

International Differences in Preparing for, Experiencing and Managing Pandemic Influenza A(H1N1) 2009 and Possible Future Influenza Pandemics

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Introduction

During the influenza pandemic in 2009 many countries were affected and response to that threat diverged in a wide range according to the countries medical and financial resources. This report intends to show which factors in preparation for pandemic were responsible for the differences and to reveal the weak spots in less sufficient pandemic preparedness plans. It has to be declared that different outcomes are not only due to differently taken measures but as well to not controllable factors, which will be explained within this report. Further it depends also on the accuracy of the reporting system to interpret differences in international outcome, for example numbers of dead.

Further it is specified how different regions and countries are preparing for the next pandemic threat what are the priorities in the pandemic preparedness plans.

The report is divided into the different global regions focusing on the pandemic preparedness plan and on the pandemic burden. At the end some general aspects about differences in pandemic respond are discussed.

Europe

After the first cases of this novel Influenza A(H1N1) were reported in Mexico and the USA, Spain and the UK were the first countries to be hit by infections. In Europe the UK was the only country which experienced a first pandemic wave in early summer followed by a second one in autumn, which represented the first wave for the rest of Europe. While in the rest of Europe most of the infections were due to history of travel to a high risk country, in the UK over 90% of infections occurred via in-country transmission. The reproduction number R_0 in the UK was over 1, which means pandemic is spreading. Reasons for this unique situation in the UK are possibly the large number of travelers in general, large amount of early infections, low level of absolutely humidity and the late school closure for summer holidays in England and Wales. After the start of holidays the infection rate decreased rapidly. In the first European wave of Influenza A(H1N1) a clear spread from west to east was detectable, as well as sometimes during other years regarding seasonal flu.

Within Europe recommendations for containment measures were more or less the same. One slight difference with regard to social distancing was applied in the UK and France, where school closures were established for preventing further transmission. No evidence was found that containment strategies in the UK were less elaborated and efficient than in the rest of Europe, hence reasons for being the unique country in Europe with a large number of infections and two waves must be explored somewhere else, most probably the above mentioned factors are responsible for this epidemiological difference.

USA

The United States were together with Mexico the origin of the spread with influenza virus A(H1N1). Center for disease control (CDC) estimates that 61 million people were infected within the year after the onset detection. Exact numbers are impossible to obtain because many people didn't seek medical care. Although immediate containment measures were taken further transmission could not been prevented. With regard to vaccination policy in the USA the government chose a different option by using vaccine without adding an adjuvant. Normally an adjuvant in a vaccine allows to use less viral antigen but with

the help of the adjuvant it is still able to provoke an immune response. With this method vaccination would be available for more people because less antigen material is used per vaccination. In numbers: 3.8mcg or 7.5mcg of antigen were used for a vaccination with an adjuvant while for production without adjuvant 15mg were needed. On the other hand an adjuvant can cause side effects and must be approved by federal authorities, which can prolong the procedure of admission and production of the vaccine.

The US and some other countries chose to take a calculated risk producing vaccine without any adjuvant. In a point of view from a developing country this decision reduced the amount of vaccines which could have been provided for a non-manufacturing and developing country.

Mexico

The first worldwide case was detected in April 2009 in Mexico City. Government immediately induced a variety of containment measures like school closure, cancelling mass gathering events and social distancing. The federal strategy was expanded a few days later with nationally closing schools, restaurants and sports events from audience. In the following two weeks public life came to a complete standstill. Population accepted all measures without protest and followed the governmental safety instructions frequently brought in the media.

But of course not everything was perfect. There was a big quality difference in epidemiological surveillance and case reporting. Some states were well equipped with computerized systems while other only had handwritten records or even nothing of documented cases. A lot of time was lost sending virus samples to Canada and the USA for identifying the virus genome, since Mexico had no appropriate laboratory for this.

Despite excellent public health risks communications some recommendations were not well adopted especially among teenagers (sneezing etiquette and personal hygiene).

Three geographically different pandemic waves were identified in Mexico (spring, summer, and autumn). A survey concluded an increase in reproduction number in the first wave at the same time of the end of spring breaks. After that, reproduction number decreased when school closures and other social distancing measures were implemented.

In the same survey the conclusion was raised that the early measures were effective in mitigation and delaying the spread of influenza.

Latin America

An investigation about the pandemic preparedness in countries of Latin America revealed that almost all countries have elaborated strategies for surveillance systems for influenza and for communications measures to the public and health care workers.

Containment and national border measures are not yet integrated in every country's preparedness plan. The aspect of antivirals and pandemic vaccine is poorly elaborated, since no country except for Brazil has inland facilities to produce vaccine

Most of the countries still lack of a sufficient operational implementation of their pandemic preparedness plan. Only Brazil has taken detailed decisions how to increase resources in border management and improve collaboration with neighbor countries.

