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WHO IS GOING TO DIE?

The Influenza A (H1N1) (Swine flu) Pandemic and Other Infectious Diseases as Global Challenges

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A breaking news pandemic

When on June 11th WHO announced that the Influenza A (H1N1) was a pandemic, the first pandemic declared since1968, it took nobody by surprise. In fact the US government had already acted as if the pandemic had been announced. A careful strategy was mapped to explain that even though the level of the epidemic was raised to the highest, grade 6, this did not indicate that the flu had become more severe. However, this discussion around the Influenza A (H1N1) flu revealed that the set of tools to describe a potential pandemic was limited. There are at least three important elements that need to be assessed. One is the way the virus is spreading geographically, another, which is linked to the first one, is how contagious it is, i.e. how easily it spreads from person to person, and the last the actual severity of the disease the virus causes. The WHO staging on epidemics takes only into account the first feature of the virus. Being a pandemic just says that the virus now shows a community-wide spread in different regions of the world. By definition there must be evidence of sustained transmission between human beings in two distinct parts of the world at the same time. The speed of the spread may to some extent indicate how contagious the virus is. However, to better describe this, the reproductive number or RO is used. It tells on average how many subjects one patient transmits the virus to. Based on data from Mexico, this number was assessed to be 1.4, which is not a huge number. Some other focus of flu may have a factor of 3 or more, i.e. one infected person will transmit the disease to 3 other persons. An analysis from the New York St. Francis School concluded however that the Influenza A (H1N1) virus spread with an RO of 3.45. It illustrates how difficult it is to really assess this feature of the virus. Much is linked to the fact that the actual number of cases is underreported. Officially only about 56,000 cases have been reported so far. This is considered by most experts as a grave underestimation. More likely hundreds of thousands or millions have already been infected at this stage; some with very mild symptoms and some with a total subclinical course. However, due to lack of tests of all people with slight symptoms of flu (somebody may mistake it for hay fever) we do not know how contagious the virus is.

However, what seems to be the case is that the virus for the time being is mild. 238 deaths had been reported by June 24th, 2009. With the very conservative estimate of 56,000 total cases, this gives a case fatality rate of less than 0.5% (i.e. the percentage of patients dying from the diseases, CFR). More likely the CFR is much less and since most cases are mild, the virus is a limited threat to public health for the time being. It seems to be less lethal than forms of routine seasonal flu that kills 250,000 to 500,000 persons a year, and of course cannot be compared to the 1918 Spanish flu that killed 40 to 50 million people. Neither can it be compared to the H5N1 bird flu which is extremely virulent with a high case fatality rate, but which does not spread easily between human beings. What is however, surprising and worrisome, is the unlikely high number of healthy young and middle aged people falling se-

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riously ill; a third to a half of fatal cases have occurred in this category. This is not the typical pattern with routine seasonal flu epidemics where the elderly are hardest hit. It became also clear that certain other patient groups could be more vulnerable such as people with asthma, heart disease, diabetes, obesity and autoimmune diseases. Pregnant women and children were also considered to have increased risk.

As has been stated by the WHO, the virus may develop into a more aggressive form. The Spanish flu also started as a mild variant before turning more aggressive. However, the probability is not very high. A flu virus that spreads easily in general tends to be more mild. It keeps the host alive so it can spread further. To kill the host and then die itself is not a strategy for survival for the virus. Even though the Ebola virus has got a lot of international attention due to its very high case fatality rate, the short incubation period combined with the rapid death of the patient, makes the virus very unlikely to spread internationally.

HIV did not spread easily. Politicians and decision makers were not potential targets of the disease. Even though data suggesting that this epidemic could be devastating were at an early stage, the global response was lacking

Since we do not know what will happen regarding the Influenza A (H1N1) virus and its virulence, there is a clear rationale to stay on alert and follow closely the spread of the virus. There is also likely to be a second wave that will appear in the autumn, especially in the colder northern hemisphere when viruses more easily spread. Typically pandemics take six to nine months to move across the world.

The response to the disease has been swift. There was some criticism blaming the authorities of slow response at the very beginning in Mexico, but over all it seems that governments and WHO have put together an effective response based on strategies developed to fight the more serious H5N1 bird flu. After years of neglect there has, since 2005, been a lot of pandemic planning at all levels from WHO in Geneva to local communities. The plans are all put into effect when a pandemic is announced. Moreover, stating level 6 is also a signal to the pharmaceutical industry to accelerate vaccine development which may take another 4-6 months. Political leaders paid attention rapidly to the Influenza A (H1N1) fight. US President Barack Obama told people how to wash their hands. In US measures were taken before the pandemic was declared by WHO. 1 billion dollar has already been allocated to vaccine development. Ministers of health in many countries talked seriously about the flu on television and reassured their respective constituencies that governments were well prepared. Worst case scenarios were easily presented and grabbed by media which at times fed public hysteria. However, things cooled down and people were able to relax. The reason for the hysteria was apparently the fear that there was a kind of avian flu on its way, especially after what was considered a high initial mortality in Mexico. This was a "breaking news" epidemic and media could easily have a day to day follow-up of the spread as if this was going to be threatening the lives of all of us.

