of the United Nations Millennium Development Declaration, September 2001

Along similar lines, and based on prevalence and DALYs , Hotez et al. (2008) consider ancilostomosis and other soil-transmitted verminoses , and Chagas disease as the most important transmissible tropical diseases neglected in Latin America and the Caribbean, followed by dengue, schistosomiasis, trachoma, leprosy and filariosis. In Brazil, the Ministry of Health's Department of Science and Technology (Decit/MS) has placed many of these diseases on its National Research Priorities in Health Agenda (Brazil 2006b). In a Decit announcement in conjunction with the National Council for Scientific and Technological Development, the sphere of interest in neglected diseases was limited to seven: dengue, Chagas disease, schistosomiasis, leprosy, leishmaniasis, malaria and tuberculosis (CNPq, 2008).

It is surprising the extent to which the Third World is discriminated against because of the lamentable epidemiological situation in which its populations find themselves and because of the apparently irresistible tendency to associate these diseases with the tropical climate. However, it is good to note that the WHO Health Statistics Report for 2008 turned up some surprises among its ten highlights (Box 2). In addition to those diseases described as neglected and essentially transmissible, we also see breast cancer and smoking-related diseases.

Box 2 – Ten Health Statistics Highlights

Progress toward MDG 5: maternal mortality
Coverage gaps and quality inconsistency in maternal, neonatal and infant health
Estimates for HIV/AIDS adjusted downwards
Progress in the fight against malaria
Reduction in smoking-related deaths
Breast cancer: mortality and selective exams

Varying degrees of progress in lowering mortality rates are holding back an increase in European life expectancy
Disease outbreak tracking: meningococcal meningitis in Africa
Future tendencies in global mortality: bigger shifts in mortality patterns
Reduction in impoverishment caused by catastrophic health costs

Source: WHO (World Health Statistics)

Endemo-epidemic Process

Major human health scourges have been present for as long as there have been conditions for populational agglomerations (Carvalheiro, 1992). Known today in their biological essences, transmissible diseases dominated history and even pre-history, as paleoparasitological studies have shown. According to Enrique Najera, since the time of Hippocrates, the Greek roots of the words endemy and epidemy designated, respectively, resident and visitor (Buck et al., 1988). An epidemic was an unwelcome visitor while an endemic was a "homegrown" problem.

The fundamental concepts in this area of knowledge were constructed in association with these classical scourges. It became more convenient to stick to this known territory and try to understand how to adapt them to other fields of diseases and disorders in general. Transmissible diseases are those in which the "endemo-epidemic process" is best explored (Sinnecker, 1976). With the development of germ theory in the 19th Century, it was thought that this process occurred with the transfer of the agent from one host to another, comprising an "epidemiological chain of hosts". This rudimentary notion became more complex when it was realized that infectious agents could also be propagated throughout the environment by other vertebrates and even invertebrate vectors. Typical examples of person-to-person transmission, as seen in flu or measles, become rather more complicated in relation to other agents. In the case of tetanus, for example, the agent is acquired from the environment with no person-to-person transmission involved. In human rabies, thankfully quite rare today, transmission depends on contact with animals, whether domestic (dogs) or wild (bats). In schistosomosis, the chain starts with a freshwater snail, which disseminates infectious agents – cercariae - into the water, which then invade the skin of humans who come into contact with their liquid environment. In the case of dengue and the urban form of yellow fever, person-to-person transmission depends on a vector – *Aedes aegypti*. In its wild form, yellow fever is passed by monkeys to mosquitoes and subsequently onto humans who 'invade' the wilderness. So there are clearly epidemiological chains that are exclusively person-to-person and others that break with the paradigm.

In all cases, the determination of the occurrence is not exclusively biological, especially where contact with an urban, rural or wild environment is involved. This social determination of the endemo-epidemic process was best

translated in the Eastern European, and specifically the Russian, epidemiological tradition through the introduction of the concept of *focus*, defined as the spatial range of an infectious agent. In short, it considers the epidemiological chain as a succession of foci rather than hosts (Sinnecker, 1976). In this line of thought, the theory of natural foci, attributed to the Russian parasitologist Pavlovsky (1966), argues for the environmental circulation of potentially harmful pathogens with which man comes into contact when he shares given landscapes.

