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PANDEMIC H1N1 FLU ACTIVITY WIDESPREAD AS MUTATIONS APPEAR

Summary

- The 2009 pandemic A/H1N1 virus is currently the dominant flu strain. It has entirely replaced the seasonal A/H1N1 virus and has drastically reduced the other circulating influenza A and B viruses.
- A new H1N1 mutation has emerged that severely increases virulence and makes the 2009 virus genetically similar to the 1918 pandemic virus.
- Isolated cases and clusters of Tamiflu-resistant H1N1 continue to appear throughout the globe.
- Individual cases of pandemic H1N1 infection, especially mild infections, are no longer being counted, leading to official figures that are significantly lower than the actual number of cases and deaths that have occurred.
- H1N1 vaccine supplies are limited globally. Only small proportions of the population have received the H1N1 vaccination. The vaccine has been allocated almost exclusively to high risk groups, such as young children, pregnant women, and those at risk for complications.
- Uncertainty remains around the extent of asymptomatic infections, the degree of effectiveness of pharmaceutical countermeasures, and the evolution of the virus. These parameters, as well as the potential changes in transmissibility, virulence, demographic distribution, and vaccine efficacy, are captured probabilistically in the RMS H1N1 model.

1 CURRENT SITUATION

1.1 Pandemic H1N1 is dominant flu strain in the current winter flu season

Pandemic H1N1 influenza virus activity is beginning to show signs of peaking in some areas of the globe, but widespread transmission continues in many countries with the arrival of the typical winter flu season. As of 22 November, the World Health Organization (WHO) has recorded over 622,000 cumulative laboratory-confirmed cases of pandemic H1N1 reported in more than 207 countries worldwide, with at least 7,826 confirmed deaths.

1.2 Pandemic H1N1 mutation results in increased severity

Mutations in flu viruses are common and most mutations will have little or no public health significance. The pandemic H1N1 flu virus has remained, for the most part, genetically stable. On 20 November, the

Norwegian Institute of Public Health announced that a mutated version of the pandemic H1N1 flu virus has been found in 3 patients in Norway. This particular mutation, also called the D225G mutation, has gathered attention because it was found in the first two fatal H1N1 cases in Norway; the third patient has severe illness. The WHO has reported a similar mutation in several other countries around the world, including Brazil, China, Japan, Mexico, Ukraine, and the U.S. There is evidence that the mutated virus is more apt to infect the deep lung, causing more severe illness. This mutation, a receptor binding domain change, was also seen in some 1918 flu cases. Health authorities believe the mutations are spontaneous, and that this viral strain is not transmitted effectively. There is evidence that the mutated virus will cause more severe illness or death by being able to infect deeper in the lungs and cause lung hemorrhaging. However, transmissibility often decreases when the virus does not prefer the upper respiratory tract. There is evidence that at least one isolate of the mutated virus showed limited reactivity to the current H1N1 vaccine. With the exception of one case, the virus with this mutation remains sensitive to the antivirals Tamiflu (oseltamivir phosphate) and Relenza (zanamivir).

1.3 Clusters of Tamiflu-resistant cases in Wales and U.S.

Flu antivirals are effective in reducing the severity and duration of flu symptoms and work best when started within 2 days of getting sick. To date, the vast majority of cases of pandemic H1N1 infection have been treatable with the antivirals Tamiflu and Relenza. Approximately 75 tamiflu-resistant cases have been reported sporadically around the world since the start of the pandemic, and there has not yet been evidence of ongoing transmission of resistant strains. Tamiflu-resistant pandemic H1N1 viruses identified so far have been susceptible to Relenza.

On 20 November, a cluster of five Tamiflu-resistant pandemic H1N1 cases was identified in patients at the University Hospital of Wales, Cardiff. An additional patient, linked to the first five, tested positive for the resistant strain a week later. Health officials have said that this strain does not appear to be any more severe than the virus that has been circulating since April of this year. Another cluster of Tamiflu-resistant cases has been identified in 4 patients at Duke University Medical Center in Durham, North Carolina. These patients were also being treated in units where patients had compromised immune systems. Immunocompromised patients typically have a higher risk of suffering complications from pandemic H1N1 flu. Health officials have said that these are isolated incidents of person-to-person transmission of Tamiflu-resistant pandemic H1N1, but not sustained transmission.

1.4 Underreporting and estimates of caseloads

The United States Centers for Disease Control and Prevention (CDC) reports that the virus is widespread in 32 states. Although flu activity is decreasing in the U.S. as suggested by declines in visits to doctors for flu-like illness and declines flu hospitalization rates, these indicators still remain very high for this time of year. Flu activity is still increasing in some states. Federal officials have said that it is still unknown whether a peak has occurred, and if the pandemic will pick up again. Health officials note the potential for transmission to increase in the next few weeks, as people travel for holidays and as the contact rate is increased between people from different parts of the country.