Later another focus emerged. Political leaders became more concerned about a spread of a virus that could incapacitate large parts of the working population for a long time. Such a phenomenon on top of an already well established economic crisis could make matters much worse. Thus, even though early on, the WHO realized that there was no way of actually stopping the epidemic, there were still options to slow down the spread at which it was spreading, so that just a limited part of the population suffered at a given time. In this way the potential strain on healthcare systems could also be eased.

A pandemic threatens all parts of the world, there are no boundaries, no links to behavioral patterns, and effective containment is impossible. But an important fact is that this pandemic will be much more threatening to the population of developing countries because of extensive co-morbidity.

As mentioned, this is not the first time we have been engaged by the potential devastating effects of a pandemic. The H5N1 bird flu triggered a lot of attention being paid to the possible new viruses emerging. Luckily, the bird flue has so far not reached any threatening epidemic level. SARS was also considered a public health threat that got a lot of political attention. At the G8 meeting in 2003, the only section of the Action Plan that showed determination was for SARS. Diseases that primarily affected poor people and occurred in places of little consequences to the global economy were not treated with the same urgency. Money was invested in developing diagnostic tests very swiftly, along with vaccine development. Rarely have we seen such a rapid and effective response to a new infectious agent.

Ongoing desvatating epidemics: a mute response

These responses are in stark contrast to how the world and the same western politicians responded a few years back to other ongoing devastating epidemics. In the period 1981 to 2008 HIV/AIDS killed *at least* 25 million people. 33 million people are currently living with HIV, whereof 10 million urgently need antiretroviral therapy to avoid rapid death. Only about 3 million get this treatment. 2 million died from AIDS in 2007. 67% of the cases are in the poorest parts of the world, - the Sub-Saharan Africa. The epidemic has had devastating economic consequences in that the adult work force suffers most. Teachers, health workers, public servants die. Millions of children are orphaned. In some countries the average living age has fallen to around 40 years. There is yet no vaccine available. Have the investments in vaccine research been sufficient? How can we have let such a lethal epidemic go on for such a long time?

There are many factors that explain the current tragic state of affairs and the difference in response compared to the current pandemic. The AIDS epidemic did not start as a breaking news pandemic. It started slowly and affected mostly the poorest part of the world and marginal groups in the western world such as the gay community and drug addicts. Moreover, the epidemic was mainly related to sexual behavior, i.e. the patients themselves were perceived to be responsible for contracting the disease. They were in many people's opinion not quite as "innocent" as flu victims. AIDS was easily linked to promiscuity and infidelity. This view was recently enforced by the Bush administration's focus on fidelity in their support for AIDS programs, in fact introducing new stigma to a vulnerable patient group.

Moreover, HIV did not spread easily, and did not seriously affect the rich western world. Outside Africa, the disease posed no threat to countries' economy and social stability. Politicians and decision makers were not potential targets of the disease. Even though there were at an early stage data suggesting that this epidemic could be devastating, the global response was lacking. This contributed to a further spread of the disease and as a consequence created the dangerous perception that the disease constituted a "normal" part of life in certain areas of the world. This gave rise to more inaction and less urgency in approaching the epidemic. Two million patients died last year, 2 million will die this year, and yet 2 millions next year. This fact became a perverse state of normalcy, and just added to the perception of hopeless conditions on a continent like Africa already affected by famines, other infectious diseases and wars. It became pretty clear that the actual number of deaths is not as important as potential consequences for the global economy and the rich world to justify a rapid effective response. The fight against AIDS which has gained some momentum in recent years is now based on a combined effort of governments funding international bodies such as the Global Fund, and many private actors such as NGOs. One interesting player is the Foundation of Bill Clinton. It is telling to see how Bill Clinton who could have had a lot of influence on the AIDS epidemic in his former position as US President, really gets his engagement running after he left the office. Why was not more done during his Presidency? What limitations did he face and what does it tell about governance? Or was he not really aware of this devastating epidemic at that time? It is also interesting to note that leaving important parts of the fight to the private and volunteer sector was never an option in battling the Influenza A (H1N1) pandemic. In this case the governments took full control. The health of their own population, i.e. their voters, was at stake, and they considered the pandemic as real emergency.

