Facts About the Definition of the Pandemic Influenza (H1N1) 2009 and Vaccine Safety

Topics

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1. Brief overview of the pandemic influenza (H1N1) 2009

- Although the current influenza (H1N1) 2009 pandemic is considered moderate in severity, the pandemic influenza virus has caused an average of 6-14 deaths per 1 million population.[1] In the Americas, as of 16 April 2010, there have been at least 8,309 deaths from confirmed cases reported in 28 countries of the Region.[2]

- From September 2009 to 16 April 2010, **over 350 million doses of the vaccine against pandemic influenza (H1N1) were administered** around the world to health workers, high-risk groups, and the general population.[3]

- In the Americas, as of 16 April 2010, **49.4 million doses had been administered in 22 countries of the Region**: Anguilla, Argentina, Bahamas, Barbados, Belize, Bermuda, Brazil, Cayman Islands, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Montserrat, Nicaragua, Panama, Peru, Suriname, Trinidad and Tobago, and Uruguay.[4]

2. Criteria for the definition of the influenza (H1N1) 2009 pandemic

- The influenza (H1N1) 2009 pandemic is a scientifically documented event in which a new influenza virus caused unusual disease patterns worldwide, predominantly impacting young people.
- In 2005, the World Health Organization (WHO) published a global plan defining six phases of a pandemic in order to identify increasing levels of risk. The document, which provided recommendations to guide national authorities in pandemic planning, was the result of a December 2004 WHO advisory meeting to recommend national and international steps to take before and during pandemics. In the plan, pandemics are defined not in terms of their severity, but of the transmission of a new subtype of influenza virus with broader and sustained transmission throughout the community.[5]
- After consultations in 2008, in April 2009 WHO published an updated version of the 2005 global plan, which retains the six-phase structure of the response but regroups and redefines the phases to more accurately reflect the pandemic risk based on observable phenomena.[5]

3. Definition of a pandemic

A pandemic is defined as the emergence of a new influenza virus that has caused sustained community outbreaks in two or more countries in a WHO Region and sustained community outbreaks in at least in one other country in a different WHO Region. The criteria for the definition of a pandemic remain geographical dispersion and viral transmission. The clinical severity of the disease is an important consideration but differs from geographical dispersion, and is not currently included in the definition of a pandemic. WHO is working in substantial and measurable ways to incorporate definitions of clinical severity in the general definition of a pandemic.[6]

4. Chronology of the declaration of the pandemic

- Pursuant to the procedures established in the International Health Regulations (IHR-2005) and adopted by WHO Member States in 2005, WHO Director-General Dr. Margaret Chan called a meeting of the emergency committee on 25 April 2009.[6]
  - → The emergency committee, including international experts from different disciplines as stipulated in the IHR (2005), convened to assess the situation and advise the Director-General on an appropriate response.
  - → In the emergency committee's second meeting on 27 April 2009, the decision was made that the epidemiological data from Canada, Mexico, and the USA showing person-to-person transmission was sufficient to recommend that the Director-General raise the Phase from 3 to 4.
  - → On 29 April, based on evidence of sustained transmission in North America and the emergency committee's recommendations, the Director-General raised the Phase from 4 to 5.
  - → On 11 June, when the pandemic virus had already shown sustained circulation in more than one WHO Region, the Director-General declared Phase 6 of the pandemic.

5. Severity of the pandemic

5.1 Estimates of mortality from seasonal influenza

During the annual peak of seasonal influenza, some 90% of deaths occur in individuals aged >65 years who often already have underlying illness. Although influenza can exacerbate these preexisting conditions, diagnostic tests for influenza are usually not conducted, and the deaths are often attributed to the underlying condition. Deaths from seasonal influenza are estimated using mathematical models to determine the excess deaths caused by influenza.[7]

5.2 Deaths from pandemic influenza

- The number of deaths from the pandemic influenza (H1N1) 2009 reported by national authorities and compiled by WHO are laboratory-confirmed cases and not estimates. These numbers do not reflect the actual mortality rate during the pandemic, which is undoubtedly higher than the laboratory-confirmed cases indicate. Since the signs and symptoms of pandemic influenza are similar to those of many common infectious diseases, physicians often do not suspect infection due to the pandemic influenza (H1N1) 2009 and thus do not order diagnostic tests. It is especially frequent for cases to go undiagnosed in developing countries, where deaths from respiratory diseases (especially pneumonia) are common. Even when tests confirm infection with the pandemic influenza (H1N1) 2009 virus in patients with some underlying illness, many physicians attribute the death to the latter and not to influenza; therefore, these deaths do not appear in the official statistics.[7]
- The impact of mortality from the pandemic influenza (H1N1) 2009 differs from that of seasonal influenza, since pandemic influenza predominantly affects young people, who get infected more often, end up hospitalized, require intensive care, and die.
- WHO continues in the view that the pandemic influenza has had a moderate impact. Most likely, it will be impossible to calculate the precise number of deaths and mortality rates until a year or two after the pandemic has peaked, and that calculation will be based on methods similar to those used to calculate excess mortality during seasonal influenza epidemics.

