Pan-Canadian Public Health Network

Partners in Public Health

H1N1 VACCINE PROGRAM PLANNING SCIENTIFIC AND CLINICAL QUESTIONS FOR WHICH WE MAY NOT HAVE ANSWERS

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Pandemic epidemiology

What we know

- Most H1N1 disease to date has been mild and self limited.
- Severe disease occurs most frequently in children and young adults.
- Risk factors for severe disease include chronic medical conditions including morbid obesity, pregnancy, aboriginal population *(more detailed analyses needed).*
- A significant proportion of hospitalized patients require extended mechanical ventilation.
- Increased frequency of secondary bacterial pneumonia has not been observed.
- Little illness has occurred in persons over age 60, probably as a result of residual. immunologic memory from H1N1 exposure before 1957.

What we don't know– and when will we know it

1. Will disease severity of successive waves of illness be more, less or the same as that observed to date?
2. Will the age distribution change for persons with illness or severe disease?
3. Will the novel H1N1 virus replace seasonal influenza strains as the predominant circulating influenza virus?
4. Will new risk factors for severe H1N1 disease be identified?

Results may emerge over the next 2 -3 months in the Southern Hemisphere, or during the fall and winter in Canada and other Northern Hemisphere countries.

Vaccine

What we know

- Based on studies on H5N1 vaccine an adjuvant was required to allow dose sparing, and two doses were required to induce immunity.
- Inclusion of an adjuvant broadens the immune response and provides some cross protection against drift (H5N1 studies).

- There is no cross protection induced by the H1N1 component present in seasonal influenza vaccine.

What we don't know – and when will we know it

5. What amount of antigen is needed for each dose of vaccine?

   Results will come from manufacturer clinical trials of adjuvanted and non-adjuvanted formulations which are due to start in early September in Belgium using material produced by the Dresden GSK site. Preliminary data will be available in October and final data available in November. There will be no results available from Canadian trials until February 2010. BGTD will rely on the Belgian trials which will look at two doses of vaccine of adjuvanted versus unadjuvanted vaccine in adults age 18-64. There will be separate trials in children run concurrently using adjuvanted vaccine alone. For children age 6-35 months, a half dose of 1.9 ug will be tried in comparison to the 3.8 ug dose. Paediatric results will not be available until February 2010.

6. Are two doses of vaccine needed for individual protection? Is this true in all target groups?

   Current assumption is that two doses will be needed; however the manufacturer clinical trials will analyze results after the first dose as well as the second. Preliminary information on whether one dose is adequate for some age or target groups may come from countries where clinical trials are beginning sooner e.g., Australia.

7. What will be the time interval between doses?

   GSK trials will use a 21-day interval between doses.

8. Should we use adjuvanted vaccine? Is adjuvanted vaccine as safe and effective as non-adjuvanted vaccine? Is this true for all ages and target groups?

   There are no clinical data at present to assess the risk or benefit of using adjuvanted or non-adjuvanted influenza vaccines against the novel H1N1 virus. However no significant safety concern or barriers to evaluating or using adjuvanted vaccines for the current H1N1 virus were raised (WHO virtual consultation on adjuvant safety). WHO urges the use of dose-sparing formulations like oil-in-water adjuvants to maximize antigen sparing and induce broader immunity.

   Clinical trials (schedule provided above) will assess safety and immunogenicity of adjuvanted and non-adjuvanted formulations. Manufacturers will not be conducting trials in pregnant women or immunocompromised persons; we are unlikely to have data for these groups unless government-sponsored trials are conducted. Such trials are being planned by the PCIRN network among others.

9. What do we know about the GSK oil-in-water adjuvant?

   The AS03 adjuvant has been evaluated in 45,000 individuals. An integrated summary of safety (ISS) from 15,400 subjects with a 6-month follow-up suggests an increase in local

reactogenicity but no increase in immune-mediated events above background rates (WHO Consultation on Safety of Adjuvanted Influenza Vaccines). The Pandemic Vaccine Task Group is currently reviewing the ISS. The power of these studies to detect rare events is limited, especially for anything occurring at a frequency of one per 10,000 persons vaccinated or less. Such events can only be detected after roll-out into large populations, emphasizing the need for post-market surveillance (see below).*

10. Are there vaccine safety concerns? Will there be a risk of Guillain-Barre Syndrome with the novel H1N1 vaccine, given that it is of swine origin?

Rare adverse events may be detected when vaccines are given to millions of people within a short period of time. These can only be identified by post-marketing surveillance. Severe coincidental events may also be temporally associated with vaccination. A comprehensive pharmacovigilance plan is being developed for Canada in collaboration with other countries.

The attributable risk of GBS following swine flu vaccination in the US in 1976 was approximately one case per 100,000 persons vaccinated. The vaccines used in 1976 were both whole virus and split product and were made by many manufacturers; none were adjuvanted. There was no difference noted in the attributable risk across vaccine types or manufacturers. Studies of flu vaccines since 1976 have shown no association, or in some studies a very small risk (attributable risk of less than one per million vaccinations).

It is not possible to predict an attributable risk for GBS when H1N1 vaccine is rolled out – it could be as low or lower than one case per million doses or as high or higher than one per hundred thousand doses. For this reason it is essential to conduct active surveillance for GBS and to calculate expected background rates ahead of time and determine a threshold for observed cases that would have implications for vaccine programs.

11. How effective will the vaccine be?

"Real-time" vaccine effectiveness will be evaluated using the sentinel surveillance methodology employed for seasonal flu vaccine effectiveness. Note that adjuvanted vaccine is expected to provide some protection against strain drift, should that occur.

12. When will vaccine be ready?

GSK vaccine is expected to first become available in Canada as filled product (in vials ready for use) by the end of October and should receive regulatory approval by mid November. It will take several months for enough vaccine to be supplied for the whole Canadian program.

The actual production rate will depend on many factors such as yield which WHO reports as disappointing according to a manufacturer survey (only 30-50% of usual yield for seasonal H1N1 vaccine in eggs). The rate limiting step for Canada, however, is fill-line capacity; even if production is reduced, it is still expected to match or exceed the quantity of vaccine that can be filled in Canada.

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* http://www.who.int/vaccine_research/InfluenzaMeeting/en/index.html

13. Can the novel H1N1 be given concurrently with seasonal influenza and other vaccines?

    This will be addressed in trials sponsored by NIH.

14. Who should be vaccinated and in what order?

    National recommendations need to be tailored to each country's needs, depending on pandemic goals, epidemiological situation, resources and ability to access vaccine. Preliminary Canadian recommendations will be developed over the summer by the Pandemic Vaccine Task Group. WHO and CDC have already issued preliminary recommendations for vaccine.

15. What uptake can we expect? Can we achieve useful coverage levels in populations at risk? Can we achieve sufficient coverage for herd immunity?

    Anticipated uptake is best estimated by provinces and territories. It may depend in large part on the situation in the fall in terms of severity of illness, stage of the pandemic, perceived shortage of vaccine etc.