The fight against AIDS did not only reveal lack of international governance. On top was the failure of leadership in the countries mostly affected by the AIDS epidemic. Denial was more the rule than the exception. The most devastating misjudgments and lack of pertinent leadership was seen in President Thabo Mbeki's South Africa. His denial of the association between the HIV and the disease, and his health minister Manto Tshabalala-Msimang's mistrust of antiretroviral drugs and recommendations of beetroot and lemon, contributed to the lethal spread of the disease giving South-Africa the largest population of HIV positive in the world today. 5.2 million South Africans were living with HIV last year according to a newly released report by the nation's Human Sciences Research Council. At the peak about 1,000 people died every day in that country; that constitutes more than four Air France flight crashes a day. How can anyone doubt that we face an emergency?

Luckily things are changing in South-Africa. New policies have managed to halve new rates of infection among 18-year old from 2005 and 2008 according to the report from the Council. There has also been a substantial reduction in new cases among 20-year old. Most of this is due to increased use of condoms among young males between 15 to 24 years old, from 57% in 2002 to 87% in 2008. The leaders of the Catholic Church should take this fact seriously, and stop spreading false information about condom use, a strategy that leads to more deaths. Still, however, 10.9% of the population of those aged two and over in South-Africa, are HIV positive.

As another example of lack of governance, the public sector abdicated its responsibility in drug development leaving the initiatives to the private pharmaceutical industry. But this industry depends on market mechanisms

The spread of tuberculosis (TB) is a threat mostly to the poor and in much the same countries afflicted by HIV/AIDS. In 2007 there were 9.27 million new TB cases. Co-infections with HIV are now very common. 25% of TB deaths are associated with HIV. Due to failure in combating the disease efficiently, there is an increasing emergence of multiple resistant strains of the bacteria. In 2007 there were estimated to be around 500,000 persons with multidrug-resistant TB (MDR-TB), but less than 1% of these patients received recommended treatment according to WHO. Due to these challenges there has been an increased focus on the disease in recent years, especially linked to the risk of having MDR-TB spreading to the rich countries of the world. In some countries of the former Soviet Union, tuberculosis is common, and they are close to Western countries. Once more the proximity principle seems to be an important factor in defining the political response to an epidemic. Unlike HIV/AIDS, TB is a treatable disease; still 1.6 million patients die every year, and the political commitment is not sufficient. The funding shortfall in combating this disease is estimated by WHO to be US$ 1.5 billion in 2009. That is only 50% more than the money rapidly allocated by the US government to vaccine development for the Influenza A (H1N1) virus.

Malaria is another infectious disease that is considered one of the three big killers in addition to HIV/AIDS and TB.

About 247 million cases were reported in 2006. 1 million died, most of them children. The killing combination of malaria, malnutrition and anemia is particularly frequent in children. Half of the world's population is at risk, and the economic toll has also been calculated. Malaria reduces the growth rate in poor countries by 1.3%. In heavily hit countries up to 40% of public health expenditures go to malaria treatment, and 30 to 50% of inpatients hospital admissions are due to this disease. Effective treatment still exists, artesunate based combination therapy being the drug of choice, but reports from Cambodia this year indicate increasing resistance to artesunate, the most effective drug we have today. More worrying, due to lack of investment, there are no new drugs coming soon from the drug development projects. Malaria has a clear epidemic potential, and with lack of effective drugs, the world may face big new epidemics in some tropical areas as it has in the past.

The pandemic will most probably strike much harder in the developing world . To what extent will the rich world be ready to give away its stored antiviral drugs to developing countries where the risk of deaths will be much higher ?

Lack of effective and affordable drugs is a common feature shared among these infectious diseases. New effective short term TB drugs are also lacking, and research on new drugs has not been a priority. As another example of lack of governance, the public sector abdicated its responsibility in drug development leaving the initiative to the private pharmaceutical industry. But this industry depends on market mechanisms. It develops drugs that give income to share holders. Diseases mainly afflicting poor patients are not a priority since the patients will never be able to buy the drugs. They do not constitute any viable market. This lack of effective drugs to treat infectious diseases contributes to ongoing epidemics. We have seen this in neglected diseases that also reach epidemic proportions such as Chagas disease, sleeping sickness and visceral leishmaniasis. All of them are deadly, all of them mainly afflicting the poor.

This year we are in fact marking one hundred years anniversary of one of these diseases. In 1909, the Brazilian physician Carlos Chagas discovered a parasitic disease spreading by means of a bug. It affects the rural, poor part of Latin America, and about 16 to 18 million people are now infected. In Boliva 20% of the population are infected. 50,000 die every year and Chagas disease kills more people than any other parasitic disease in Latin America, including malaria. Most patients die from heart failure developing 10 to 30 years after they got infected. 40 year old drugs with severe side effects are used in the treatment, and there are no pediatric formulas for treating children. There is no effective treatment of the disease's chronic stadium. Chagas disease is thus a typical example of a neglected disease. Good diagnostics are lacking and drugs are old due to lack of interest from the pharmaceutical industry.