Asia-Pacific region

In the beginning of May the first case was detected in Hong Kong, where the health care system is one of the most advanced in Asia (together with Singapore). Having experience with SARS these two countries induced an aggressive strategy trying to delay the beginning of spread in the country. Despite early quarantine and public measures, like social distancing, travel restrictions and border control, in most of the countries infection spread widely leaving the public health system with its facilities overwhelmed. Unfortunately insufficient coordination within the authorities in some countries led to situations like having ICU-Patients in one hospital in normal ward beds because of lack of beds in the actual ICU-department while in other hospitals enough free ICU-capacities were available. Furthermore in some countries sharing capacities (beds, material) between public and private health facilities did not occur, although private hospitals had free capacities left over.

According to the spokesman of the WHO's Pacific Western office this region is better prepared for a pandemic threat like Influenza A(H1N1) because of a wider experience with influenza and other virus outbreaks (H5N1, SARS). But a large stockpile of antivirals and experience on that specific topic does not mean automatically a country is well prepared for a possible pandemic. An analysis of different pandemic preparedness plans revealed a great diversity among the countries. While Hong Kong, Singapore, Australia and New Zealand have plans of very good quality and are well comparable with European standard, Thailand, China and Vietnam have developed strategies for achieving capacity to trace and respond to a pandemic, but without any operational strategies how to act in detail in case of a pandemic. Other countries haven't completed their preparedness plans yet. Gaps in plans are:

- Although stockpiles of antivirals are established, only a few countries have strategies about the distribution/use/prophylaxis and defining priority groups.
- Insufficient vaccination strategies in some countries, especially lack of defining vaccination priority groups.
- Home treatment is not considered by most of the countries.
- Only a few countries made strategies regarding maintaining basic public services.

Nevertheless there are some points in which some Asian countries show differences in a positive way regarding pandemic preparedness plans in comparison to Europe. During SARS for example police databases, usually utilized for tracking criminals, were used to coordinate mass-tracking contacts. Cooperation between human and animal surveillance is well established, in order to detect early transmission as well as instructing persons working with animals about appropriate measures. There is a high focus in the early containment, based on the assumption that a future pandemic will start in one of these countries. Once the pandemic has spread it will be difficult for this countries to cope with the threat because of a relative lack of antivirals and vaccine.

Africa

In general pandemic plans for animal influenza are quite well established but for human influenza pandemic the concepts are poor. Most of the countries focus on communication strategies to raise awareness of contagion factors and to promote hygiene measures. There is a lot to improve regarding case management, prioritization of groups, defining health care facilities for patient treatment, distribution of antivirals and other medicine. Almost no country has guidelines for maintenance of basic

service during a pandemic.

General differences in response

Vaccination

A lot of governments of developed countries purchased vaccine in spring 2009 not knowing exactly how severe the influenza virus is going to spread. An intense human to human transmission and thus a severe pandemic of huge dimension was a possible scenario government had to be prepared for. For developing countries which couldn't afford to buy the vaccination at the same price only a small proportion of initial vaccine manufacture was left over.

Even Mexico, the country where everything began, had problems to obtain enough vaccinations doses. In January 2010 Canada shipped 5 million doses of vaccine to Mexico to cover the urgent needs of the country.

Vaccine production for a pandemic virus is only possible (from a technical point of view) if there is already an infrastructure which is normally used for manufacturing vaccine for seasonal influenza. Therefore countries which don't attribute the appropriate importance to seasonal influenza and its vaccination won't have the facilities to produce a vaccine in case of pandemic.

At the moment worldwide vaccine manufacturing capacity for seasonal influenza is about 800 million doses and constantly expanding of the capacity is organized and promoted by the WHO.

Preparedness recommendations

There is an enormous variety on recommendation from countries worldwide. A survey which investigated 10 countries all over the world reports that only 2 recommendations are common to all 10 countries, namely washing hands and coughing etiquette. Only 2 countries had more than 80% of all correct recommendations. 6 countries did not reach the percentage of 40%.

Most of the countries recommend avoiding social contact in case of showing symptoms. This effective advice is made absolutely meaningless when 4 of the 10 countries recommend visiting the nearest health institution in such a situation, putting the public at transmission risk on the way to the doctor and in the hospital itself as well.

Only 40 % of the countries established well-founded recommendation regarding home treatment and identifying severe case which would have to be transferred to a hospital. The proper use of antivirals was explained only by half of the countries, while the other just warned from unsupervised use.

General factors influencing transmission and spread of pandemic

- Climatic factors such as absolutely humidity. Analyses have shown strong correlation between low absolutely humidity and increased airborne survival and transmissibility of influenza virus.
- Human mobility, especially air transport
 - In Europe most of the trips are from and to Western Europe, mainly UK, Germany, France, Italy and Spain. The Travel from and to these countries form 85% of whole international traffic within Europe.
 - Simulation models (latent period 1.5 days, infectious period 2 days, reproductive number $R_0=2$, symptoms in 50%) assume that for a Western European country the first case is more likely to be imported. For evaluating the duration of distribution of the first worldwide case to a European country it depends on which country the first case is imported in. In the UK the first case is reported average 44 days after the first world

