Hypothetic Scenario of a Influenza (H5N1) Pandemic
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Introduction
What would happen if the current H5N1 virus, causal agent of the avian influenza, would mutate into a pandemic form? How can we prepare ourselves for an unpredictable but potentially devastating event? How can we give priority to such a hypothetical situation when at the moment there are existing more urgent needs in healthcare. This report intents to answer these questions under best assumptions how the numerous individual factors would perform and interfere. However nobody knows the exact dimension of a upcoming pandemic, but preparing and organizing efforts regarding pandemic preparedness are much less intense than pandemic consequences without preventing measures.

Point in time
Next pandemic can not be prevented, it is just a matter of time and no one can predict the moment. There is a documented history of pandemic influenza:

- 1918 Spanish flu H1N1
- 1957 Asian flu H2N2
- 1968 Hongkong flu H3N2
- (2003 SARS, no influenza virus but corona virus)
- 2009 Influenza A(H1N1)

H5N1
1878 researchers noticed a disease of poultry for the first time. Since then the avian influenza virus mutated to a highly pathogenic virus with different strains and genetic diversity. Since 2003 the H5N1 virus has differentiate into 10 strains of which only 4 have been isolated in humans. In the period 1995 to 2008 over 60 countries were affected counting hundreds of millions of dead birds.

There are some general characteristics of an influenza pandemic:

- Virus transmission mainly through air (droplets).
- Incubation period: 1-4 days, infectious 4-5 days from the beginning of symptoms.
- Manifestation in waves lasting 6-8 weeks, uncertain time intervals between waves.

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- Maximum case fatality rate of 2.5%.

Avian influenza has slightly different features:

- Contagion through life or dead infected poultry of infected environment.
- Incubation period of 2-8 days, WHO recommend to use an incubation period of 7 days regarding monitoring patient contacts.
- Case fatality rate is much higher compared to other influenza types: 60%
    - With normal influenza, pneumonia, mostly caused by secondary bacterial infection and therefore curable with antibiotics, is less threatening whereas the avian influenza virus induces viral pneumonia directly, which doesn't respond to antibiotics or any medication.
- Probably no virus of the H5 subtype has ever circulated among humans which means there is no immunity worldwide against a potentially mutated pandemic form.
- In January 2004 there was a severe H5N1 outbreak among poultry in Asia and several human fatal cases were reported, which rose the fear of a severe avian influenza pandemic involving the entire global population. This new dimension of transmission from animal to human could be one of the first alterations within the adjustment of a potential avian influenza pandemic threat. Should the virus develop its transmissibility further so that it can easily spread between humans, then all the requirements for the start of a pandemic are present, namely:
    - New kind of virus to which no one is immune
    - The new virus must have the ability to replicate in humans and cause severe illnesses
    - Human to human transmission

The first two points were fulfilled, the only point missing was infections between humans. A subject which recently has been achieved in a laboratory by researcher Fouchier, who modified H5N1 with a few mutations on its genome so it is supposed to easily spread via droplets from human to human.

- New evolving feature of the avian virus since 2004 :
    - Virus is more deadly in poultry and capable of survive longer in the environment.
    - New animals (cats and tigers) can be infected, which means the avian influenza virus has enhanced its range of hosts.
    - Domestic ducks excrete high viral load without showing any symptoms and therefore make it hard to give local residents useful advices on how to recognize sick animals

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- For the first time migratory birds have been infected.
- Infection of humans of a non-traditionally group, namely young healthy people.

Hypothetical Outbreak of an avian influenza pandemic
The Global Influenza Surveillance and Report System (GISRS) of WHO would detect an early beginning of a rising pandemic. In May 2011 the Pandemic Influenza Preparedness (PIP) Framework was started to improving the GISRS by linking all the relevant worldwide laboratories for a better exchange of knowledge/reports and an increased access to vaccination for countries with less resources.
In case of such news of detection WHO would at first put the local partner (Healthcare systems, laboratories, intervention teams) in the Global Outbreak Alert and Response Network (GOARN) on stand-by and prepare an investigation. First GOARN-team arriving would identify and confirm the outbreak.

Three main targets will be declared by WHO:

- to avoid the pandemic
- to control the outbreak in humans and
- to initiate monitoring and research, including immediate developing of corresponding vaccine.

Controlling the outbreak would mainly mean prevent humans from beeing infected by poultry with measures of killing infected or exposed birds. Poultry slaughterer would have to wear protective gear and take antivirals in a prophylactic sense. Additionally the application of vaccination against normal influenza virus would be recommended to reduce the chance that the avian influenza virus could exchange genes with a co-infecting normal influenza virus in humans.
Research would include identification of molecular viral structure, tracking its evolution in birds, defining pathogenicity in humans and pandemic potential as well as evaluate resistance towards antivirals and prepare/initiate vaccine production.
Public health interventions which were applied when SARS and Influenza A(H1N1) threatened the world and partially were successful won't control a pandemic virus, which is far more contagious, has a very short incubation period and which can be transmitted before the beginning of symptoms.
Besides that, pandemics manifest in waves which not always affect the same geographic region and the

same age groups, the second wave normally tends to be more severe than the first one.
A World Bank report assumes as a worst-case scenario that a severe pandemic would kill about 71 million people worldwide. A few experts cited in the report estimated death toll of 180-250 million people. Prognosis of a mild pandemic speaks of 1.4 million deaths (decrease of GDP 0.7%), a moderate pandemic of 14.2 million deaths (GDP -2%).
The WHO estimates a mild pandemic to cause 2-7.4 million deaths . Looking at this numbers shows clearly how hypothetic and uncertain such estimations are and that a reliable prognosis is absolutely impossible.