The European Centre for Disease Prevention and Control (ECDC) has reported that in Europe the weekly number of deaths due to the pandemic virus has steadily increased, nearly doubling every 2 weeks over the last month. A cumulative total of 858 deaths have been reported in Europe since April 2009, and flu activity is high in 27 EU countries (with 13 countries reporting a rising trend). Most of the deaths have occurred in Western Europe, but fatalities are increasing in Central and Eastern Europe. In the UK, flu activity has decreased slightly, but rates still remain above baseline levels. During the week ending 27 November, more people (31) died from pandemic H1N1 in the UK than any week since the beginning of the outbreak.

Most countries have stopped counting the number of individual cases of pandemic H1N1 infection, especially those causing milder illness. Thus official figures are likely to be significantly lower than the actual number of cases and deaths that have occurred. A recent report published in *Emerging Infectious Diseases* estimated between 14-34 million cases, 63,000-153,000 H1N1-related hospitalizations, and 2,500-6000 H1N1-related deaths occurred, between April and October 17, 2009¹. These numbers are much greater

than the laboratory-confirmed figures being reported, due to several reasons, including incomplete testing, inaccurate test results, or attributing hospitalizations and deaths to causes other than influenza.

2 PANDEMIC H1N1 VACCINE

2.1 Vaccinations still the most effective tool against pandemic H1N1

Vaccination is currently the best tool in the prevention of both the spread of influenza and serious illness from influenza. The pandemic H1N1 vaccine is not intended to be a replacement for the seasonal flu vaccine; the two vaccines are intended to be used alongside each other. Pandemic H1N1 flu vaccine products are currently manufactured in inactivated (killed virus) or LAIV (live attenuated intranasal vaccine) form. The inactivated vaccine is given by injection into the muscle ('flu shot'), while the LAIV formulation is administered via nasal spray. Groups initially targeted for the new vaccine include pregnant women, healthcare personnel, those with pre-existing health conditions or caregivers of immunocompromised persons, and infants and their caregivers.

Global health officials have stated that the new vaccine works much better than expected, and a single dose appears to protect people against pandemic H1N1 flu. Early experience in several countries shows the new pandemic H1N1 vaccine to be as safe as seasonal flu vaccines. A batch of GlaxoSmithKline H1N1 vaccine has been recalled in Canada, after it was linked to more allergic reactions than expected. There has been no other evidence that the pandemic H1N1 vaccine is causing serious side effects.

Pandemic H1N1 vaccinations began in October, when the first doses of the new vaccine were shipped, and are expected to continue throughout the flu season and beyond. Supplies of the new vaccine have been limited by manufacturing delays but continue to increase.

2.2 H1N1 vaccine distribution

In the U.S., over 61.2 million total H1N1 influenza vaccine doses have been allocated as of 27 November. Latest CDC reports indicate improvements in H1N1 vaccine supply and shipment, with 56.5 million doses available for order. Despite progress, a shortage remains. States have been keeping up with the increased supplies, and doses are being promptly used by providers.

Vaccine distribution is controlled by local authorities, who have a better understanding of how to reach their respective populations. However, the lack of a uniform allocation protocol has led to unhappiness and complaints. For example, Santa Clara County initially received only 1/10th of available H1N1 vaccine from the state of California despite being the largest county in the Bay Area. In some places allocations are made based on population size, while at other locations private healthcare facilities such as Kaiser are given a higher number of doses.

Doses continue to be administered preferentially to targeted subsets including pregnant women, children 6 months to 4 years old, high-risk children aged 5-18, infant caregivers, and health care workers. Some areas have expanded vaccination to high-risk adults and healthy individuals aged 25-64, depending on availability. Locally controlled dose distribution has resulted in varied vaccination strategies. Some locations have chosen to vaccinate all people under 24 and high-risk adults while others vaccinate all school-aged children before high-risk adults, a technique that may reduce transmissibility but not fatalities.

Given high demand for the H1N1 vaccine there has been expressed interest in the use of adjuvants, or substances added to vaccines to improve immune response to them. Because adjuvants can increase immune response with a lower amount of antigen in the vaccine they are advantageous in cases where there is a limited supply of vaccines, or the virus becomes more severe. As it stands now, children and adults have had a good antibody response to 15 micrograms of the current H1N1 vaccine. Although adjuvanted vaccine is one possible solution to supply shortage, it would require ceasing use of the current vaccine in order to prepare the new treatment. Outside of the U.S., many countries in Europe, Canada, the Middle East, and Asia have ordered H1N1 adjuvanted vaccines.

2.3 Vaccine availability in poorer countries

GlaxoSmithKline and Sanofi Aventis have donated 50 and 100 million H1N1 vaccine doses to the WHO for poorer countries, amounting to 10% of their production capacity. The U.S., UK, Italy, Switzerland, France, Australia, Norway and Brazil will donate 10% of vaccines, for an additional 50 million doses. Currently the H1N1 vaccine is sold at \$10 – 20 in OECD countries, \$5 – 10 in mid-level economies and \$2.5 – 5 in poorer countries. The WHO's goal is to provide 10% of the population in 95 developing countries with H1N1 vaccinations, however vaccine shortages are expected to affect donations.