6. Vaccine production process

- Vaccines have a clearly established three-stage production process. The first stage is research, which consists of three phases: Phase 1 focuses on safety and immunogenicity; Phase 2 assesses safety, immunogenicity, and dosage; and Phase 3 evaluates safety, efficacy, and immunogenicity. Finally, the post-licensing stage is reached, which includes Phase-4 studies (volunteers) to assess safety and efficacy/effectiveness, monitor adverse events, conduct quality-control studies for the release of vaccine lots by the national regulatory authorities, and conduct inspections of the manufacturing laboratories.[8]
- The process for producing the pandemic influenza (H1N1) 2009 vaccine has been the same used to produce seasonal influenza vaccines. Because of the urgency to rapidly produce the pandemic vaccine, some production phases were accelerated. However, vaccine production quality standards have been maintained, which can be confirmed

by the constant drug surveillance established by the manufacturing laboratories themselves and by quality controls established by the countries.[9, 10]

7. Types of vaccine and efficacy

- The pandemic vaccine used in the countries of the Region is inactivated, with and without adjuvant. There is also a trivalent vaccine, which includes the pandemic strain (H1N1) and seasonal (H3N2) and Brisbane strains. This formulation is similar in the Northern and Southern Hemispheres. Some countries in the Region have procured the trivalent vaccine through PAHO's Revolving Fund. This formulation was recommended by WHO for the 2010-2011 period.
- Current data show that the pandemic influenza (H1N1) 2009 vaccine is immunogenic. A single dose is recommended for adults to obtain high immunity and two doses for children aged <9 years.

8. Safety of the pandemic influenza (H1N1) 2009 vaccine

- The safety profile of the pandemic influenza (H1N1) 2009 vaccine is quite similar to that of the seasonal influenza vaccine. Since vaccination activities began, **no event has occurred that puts into question the safety of the pandemic influenza vaccine**:
  - → No increase has been observed in the rate of abortion or intrauterine fetal death in pregnant women who received the pandemic influenza (H1N1) vaccine, compared with pregnant women who have not been vaccinated.[3]
  - → The reported rate of anaphylaxis continues to oscillate in the expected range (0.1-1.0 cases/100,000 doses).[11] Special emphasis has been placed on the detection, accurate diagnosis, and treatment of anaphylaxis in order to avoid fatal outcomes. To this end, the Brighton Collaboration Group developed definitions and degrees of diagnostic certainty that were included in the Pan American Health Organization's field guide *Surveillance of Events Supposedly Attributable to Vaccination or Immunization (ESAVIs) Linked to the Pandemic Influenza (H1N1) 2009 Vaccine and Crisis Prevention*.
  - → Only two deaths associated with program errors have been reported (in Canada and the Netherlands).[3] In the case in Canada, **timely adequate medical treatment was not given to the person, who developed anaphylaxis**, which triggered death. In the case in the Netherlands, **insulin was administered** instead of the vaccine.
  - → The regulatory authorities in several countries around the world have jointly examined the adverse effects of the vaccine that were identified in clinical trials and compared these results with those for seasonal influenza. The conclusion reached was that the safety profiles of the two vaccines coincide; that is, the adverse effects of the pandemic vaccine observed in clinical trials are similar to those of the seasonal influenza vaccine.[1]

→ After analysis of the data reported by the VAERS system (U.S. Vaccine Adverse Event Reporting System) from October-November 2009, it was concluded that the pandemic influenza (H1N1) vaccine continues to be safe, since there was no increase in ESAVIs reported compared with the frequency of ESAVIs reported with the seasonal influenza vaccine.[9]

→ Results on the vaccine's safety are available from three recent clinical trials in China (12,691 people aged 3-87 years/different formulations of the vaccine),[12] the United States (children and adults/vaccine without adjuvant)[13] and Hungary (355 people aged 18-60+/vaccine without adjuvant).[14] Briefly, these studies conclude that:

a) The adverse events reported were moderate and limited; the most commonly reported ESAVIs were pain at the injection site, cough, rhinorrhea, and nasal congestion. The most common severe event was fever.

