Swine Flu Issue Brief

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2009 H1N1: International Progress in Vaccine Development and Distribution

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Shortly after the detection of the 2009 H1N1 influenza virus, the U.S. and other governments decided to develop vaccine against this novel influenza virus in anticipation of and preparation for a second wave of flu in the fall. As we pass through the fall flu season, progress in the licensure, distribution, and administration of vaccine is at various stages around the world. This issue brief provides an overview of the major vaccination efforts around the world, highlighting specific events and controversies that have arisen over the past 6 months.

Status of Vaccine Production

Manufacturers headquartered in the U.S., Europe, China, Australia, Korea, and Japan have developed and produced vaccine against 2009 H1N1 influenza using a variety of technologies and formulations. Generally, each vaccine must gain approval from a country's regulatory authority, like the U.S. Food and Drug Administration (FDA), prior to use. The European Union (EU), Canada, and Korea have approved vaccines with immune-boosting adjuvants, and the EU has also approved a vaccine produced through newer, cell culture based technology. Table 1, below, provides an overview of major vaccine efforts worldwide.

Table 1: Major International Vaccine Manufacturing Efforts

Vaccine	Manufacturer	Countries of Manufacture	Manufacturing Technology	Adjuvant	Countries of approval (date approved, if available)
Pandemrix	GlaxoSmithKline (GSK)	Germany[1]	Egg-based	Available with and without	EU (9-22-09);[2] Saudi Arabia (11-2-09),[3] Singapore (10-15-09)[4]
Arepanrix	GSK	Canada[1]	Egg-based	Available with and without	Canada (10-21-09);[5] WHO (12-1-09)[6]
Celtura	Novartis	Germany[7]	Cell-culture	Yes	Germany (11-05-09),[7] Switzerland (11-13-09)[8]
Focetria	Novartis	Italy[9]	Egg-based	Yes	EU (11-22-09)[2]
Celvapan	Baxter International	Czech Republic[10]	Cell-culture	No	EU (10-6-09)[2]

Vaccine	Manufacturer	Countries of Manufacture	Manufacturing Technology	Adjuvant	Countries of approval (date approved, if available)
PanVax	CSL Biotherapies	Australia[11]	Egg-based	No	U.S. (9-15-09),[12] Australia (9-18-09),[13] Singapore (10-9-09)[4]
Panenza	Sanofi Pasteur/ sanofi-aventis	France[14]	Egg-based	No	France (11-16-09)[14]
Humenza	Sanofi Pasteur/ sanofi-aventis	France	Egg-based	Yes[15]	None
PANFLU.1	Sinovac	China[16]	Egg-based	No	China (11-2-09),[17] Mexico (10-22-09)[18]
Inactivated H1N1 Influenza Vaccine	Hualan Biological	China[16]	Egg-based	No	China (9-4-09)[19]
Green Flu-S	Green Cross	Korea[20]	Egg-based	Available with and without	Korea (10-21-09)[20]
Fluval P	Omninvest	Hungary[21]	Egg-based	Yes	Hungary (9-29-09)[22]
Inactivated A/H1N1 Influenza Vaccine	Denka Seiken Co	Japan[23]	Egg-based	No	Japan
Inactivated A/H1N1 Influenza Vaccine	Kaketsuken (The Chemo-Sero-Therapeutic Research Institute)	Japan[23]	Egg-based	No	Japan
Inactivated A/H1N1 Influenza Vaccine	The Kitasato Institute	Japan[23]	Egg-based	No	Japan
Inactivated A/H1N1 Influenza Vaccine	Research Foundation for Microbial Diseases of Osaka University (Biken)	Japan[23]	Egg-based	No	Japan

Progress in Vaccine Distribution

China: China was the first country to approve and begin administering 2009 H1N1 influenza vaccine. The country's mass vaccination program commenced on October 1, 2009, when 200,000 volunteers for China's National Day celebration were immunized. China's priority groups for vaccination are pregnant women, children aged 5-19 years, those with respiratory conditions, and front line public service personnel. On November 6, 2009, the Beijing health authorities opened vaccination to the city's entire population of approximately 16 million people.[24] As of Monday, November 9, China had vaccinated 87 million people.[25]