The extension of these concepts to other areas: an outbreak is not a small epidemic

Mankind is not plagued by transmissible diseases alone. Even before the unveiling of the inner mechanisms of disease, clinical science armed with technological instruments and the epidemiology of transmissible diseases, concepts of frequency were already being extended to diseases catalogued outside this specific field. The spatiotemporal distribution of diseases and ailments in general has always warranted the attention of the health sector, especially in identifying which areas should be attended with more emphasis. It is not surprising, then, that the notions of endemy and epidemy were extended to non-transmissible diseases and even to violence and trauma. In fact, these ideas have even been applied as broadly as in politics, economics and public security. The term epidemic can be heard in relation to everything from widespread crack use by streetkids to the bankruptcy of financial institutions in central nations and corruption in the world's parliaments.

The idea of an exclusively biological determination of transmissible diseases is, as we have seen, insufficient, but widening the net to include the ecological sphere does not redress the shortfall either. Social determination is a logical consequence of the insufficiencies of these approaches. With the notions of endemy and epidemy adapted to other areas, it is inevitable that social determination should accrue constant value while the concepts shed their equivocal association with this or that disease, or that the term epidemic be considered an intrinsic attribute of a given malady. Above all, what we have here is an instrument for the analysis of reality, a tool for understanding the manner in which a studied phenomenon is distributed in space and time.

Even in the field of transmissible diseases a certain befuddlement surrounds these concepts, expressed in particular when concrete threats to health emerge within the population. There is obvious disagreement between health authorities and the press when it comes to the difference between an outbreak and an epidemic; a disagreement that is played out tediously each time a spate of cases occurs. It would seem that what the event should be called is more important than what the event actually is and the response it demands. The *Folha de S. Paulo* style manual (2008) offers very reasonable definitions for outbreak, endemic and epidemic. However, it also indicates that, in the case of the latter, the health authorities tend to try to cover up the reality. The affirmation is not

entirely void of truth, but it is completely out-of-date. It is an idea that lingers since dictatorial times, when, in the 1970s, the military regime covered up an epidemic of meningococcal meningitis in São Paulo while another newspaper accompanied the registration of cause of death at a civil registry near the city's main hospital complex. The result was what epidemiologists call a control chart, which is nothing more than a proxy.

These control charts are often taken as quantitative evidence of the endemo-epidemic process. They are based on the number of notified cases of diseases considered essential and subject to epidemiological surveillance. This is a very old idea that harks back to the creation of international mechanisms for the control of transmissible diseases with potential for global spread. These are the so-called "quarantinable diseases" listed under the International Health Regulations (IHR). As notification is obligatory by law, it is believed that practically all cases are reported to the authorities. This is what allows them to draw a baseline for the behavior and incidence of diseases in accordance with the level of development of national health services. The average monthly distribution over recent years (usually 5), with its statistical variability, provides an "endemic channel", which is little more than the behavior expected of a "resident" disease. When the channel maximum is surpassed, authorities have to be alert to the possibility of an epidemic. In this case, an epidemic is understood as a higher than normal incidence of a disease at a given place and time. This brings us to a possible definition of the concepts of epidemic (concentration in space and time) and endemy (concentration in space alone) of a disease (Sinnecker, 1976). Frequency records are far less reliable for diseases not under epidemiological surveillance, but there are some trackable indicators nonetheless: mortality, cases attended at health service units, especially hospitals, coverage in print and TV news and even rumors.