Sleeping sickness falls into the same pattern. It is a similar parasitic disease with 100% mortality if not treated. 60 million Africans are at risk. Earlier this year the humanitarian organization *Medecins Sans Frontieres* had to stop its sleeping sickness program in North Eastern Congo because of an attack from rebels. About 6% of the population is infected in this region according to the health authorities in Congo. 60,000 of them are now in danger of dying or developing severe brain damage if the treatment is not made available. Here again an old drug has been used extensively. Partly based on arsenic it kills 6-8% of the patients and has severe side-effects. Until recently there was lack of alternative treatment. The drug eflornithine was a good alternative with few side effects, but the treatment was cumbersome; four intravenous infusions per day for a two weeks period. Since there was no other use of the drug, the company that produced eflornithine wanted to stop the production due to lack of profit. Medical organizations protested and tried to push the company to continue production. However, the turning point occurred when it was discovered that eflornithine as an ointment could remove facial hair in women. Then there suddenly was a viable market: Rich, western women with facial hair, and the production could continue. Dying, poor Africans had not been enough, illustrating the perverse state of affairs in drug development. Luckily, there has been some important progress recently. In April this year, WHO approved a new treatment for sleeping sickness developed by the Geneva based non-for-profit organization DNDi (Drugs for Neglected Disease initiative). By combining eflornithine with another drug, severe side effects have been eliminated, and the course is more efficient and easier to implement. Still it includes some intravenous infusions, but only over a period of one week. It is now of outmost importance to developed new oral drugs to combat this disease, and DNDi is currently working on a new promising oral drug which is about to be tested in humans.

Visceral leishmaniasis is another killing parasitic disease that is spread by the sandfly in areas of Africa, India and South-America. There are 500,000 new cases every year, and more worrisome, the last 10 years there has been an increase in the disease. There has been explosive increases in Sudan and a rapid increase in Brasil. The non-lethal cutaneous version of the disease, which gives vast skin defects often on the face, is also spreading. In 2002 the disease flared up in Kabul, Afghanistan, with about 100,000 cases.

It is estimated that 12 million persons are infected by this parasite in its various forms. Co-infection with HIV has increased the spread into urban settings and made treatment more complicated. Despite the current spread of the disease, the global response has been much muted. Once more, the poorest parts of the population are affected. Once more effective, affordable drugs are lacking, and there is limited research.

Since the start of the Influenza A (H1N1) epidemic in April 238 patients have died from this disease. During the same period more than 1 million patients have died from the diseases just mentioned. In addition lower respiratory tract infections and diarrhea have killed a similar number in the developing world, most of them being children. And they will all continue to die in these numbers in the months and years ahead.

A lesson to be learned

The general problem illustrated by all these infectious diseases is that they mostly affect poor people in tropical countries. This is not likely to change rapidly, but some new developments may increase the rich world's interest in such diseases. What happened in the small village of Castiglione Di Cervia in northern Italy in 2007, illustrates the point.

That year a mysterious disease emerged whose symptoms were high fever, exhaustion and severe bone and joint pain. It was spreading rapidly among the 2,000 inhabitants. Nobody could figure out what was happening. After quite some investigation, it was found that the inhabitants were suffering from a tropical disease – Chinkungunya, a virus which is close to the more known Dengue fever. The disease spreads by the tiger mosquito which now thrives for the first time in a warmer Europe. The incident was the first clear example of a tropical disease spreading to other none tropical parts of the world because of the global warming. Because of the appreciation we are all going to be affected by climate change there may, in the future, be more interest about tropical diseases, shown in richer countries of the world. They may soon threaten people in Italy, France and Spain. The tiger mosquito is already there.

Moreover, governments of rich countries may soon face a new challenge regarding the Influenza A (H1N1) pandemic which will offer a test of their real commitment to deal with epidemics in the developing countries. Most of the rich countries have stored millions of antiviral drugs to treat and prevent the flu. Some countries have stocks to treat half of the population. At the same time the pandemic will most probably strike much harder in the developing world. To what extent will the rich world be prepared to give away its stored antiviral drugs to developing countries where the risk of deaths will be much higher? Will it allow more untreated mild cases in its midst in order to save lives in the developing world? We may soon see.

The current Influenza A (H1N1) pandemic has shown that the international community has tools and ways of fighting infectious diseases which threaten public health. We should not blame the WHO or the governments for their maybe exaggerated focus on this current pandemic. What we should do is hold them to account for their mute response when faced with the ongoing deadly epidemics that today have consequences which are much more serious than the Influenza A (N1H1) pandemic most probably ever will have.