3 MODELING INSIGHTS INTO PANDEMIC A/H1N1

RMS has recently developed a stochastic representation of 2,016 different pandemic events to model the impact of pandemic A/H1N1. The key variables from the stochastic model are transmissibility and virulence, demographic impact, vaccine production, non-pharmaceutical interventions, and antiviral efficacy. This model provides probabilistic insights into the impact of pandemic A/H1N1 on lines of business related to mortality during the upcoming flu season.

3.1 Transmissibility and virulence

Transmissibility represents the speed at which the pandemic will spread and the total number of people that will be infected. It is measured by R_0 , the initial reproductive number, or the number of people each infected individual will infect in a susceptible population. The virulence of the virus is measured in terms of its average deaths per case (or case-fatality rate). These two parameters are the key elements in understanding the way a virus is likely to spread and the potential impact of a virus in the absence of intervention.

RMS employs a probabilistic approach to the likelihood of different combinations of transmissibility and virulence. A statistical distribution is used to represent the variability associated with R_0 using data from published studies and case reports of transmission through the population. The virulence is represented using a long-tailed distribution often employed in epidemiologic studies. As currently modeled, there is an 80% chance of the pandemic A/H1N1 deaths per case value being in the range of seasonal flu.

3.2 Demographic impact

In normal seasonal flu, the elderly bear the burden of a disproportionate number of the flu-related fatalities, even though they are a relatively small percentage of the population. In typical pandemics, mortality patterns are similar to what was observed in 1918, where the very old are likely to experience high rates of mortality as well as the young and healthy, who typically do not die of seasonal flu. In addition, children and the middle-aged are likely to have lower mortality than working age adults.

The pandemic H1N1 flu virus has affected a disproportionate number of people less than 65, but has yet to impact the elderly in the way the 1918 pandemic or the seasonal flu did historically. There is research to indicate that older people may have residual immunity resulting from a genetically-similar virus that circulated in the past. RMS models the probability and impact of a range of viruses exhibiting all of these demographic profiles. The current model assumes the greatest probability is that the virus will continue to exhibit the H1N1 profile or become more like seasonal flu.

3.3 Vaccine production

RMS models different assumptions about the development of a new vaccine to combat the pandemic, including the time required to develop the initial seed culture, manufacturing capacity, and distribution and administering logistics. Factors that will accelerate the availability of a new vaccine include new cell-based production techniques and the addition of manufacturing facilities. Factors that could delay the production of vaccines include difficulties isolating the viral strain causing the pandemic, culturing virulent viruses, overwhelmed vaccine manufacturing facilities, or delays in getting a new vaccine approved by federal regulatory agencies.

3.4 Non-pharmaceutical interventions

The speed and effectiveness of response is a key variable in the overall impact on each of the localities affected. Response might include travel restrictions, quarantine, supply stockpiling, hospital preparedness and social distancing.

RMS has taken into consideration official public health plans, past response, public statements, independent critiques, and resources available for the countries of interest. RMS advisors include senior figures in the development and implementation of government plans in the U.S. and UK. The efforts to combat the pandemic in each country are assessed in terms of their likely impact in slowing the spread of disease, moderating its impact and reducing the mortality and morbidity of potential pandemics. The relative impact of country counter-measures is severity-dependent. Government and individual actions are likely to be more extensive in the event of a pandemic with high virulence.

3.5 Antiviral efficacy

Tamiflu, an oral antiviral drug for the treatment of uncomplicated influenza, works by blocking the final stage of the flu virus life cycle. Trials by the drug's manufacturer, Roche, show it can reduce mortality by up to 70% when administered correctly within 48 hours. During the course of an infection, treatment with Tamiflu may lead to the selection of novel viruses harbouring mutant proteins that no longer bind to oseltamivir; and therefore, are not vulnerable to its inhibition. This leads to the emergence of 'Tamiflu-resistant' strains that circulate in the population and compete with the Tamiflu-sensitive strains.

As of now pandemic A/H1N1 has shown limited resistance to the commonly used antiviral medications. Experts worry the pandemic strain of H1N1 will reassort with Tamiflu-resistant seasonal H1N1 viruses. If the pandemic strain picked up the neuraminidase (NA) gene from the seasonal H1N1, it would likely acquire the resistance its seasonal cousin has developed. RMS models 3 scenarios for antiviral resistance: no resistance, moderate resistance, and severe resistance. The overall mortality among all age groups will increase from what has been observed thus far if viral strains become moderately or severely resistant.

¹ <http://www.cdc.gov/eid/content/15/12/pdfs/09-1413.pdf>