This brings us to the concept of outbreak, empirical evidence that something is driving a disease or malady above its baseline levels of incidence. Given the very manner in which outbreaks are identified, they always occur in limited environments, which can give the impression that an outbreak is an epidemic on a smaller scale - a wrongheaded notion, in my view. Taking the world's main disease control systems as our guide, we can consider an outbreak to be an event worthy of attention and causal investigation. There are practical rules for the investigation of outbreaks based on a sequence of observations considered indispensable to achieving a scientific explanation for the phenomenon. This leads to the idea that we can consider an outbreak as the direct perception of a "cluster of cases", usually identified by common sense and spread in rumors that eventually reach the press, becoming news. In this sense, it would be interesting to mention the contribution of Boaventura Sousa Santos (1989) to the process of the circulation of scientific knowledge in post-modernity. Common sense knowledge properly treated can make the epistemological leap to scientific knowledge suitable for academic use. However, this alone is not enough;

what is needed is a "dual epistemological leap" that returns the results of that scientific investigation to the realm of common sense. If we consider a outbreak as something picked up on by common sense, its acceptance demands work predicated upon scientific advances as to the nature of that disease. In the case of a disease under epidemiological surveillance, a control chart is enough to orient the authorities on the steps that need to be taken. For the public to accept and rally behind these measures requires that the return leg of the epistemological leap be competently achieved. The same ideas can be found in Carlos Vogt's "spiral of scientific culture"(2008), which envisages "not only the production of scientific knowledge, but also its circulation in society through education, campaigns and awareness drives".

Health Research and Innovation Policy

The 1st National Conference on Science and Technology in Health held in 1994, issued a base document penned by a committee coordinated by the then president of Fiocruz, Carlos Morel. We could say that it was from this document on that we truly took our place within the international debate that associates research in health with economic development. Ten years later, in 2004, a new Conference produced a document that included "innovation", a concept that widely prevails in the current scientific environment. The inclusion even extended to the title: 2nd National Conference on Science, Technology and Innovation in Health. This second conference was convened jointly by the ministers for Health, Science & Technology and Education in what was an auspicious beginning of inter-relations at least on the level of development organs: Decit, from the Ministry of Health, the CNPq and Finep, from the Ministry of Science and Technology, and Capes from the Ministry of Education. From then on we see an active presence of the Ministry of Health in this field, represented not only by an influx of "new money" into health research, but also in a shift in research priorities. In fact, Health Ministry participation in the definition and development of S&T research in health is even provided for in law (SUS Law).

The existence of the Brazilian National Health Service (SUS) is internationally recognized as a competitive edge when it comes to the speed with which technological innovations can be included and assessed: new medicines, vaccines, reagents, equipment or managerial procedures. Discussion within the ambit of a plural Conference made scientists, managers, workers and users aware of the profound significance of the idea - prevalent in quite a few scientific circles - that basic, pre-clinical, phase I (security) and phase II (immunogenicity, in the case of vaccines) clinical studies are the preserve of developed nations. Scientific work using sophisticated technology in laboratories with certified best practices was an appanage of the First World, with all other nations serving merely as fields of experimentation, especially in relation to diseases widely distributed in the target population, from which volunteers can be found for phase III tests (efficacy). The competitive advantage held by countries with a national health

system of their own resides precisely in the possibility of conducting "real world" studies into the effective implementation of health system innovations. In this sense, we have the conditions to develop rapidly in offering practical demonstrations of the effectiveness of new drugs or vaccines against local or even global threats. A good example of this was the testing, with over seventeen thousand people, of a new anti-malaria drug, ASMQ (named for its two main components, artesunate (AS) and mefloquine (MQ)), run by the Ministry of Health's Malaria Control Program (Fiocruz, 2008). This new product was co-developed by Fiocruz and the international initiative "Drugs for Neglected Diseases" (DNDi), with assistance from the NGO "Doctors Without Borders".

Health Research Agenda: Society is heard in Brazil

There are two unanimities in the scientific world today that deserve mention. First, is the 10/90 gap, the fact that only 10% of the public and private resources channeled into health research (over 120 billion dollars per year) is invested in studying diseases that affect 90% of the population. The other (near-)unanimity is that essential health research capable of combating disease involves more than just the work done at the biomedical lab bench; equally essential is research in operations and policy, health services and systems, insofar as these fields contribute to broadening the coverage of existing initiatives. Not to mention research that "fine-tunes" already existing actions, boosting cost effectiveness and ensuring wider coverage.