b) The incidence of systemic reactions was similar in all age groups in China's multicenter, randomized, double-blind, placebo-controlled trial. On increasing the amount of antigen (7.5-30 µg), the number of adverse events increased as well. On the other hand, with increasing age, the number of adverse events decreased.

c) The incidence of local reactions ranged from 12-50%, while systemic reactions ranged from 16-49% in all age groups (study in the United States). The most common systemic reactions reported in adults were headache, myalgia, and discomfort. Most common in children were frequent crying, irritability, loss of appetite, and insomnia.

d) The number of events increased when the pandemic vaccine without adjuvant was administered at the same time as the seasonal influenza vaccine (from 10-18%). This difference is due to moderate soreness at the injection site reported by individuals who received the two vaccines (study in Hungary).

9. Monitoring of Events Supposedly Attributable to Vaccination or Immunization (ESAVIs)

- One of the countries' concerns –among the authorities and general public alike– is vaccine safety. Steps have, therefore, been taken to improve the monitoring of Events Supposedly Attributable to Vaccination or Immunization (ESAVIs).

- Surveillance begins with the report of an ESAVI. An ESAVI consists of clinical symptoms occurring after an individual has received a vaccine that raise concerns and are supposedly attributable to the vaccination.[15] It is important to stress that although denoting a association in time, an ESAVI **does not necessarily imply a cause-and-effect relationship**. Subsequent investigations of the case will determine the causality between the event and the vaccination. Once the investigation has concluded, the case can be classified as coincidental (without a causal relationship), a program error (related to an operational aspect of the vaccination), or a vaccine-associated event (causal relationship with one or more components of the vaccine).

- As of 19 April 2010, 1,198 ESAVIs have been reported in the Americas, 113 of which were classified as serious.[i] Table 1 summarizes the events by country.

Table 1. Events supposedly attributable to the pandemic vaccine reported in the countries of the Americas

Country	# of Doses Administered	# of ESAVI Reported	# of Serious ESAVI Reported	# of ESAVI Under Investigation[ii]
Argentina	1,148,282	44	2	2
Brazil	26,114,599	380	87	35
Caribbean *	6,599	14	4	4
Colombia	84,966	2	0	0
Costa Rica	130,000	57	1	1
Ecuador	8,406	20	1	1
El Salvador	12,000	7	0	0
Honduras	8,000	2	0	0
Mexico	19,700,000	350	13	5
Nicaragua	51,448	285	3	2
Panama	104,149	36	1	1
Peru **	14,848	1	1	1

* Bahamas, Belize, Bermuda and Suriname; ** Peru reports only serious adverse events (not mild or moderate).

- The sensitivity of the surveillance systems in Northern Hemisphere countries such as Canada, China, European countries, and the United States (the first to administer the vaccine) was stepped up substantially in order to capture any ESAVI from the pandemic influenza (H1N1) vaccine, which was being administered on a large scale. These countries are now analyzing the compiled data so that they can provide sound and consistent evidence on the vaccine's safety. Updates on the adverse events reported are no longer issued as often as they were at the beginning of vaccination (daily or weekly reports vs. monthly or quarterly). Table 2 summarizes the events reported in some countries around the world; note that the most recent updating of some of these events was December 2009.

[i] An event is serious if it leads to death, hospitalization, prolonged hospitalization, persistent disability and/or constitutes a threat to life. Serious is not a synonym of severe (intensity/severity).

[ii] The purpose of the investigation is to confirm or rule out the reported event, determine if there are other possible causes, confirm if it is an isolated event, and inform the parties involved.

Table 2. Events supposedly attributable to the pandemic vaccine reported in some countries in the world

Country or Continent	# Doses Distributed*/Administered**	# of Reported ESAVIs	Type of ESAVI	Date Reported
Australia[16]	6 million*	1,289	The majority were moderate events.	31 December 2009
Canada[17]	25,143 million*	6,029	245 (143 anaphylaxis).	20 February 2010
United States[18]	127 million*	10,772	770 (7%) (132 GBS)***	4 April 2010
Europe[19]	42.3 million** (includes 418,00 pregnant women)	N/A	The majority of events were mild or moderate.	14 March 2010
Taiwan[20]	5.56 million**	N/A	The majority of events were mild or moderate. Only 4 cases of GBS have been confirmed.	16 March 2010

*** GBS: Guillain-Barré Syndrome; 132 cases of GBS are under investigation. In the United States, an estimated 80-160 GBS cases could occur every week, regardless of vaccination status; N/A: not applicable.