Economical impact
The report of the World Bank estimated costs of a severe influenza pandemic at more than $3 trillion, reducing the global GDP by 4.8%. Researchers at Australian National University are assuming a GDP drop of 5.5%. Other reports assumes only in the US to face costs of $167 billion in case of a severe pandemic.
This tremendous deficit is composed of different economic losses in tourism, traveling, trade and productivity. The biggest part (60%) would be caused of individual avoiding behavior (travel, restaurants, mass gatherings). Only 30% of the costs would come from the illness directly, while mortality is responsible for little 10%.

Companies are confronted with three main threats in case of pandemic:

- Human Resources:
    - Staff being absent (sick, caring for other persons, refusing to leave their house); Therefore enterprises which are able to provide their personnel vaccination have a big advantage. Possibility of working at home or in remote locations keeps up functioning a company. Identifying key staff and time-related vulnerabilities must be part of a well elaborated pandemic plan.
- Interruptions of production and services as well as in supply chain.
- Loss of market and customers: decreasing confidence and distribution systems .

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Measures

Non-medical interventions

These kind of measures (personal hygiene, facial masks, contact tracing, screening of travelers, cancellation of gatherings/mass events, isolation of patients) reduces transmission especially at the beginning of a pandemic and slows down international spread. In countries with low resources this non-medical interventions will be the principal strategy against a pandemic. Once the pandemic has spread in a large way priorities need to be changed, focusing more on reduction of morbidity and mortality than on reduction of transmission and international spread.

Antivirals

Currently there are two groups of antivirals: the adamantane derivates (amantadine and rimantadine) and neuraminidase inhibitors (zanamivir and oseltamivir).

Purpose of antivirals is to diminish the length of illness and thus length of contagious period, it reduces symptom severity as well as complications . It may slow down the spread and buy some time for developing vaccines. Antivirals must be taken within the first 48h from onset of symptoms.

A second purpose of antivirals is the prophylactic intake, but it has to be examined if prophylaxis makes medically sense (viral response, resistance, pandemic severety).

The importance of antivirals is especially high during the first wave, when vaccination is not available yet. The biggest fear in relying on and using antivirals is the virus ability to adapt and mutate and thus aquire medication resistance. Most of the H5N1-strains show already resistance towards adamantanes . Recently arising reports, having documented resistance against neuraminidase inhibitors as well, provoked serious concerns since oseltamivir has been the drug of choice for storing as part of preparedness in many countries.

New kind of antivirals such as monoclonal antibodies against conserved haemagglutinin epitopes show a reduced risk for drug-resistance and ability to provide fast and broad protection. However, selection pressure may provoke influenza virus to mutate and escape from antibodies as well.

Vaccine

Vaccination is the most effective mean in combat against a pandemic virus, but it is impossible to produce vaccines in advance if we don't know exactly the genetic profile of the pandemic virus. It takes several months to develop an appropriate vaccine, which won't be available for the first pandemic wave. In case of pandemic pharmaceutical industry will face an overwhelming demand which could not be

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satisfied. In the beginning population of the manufacture country will have first access to vaccine, making Europe, Australia, North America and Japan to privileged countries. Maybe production capacity allows, after having had enough time to produce to prevent a high amount of deaths during the second wave which normally causes a more severe form of influenza. Nevertheless countries will have to make the hard decision which group of the population will be vaccinated with priority.
The current vaccine production method with fertilized chicken eggs takes longtime and avoids a fast vaccination response. Therefore efforts have to be taken to find a way to produce vaccines in a alternative and dose-sparing way. Several new technologies (cell-derived whole-virus inactivated vaccines/recombinant-protein-based vaccines/virus-like particle-based vaccines/DNA-vaccines/viral-vector-based vaccines) for producing vaccine egg-independently are being explored at present and are showing encouraging results. Next step will be to test the new vaccines in a broad way and get official approval for mass production in the near future .

Possible prevention
It is almost impossible to prevent a future pandemic with avian influenza virus H5N1. Controlling and monitoring circulation of H5N1 in poultry and therefore a good collaboration between animal and public health authorities is essential. Fundamental changes in poultry farming could be a possible long-term solution, but it is very hard (ideologically and financially) to implement such kind of measures in a region where poultry farming forms the backbone of rural existence and where farmers have been traditionally practicing this kind of agriculture for decades.

Conclusion
The World has faced several influenza pandemic in the past and drawn appropriate lessons from. The uncertainty about the moment, the pathogenicity, the transmissibility and lethality of a future pandemic with avian influenza virus H5N1 remains at present as well as in the future. But to mitigate the devastating-looking threat, we have to emphasize that the world never has been better prepared for such kind of menace. With WHO in a supervisory and executive function, coordination of worldwide measures is one of the most important tools against a rising pandemic. Global surveillance programs observe constantly critical regions and facilitate the exchange of findings, knowledge and experience. New partnerships between scientific, industrial and government players form a powerful network to have an organized and directed acting during pandemic-free period as well as in worst-case scenario. New milestones in vaccine development promise a potential tool against a future pandemic, although it still

takes some time for vaccination to be ready and operational.
Only time will tell if we will be able to deal with a future pandemic and if our current efforts concerning preparedness plan, developed measures and means were not in vain.

This report includes inputs from a variety of sources.
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