In Brazil today we are witnessing a veritable revolution in this area. The participation of the Ministry of Health and the scientific community in the area of Collective Health in the process of drawing up the agenda for research priorities has resulted in a battery of items amply discussed with society, as normally occurs at Health Conferences. This initiative came in response to the need to prepare the nation for the 21st Century. We can ask ourselves if we are now standing on the verge of a new paradigm, one that goes beyond the "Pasteurian paradigm" of which Manguinhos in Rio and Butantan and Adolfo Lutz in São Paulo were our most notable examples. It is simply no longer enough to associate, in the academic milieu, the research done in biomedical labs and that done at the hospital bedside; epidemiological fieldwork and the production of control products and processes (serums, vaccines, medicines, organization of services). The presence of society in the equation is now indispensable. One current trend, "Translational Medicine", proposes a two-way research system linking the lab and the ward, on the grounds that the flow has always been "bench to bedside" and must now flow back as well, with hospitals subsidizing researchers with evidence-based information. Even that falls someway short. There is a growing need to insert public health into this new paradigm, including the discussion of priorities with society in a kind of "translational plus".

This was the path chosen in the context of contemporary Brazil. The creation of a "National Agenda for Health Research Priorities" (Brazil 2006a)

followed upon a complex process that went to the floor of the 2nd National Conference on Science, Technology and Innovation in Health in 2004. That same Conference also approved the "National Science, Technology and Innovation in Health Policy" (Brazil 2006b). The process incorporated professional contributions from scientists from various areas of the health sector (basic, clinical, epidemiological, planning and management), managers, businesspeople and representatives of the community. Policy formulation usually involves a triumvirate of government, business and academia, called the "triple helix", but in this special process a "quadrumvirate" was sought that could include social representation.

This drive resulted in a 24-piece Agenda covering every field of research in the area of health. One of these sub-agendas, the longest of the 24, is devoted to Transmissible Diseases. Both the Agenda and the Policy are available in print form and on a special CD-ROM (National Conference on Science, Technology and Innovation in Health, 2005), or can be downloaded directly from the Health Ministry website (www.saude.gov.br/ ciencia e tecnologia). A brief look at the Summary of the Agenda will show that the diseases present in this "epidemic dossier" issue of "Estudos Avançados" are also present there. The research proposals adopted are those that give a Conference like that held in Brazil its sense: the involvement of society in setting priorities for research that has a direct bearing on its needs as opposed to merely following the ideas of scientists. As such, we believe our Conferences escape the stigma identified by Stokes (1997), who used the central limit theorem as a metaphor for research priorities set exclusively by scientists. Without the involvement of non-scientists on these committees, the priorities remain encapsulated in a "confidence interval", built around the scientific knowledge of the epistemic community that makes the judgments; in other words they cannot escape the norm prescribed by science.

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ABSTRACT - Epidemics must not be seen as a special kind of disease but as part of a complex process of distribution of pathologies over time and space. Among the different existing disease classifications, the ICD, currently in its 10th edition, is the official one. The control charts being employed by the health system allow estimating the stage of development, endemic or epidemic, of diseases, especially those subject to worldwide control, the quarantinable diseases. The concept outbreak should be understood as a signal for the concentration of episodes worth being studied in depth. The most important communicable diseases in the developing world, the so-called neglected diseases, deserve special attention from the research funding agencies for not ranging among the priorities of the pharmaceutical industry. In Brazil, the agenda of priorities in health research includes various diseases of this nature, which have been contemplated in calls for projects launched by the National research Council and by the Ministry of Health.

KEYWORDS: Epidemics, Neglected diseases, Endemo-epidemic process, Distribution of diseases, Control charts, Endemic disease, Epidemic and outbreak, Research and innovation policy in health, Agenda of Research Priorities.

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