- Some studies have been published estimating the rate of adverse events that could occur in mass immunization campaigns against influenza (H1N1) 2009. For example, in 2009, Steven Black et al. published an article in *Lancet* stating that in a six-week period, for every 10 million people vaccinated, 22 cases of Guillain-Barré Syndrome (GBS) would occur in the United Kingdom, 83 cases of optic neuritis in the United States, and 397 miscarriages the day following vaccination for every 1 million pregnant women vaccinated.[21]

- It is important to note that these are the number of cases expected for each of these pathologies for a population of 10 million in a six-week period. However, these estimates do not indicate the number of cases of GBS, optic neuritis, or miscarriages that could occur as a result of the vaccination. The comparison between what is anticipated and what is observed serves as one more element for assessing the causal relationship between vaccination and the ESAVIs identified.

- Without denying the usefulness of predicting estimates prior to vaccination activities—since they help assess the vaccine's safety—it is important to note the following:
  - Identifying reliable base rates for any disease is difficult, due to the lack of systematic reporting of diseases, underreporting, lack of standardized case definitions, different methodologies for identifying cases, etc.[22]
  - The denominator used is also an estimate and is often unknown (for example, the number of individuals vaccinated), and it is critical information in determining whether the number of events observed is greater than expected. In many estimates, the number of doses distributed, not the number of doses administered.[22, 23]
- As a result, due to the uncertainty in estimating reliable base rates for some diseases, caution should be used in interpreting these data, bearing in mind the assumptions

used when the estimates were calculated since they could raise false alarms or lead to counterproductive information on the safety of the vaccine.

- Some countries have been able to closely monitor adverse events associated with the influenza (H1N1) 2009 vaccine during mass vaccination. The health authorities of Taiwan, for example, estimated that 27 GBS cases would occur during the six weeks following vaccination, after 15 million doses had been administered. However, by 16 March 2010, 5.66 million people had been vaccinated and only four GBS cases had been confirmed during the following six weeks.[20]
- In general, a misinterpretation of estimated base-rate and/or the results of ESAVIs could not only damage pandemic influenza (H1N1) vaccination activities but also contribute to a loss of public confidence in the vaccine and undermine the credibility of the health services.

10. Communication in risk situations

- Faulty communication strategies and uncertainty about the vaccine's safety may have caused the news media to report on pandemic vaccination in a way that contributed to lower coverage. Immunization remains the cornerstone of a pandemic response.
- Public health officials and the news media should know how to respond jointly and appropriately to any misunderstanding or inaccuracy about the safety of the vaccine that could trigger panic in the population. A joint health/news effort calls for partnerships with the media, as well as the implementation of a plan for crisis and risk communication.

11. Procurement of the pandemic vaccine in the Americas

- All vaccines procured by the countries of the Region through PAHO's Revolving Fund come from laboratories that have been prequalified by WHO. As is known, the world's principal reference on vaccines for public health is WHO, which monitors and certifies the quality and good practices of the manufacturing laboratories. Pandemic vaccine purchase for countries of the Americas was made through the Revolving Fund; a few countries also opted to purchase directly from the manufacturing laboratories; and others received donations from WHO and/or industrialized countries.
- Regarding donations from industrialized countries to developing countries, it is untrue that the reason for these donations is that the vaccine is ineffective or that the donor countries' own populations have refused vaccination. Developed countries prioritized the vaccination of up to 50% of their population and, as a result, purchased large amounts of vaccine. As the pandemic evolved, these countries adjusted their vaccination plans, putting the emphasis on the three main risk groups, which account for approximately 20% of the total population. The result was a vaccine surplus.
- The use of the pandemic influenza (H1N1) 2009 vaccine is a great opportunity for preventing infections and deaths from this disease. It is important that the population be properly informed about the benefits of vaccination and the safety of the vaccine. Its use should be promoted and reliable technical and scientific information provided.

12. Assessment

An external assessment of the global response to the influenza pandemic has begun. The purpose of the assessment is to identify ways to improve the international community's response to public health emergencies in order to protect the public. PAHO/WHO welcomes with satisfaction the opportunity to learn from this exercise and expects the assessment committee to provide clear, critical, transparent, reliable, and independent feedback to reinforce successful activities and rethink the less successful ones, facilitating a more effective response to the next health emergency.

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