Europe: The U.S. and the EU followed, approving vaccines in mid- to late September and beginning vaccination programs in early to mid-October. In Europe, the European Medicines Agency (EMEA) is responsible for reviewing data for approval of drugs and vaccines in the EU. However, member countries have also independently approved and purchased vaccines that are not currently approved by the EMEA. To date, vaccination progress in Europe is mixed. While Sweden and Norway have vaccinated 33% and 25% of their populations, respectively, Poland has yet to start. Many other countries have not completed vaccination of priority groups, and some mass vaccination efforts are just beginning.[26]

In the countries with national health systems — United Kingdom, Germany, Sweden, Denmark, Finland, and France — vaccine is being administered to high priority groups by invitation.[27] In the UK, each medical practice in Britain's National Health Service initially received 500 doses of vaccine to target high risk groups, which included pregnant women and people with underlying health conditions. There have been no reports from the UK of shortages or long lines at vaccine clinics. Exact reasons for this are unclear, but by virtue of its national health system, it appears that the UK was able to more easily identify and communicate with people who were prioritized for vaccination. And because the system also allowed for scheduled vaccinations, confusion about eligibility and vaccine availability seems to be reduced. In addition, the UK's use of an adjuvanted vaccine, which provides up to 4 doses for every unadjuvanted dose of vaccine, may have expedited vaccine availability.[28]

Canada: Of the 50.4 million doses of vaccine ordered by the Canadian government, 1.8 million are unadjuvanted vaccine from CSL Limited and GSK (Arepanrix), and the remaining 48.6 million doses are adjuvanted Arepanrix. Of the 1.8 million doses of unadjuvanted vaccine, Canada purchased 200,000 doses of CSL's PanVax vaccine.[29] The country began mass vaccination efforts in late October and early November, focusing on pregnant women, children aged 6 months to 5 years, those with chronic health conditions, people living in remote or isolated communities, healthcare workers, household contacts of infants under 6 months of age, and people who are immunocompromised.[30]

Japan: While most governments are providing vaccine at no charge, Japan is charging a fee of 6,150 yen (approximately $69) for 2 doses of vaccine. The country supplemented the 50 million doses it purchased from Novartis and GSK with vaccine made in Japan by 4 companies that are expected to produce an additional 27 million doses.[23]

Other countries have been slower to approve, purchase, and distribute vaccines. Most countries that have begun mass vaccination efforts are prioritizing vaccine in a manner similar to that of the U.S. While there is some variation in focus, pregnant women are being prioritized nearly universally. By late November and early

December, some countries had expanded their vaccination efforts from their priority groups to larger groups or their populations as a whole.

Concerns and Controversies Surrounding Vaccine Development and Distribution

On November 25, 2009, Canada and GSK advised healthcare providers to stop using a particular lot of GSK's Arepanrix due to increased allergic reactions.[31] Worldwide, with the exception of problems with this particular lot, there have not been significant reports of events that call into question of the safety of monovalent H1N1 vaccines in humans. The 2009 H1N1 influenza vaccines, which have been produced through manufacturing processes already established for seasonal flu, are demonstrating patterns of adverse events similar to those of seasonal flu vaccines.

Germany began its mass vaccination program on October 26, using 200,000 doses of Baxter International's unadjuvanted, cell-culture-based vaccine, Celvapan, and 50 million doses of GSK's adjuvanted, egg-based vaccine, Pandemrix. Both vaccines, which were purchased by the German government, were evaluated for safety and efficacy by the EMEA, and both were approved for use in the EU. However, when Germany began its mass vaccination program, it announced that Celvapan would be given to government officials and military personnel, while Pandemrix would be distributed to the public. The public perceived that the safer of the 2 vaccines was being administered to the government and military, which raised questions about the fairness of the mass vaccination efforts.[32]