- case. In the Principality of Monaco for example it lasts 79 days after the first world case until the first case is witnessed.
- The more travelers enter a country during the year, the earlier the average peak day is reached in this country.
 - Heterogeneity of a population
 - Demographic
 - Age distribution in European Countries varies in a wide range. Ireland for example has one of the youngest populations while in Germany and Italy much less inhabitants are less than 20 years old.
 - Social
 - The number of households with children, as well as the number of children in these households.
 - Employment rate
 - Fraction of students
 - Average size of primary and secondary schools
 - (School) vacations: time and length
A survey in the USA determines a rise of transmission two weeks after school opening in summer (Although staff and children as high risk patient are protected by school closures, this measure does not decrease public transmission and is very cost-intensive). The first wave in the UK decreased sharply after the beginning of summer school holidays
 - The more people in a household live and the bigger the student fraction is the more affected a population becomes by a pandemic

According to a micro simulation regarding the spread of a pandemic in the UK 30% of transmission would happen in households, 37% in schools and at work and 33% in public .

Developing countries

A survey concluded that in a future severe pandemic about 96% of the dead (estimation of 62 million dead) would live in developing countries.

Countries with fewer resources are not able to cope with any kind of pandemic without the support of developed countries, namely manufacturers of vaccine and antivirals. There are several parameters which make developing countries more vulnerable to any kind of pandemic.

- Medical und public health infrastructure
 - Not enough health care facilities. The percentage of hospital beds needed in case of pandemic is higher in low-income countries than in high-income countries. A survey calculated with the aid of a influenza computer model a percentage of 80% of required beds in case of a incidence rate of 35%.
 - Not enough specific medical equipment (ICU-Beds, Ventilators)
 - Not sufficient general medical material (syringes, gloves, masks, swabs, disinfecting liquids, antipyretics, antibiotics, etc.)
 - Not enough medical human resources
 - Reduced care for other medical problems (tuberculosis, malaria, HIV, AIDS)

- Pandemic preparedness plan
 - Some of the developing countries are following pandemic plans elaborated for industrialized countries, which don't apply for the different circumstances in developing countries.
- Financial factor
 - Less financial resources for prevention and treatment
- Social factors
 - Bigger households, housing conditions
 - Higher population density
- Host factors
 - (Untreated) co-existing medical problem, especially HIV/AIDS
 - Poor nutritional status
- Logistic factor
 - Not enough human and transport capacities for the extra effort
- Seasonal influenza vaccination
 - As mentioned above manufacturing is one of the conditions to be able to produce pandemic vaccine. Unfortunately the cost of seasonal influenza vaccine is too high to increase its use.

Although WHO has stockpiles of antivirals in some developing countries it will never be sufficient to resist a global pandemic. In developed countries the government normally is storing antivirals for about 25% of the population. The cost is only about 0.1% of the annual expenditure in national health care system. For the government of third world countries it is too expensive to store antivirals, costs for covering the 25% of population would exceed 13% of annual health expenditure.

As already discussed antivirals are a reasonable option especially in the first period of a pandemic. From the two groups of existing antivirals (neuraminidase inhibitor and adamantane) the neuraminidase inhibitors are more efficient but more expensive as well. Most of current influenza virus strains are resistant to the much cheaper adamantanes, which could be an option for the clade 2 H5N1 influenza viruses which haven't yet developed resistance as one of the few.

Other medicine (antimalarial drugs, anti-inflammatory drugs, immunomodulatory drugs, statins) which has not been developed for antiviral use, has been recently found out in laboratories and observation of small groups of patients to be a potential option against influenza virus. These results have to be interpreted with caution and further investigation and research has to be done. The point of this aspect is that most of these medication is produced as generic drugs already in developing countries and would be easily and rapidly available in case of a pandemic outbreak.

Conclusions

- It is essential to find a way to assess the severity of a possible pandemic at an early point of time to take the appropriate measures and estimate the further progression
- In general developing countries must be supported to establish an appropriate pandemic preparedness plan. A lot of low-income countries have a well elaborated pandemic concept regarding communication and awareness, but the operational implementation/application is often not specified enough. This is an aspect which must be supported as well.
- Manufacturing of seasonal influenza vaccination in and for developing countries must be increased to have sufficient vaccine in case of a pandemic. This is the only way how sufficient global availability of vaccination can be ensured. Therefore the current expansion influenza vaccine capacity must be continued. WHO estimates a capacity of 2 billion trivalent doses seasonal influenza in 2015, which will be available 6 month after identifying the prototype virus strain.
- Cost-effective and easily practicable measurement in developing countries should be applied as soon as possible such as increasing stockpiles of basic medical supplies (gloves, masks, antibiotics, etc.) including guidelines on the type and amount of material, training medical staff for infection control measures (hand disinfection, use of masks) and establishing a well organized public health care system.

It is very probable that a future pandemic will start in a developing country. There is a small chance to stop the outbreak before the virus spread nationally and internationally. Therefore low-income countries must have a well elaborated influenza reporting system as well as enough medical material and equipment (antivirals, masks, gloves, quarantine facilities, etc.).

This report includes inputs from a variety of sources.
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