On November 4, 2009, a senior member of the staff of the Alberta Health Services in Canada was fired for allowing members of the Calgary Flames National Hockey League (NHL) team and their families to receive 2009 H1N1 influenza vaccines while clinics in Canada experienced shortages.[33] The decision by Alberta Health Services to vaccinate the Calgary team was based on its assessment that they were a priority due to extensive border crossing and the close contact of the sport. However, the hockey players do not fall into the priority groups outlined by the Canadian government. Other sports teams in Canada were also discovered to have been vaccinated ahead of those in the established priority groups. As a result, Canadian vaccine clinics established stricter eligibility guidelines.[34]

Preparing for the 2010 Flu Season

The WHO added the 2009 H1N1 strain of influenza virus to the normal seasonal vaccine for the 2010 Southern Hemisphere flu season.[35] In the Southern Hemisphere, seasonal flu occurs from May through August, whereas in the Northern Hemisphere, seasonal flu occurs during the months of November through February. Even though Australia's regular flu season is over on September 30, the country is pursuing mass vaccination against 2009 H1N1 influenza. The government purchased 21 million doses of CSL's PanVax, with the intent of vaccinating the entire population.[35] This decision was made because it is expected that 2009 H1N1 influenza virus will continue to circulate in Australia and the rest of the Southern Hemisphere during their summer months, just as the virus did in the Northern Hemisphere from May to August.[36]

Vaccine for Developing Countries

The World Health Organization (WHO) is coordinating the donation of 2009 H1N1 influenza vaccines for developing countries that are unable to purchase directly from manufacturers. On September 18, 2009, the

U.S. pledged to donate 10% of its purchased vaccine to this WHO effort. Australia, Brazil, France, Italy, New Zealand, Norway, Switzerland, and the UK also agreed to share vaccine through the WHO. GSK and Sanofi Pasteur are expected to donate 150 million doses.[37] On October 30, the WHO announced plans to distribute enough vaccine for 2% of the population of 16 developing companies. As larger quantities of vaccine become available, this program will be expanded to reach 10% of the population of 95 countries.

Due to initial shortages of vaccine in countries that have pledged to WHO, the timeline for distribution has been delayed. It is expected that donations of vaccine will be supplemented with syringes and other materials needed to administer vaccine.[38] On November 10, GSK finalized its agreement with the WHO to donate 50 million doses, the first shipments of which began in late November.[39] To expedite use of donated vaccine, the WHO pre-approved GSK's Arepanrix vaccine on December 1, clearing the way for its use in developing countries as the vaccine becomes available.[40] Thus far, the Philippines has received H1N1 vaccine manufactured by GSK and Green Cross from the WHO.[41] Israel also received vaccine from the WHO and is sending 30,000 to 40,000 doses to the Gaza Strip.[42] Kenya announced that in January, it would use 700,000+ doses of vaccine from the WHO to begin vaccinating health workers, followed by pregnant women, medical and nursing students, and malnourished children.[43]

Conclusions

Vaccine for 2009 H1N1 influenza has been developed by a handful of manufacturers using several different technical approaches. While many wealthy countries have been able to purchase enough vaccine for their entire populations, developing countries will likely not receive any vaccine until the WHO obtains donated doses, which began in late November and will continue to expand into early 2010. The approach to allocation and distribution of vaccine has been similar across those countries able to purchase vaccine.

Countries that have pursued vaccination campaigns have experienced problems similar to those that have arisen in the United States, such as delays in vaccine availability, lack of interest, and/or perceived problems with safety of vaccines. Based on limited press reports to-date, it appears that those countries with national health systems were more successful than the U.S. in their efforts to identify and vaccinate high priority individuals. A more in-depth study of the efficacy of flu vaccine distribution systems is warranted.

Given the continued circulation of 2009 H1N1 influenza, it is highly likely that this virus will become a component of the Northern Hemisphere's 2010-2011 seasonal influenza vaccine. To date, the 2009 H1N1 virus has remained relatively stable; nonetheless, the exact make-up of the 2010-2011 seasonal vaccines will depend on the extent of any genetic changes in the circulating 2009 H1N1 influenza virus. Given the likelihood that the novel 2009 virus will continue to circulate, countries in the Northern Hemisphere should continue to encourage their populations, including priority groups, to get vaccinated as the normal winter flu season will last through February and into March for many countries.

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