Swine Flu: what next?

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Influenza A H1N1v: “Swine flu”: what next?

Structure
1. Why is influenza pandemic?
2. What exactly is swine flu?
3. What next (questions for the future)?
   • When will the pandemic finish?
   • Will the virus return?
   • Will the virus mutate and give rise to more severe illness?
   • Will oseltamivir resistance become more widespread?
   • What is to be done?

Influenza A virus

• There are 15 haemagglutinins
• There are 8 neuraminidases
• Influenza A viruses are ubiquitous in aquatic birds where the greatest variety of H and N combinations are to be found
• They colonize the GI tract
• They frequently cause disease

Replication cycle of influenza

1. Binding of virus to cell
2. Cell engulfs virus via endocytosis
3. Membrane of virus fuses with endosome; RNA released into cell
4. Viral polymerase produces mRNA from viral RNA
5. Protein, new RNA produced
6. Self-assembly produces virions
7. Virions bud off cell membrane

Antigenic drift

• RNA-dependent RNA polymerases have no “proof reading” and mistakes are made during RNA synthesis
• If these mistakes are non-lethal and encode altered antigenic proteins, “DRIFT” has occurred
The impact of “Drift”

- Circulating human ‘flu strains “drift” all the time, particularly during the flu season
- Immunity to previous influenza provides some protection against “drifted” virus
- The WHO monitors “drift” in human strains and vaccines are adjusted accordingly

Pandemic Influenza

Antigenic shift

- Infection of the same cell by two different Flu types, from different species e.g. bird and human
- Fragments from different types are packaged into a new virus with genes from both “parents”
- This is REASSORTMENT. The new virus has undergone “ANTIGENIC SHIFT”

Antigenic shift: reassortment in pigs

Influenza in the UK since 1889

1889-1890 H2N2 Pandemic
1898-1900 H3N8 Pandemic
1918-19 H1N1 “Spanish” Flu Pandemic, 200,000 deaths (20-40 million worldwide).
1933 Influenza A virus discovered.
1946-48 The “non-pandemic”
1957-58 H2N2 “Asian” Flu pandemic, 37,500 deaths.
1968-69 & 1969-70 H3N2 “Hong Kong” Flu pandemics, 78,000 deaths
1977 Re-emergence of H1N1
1989 Re-emergence of H3N2 (last “epidemic” year), 30,000 deaths (In Wales 1,627 deaths among an estimated 464,000 cases, a death rate of 0.35%).
2009 Emergence of H1N1v in Mexico
What exactly is H1N1v “swine” flu?

Swine Flu and Human Flu

- c1900: Influenza A H1N1 introduced into pigs in US (“classical swine flu”)
- c1930 – 1940s different human derived Influenza A H1N1 in pigs in UK (but dies out)
- 1979: different avian derived Influenza A H1N1 introduced into pigs in Europe (“Eurasia”)

Swine Influenza A (H1N1 virus)

Is Influenza A H1N1v: “Swine flu” truly pandemic?

1. “Efficient and sustained human transmission” in more than 1 country in more than one WHO region.
2. BUT qualitatively different from 1918, 1957, 1968
4. 1946
   - The HA did not cross react with previous strains
   - Spread was slow
   - Outbreak was relatively mild with low mortality
   - In 1962 the 1946 virus was shown to have arisen by extensive mutation from previously circulating H1 strains, and therefore the epidemic was not a pandemic by definition

Swine flu: What next?
When will the pandemic finish?

- Started in 1986
- Volunteer sample of 42 general practices in Wales
- Covers c10% of population of Wales
- Weekly paper-based reporting
  - age, sex, disease, practice, week
  - measles, mumps, rubella, shingles, chicken pox, bloody diarrhoea, influenza
- feedback by weekly news-sheet

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Swine flu: What next?
When will the pandemic finish?
(GP “Audit +” surveillance)
- Started in 2009
- c70% general practices in Wales
- Daily 7 day rolling average from abstraction from electronic workload
- feedback by web

Weekly influenza consultation rate in Wales: week 1 1987 to week 49 2009: GP Surveillance of Infections in Wales Scheme

Swine flu: What next?
Will the virus return? - Australia

Swine flu: What next?
Will the virus return? – New Zealand
Swine flu: What next?
Will the virus mutate and give rise to more severe illness?

- Avian influenza may be "HPAI" or "LPAI"
- Pathogenicity is dependent on basic amino acids and a CHO chain at the HA post translational cleavage site.
- HA D222G (aspartic acid – glycine) mutation observed in H1N1v human deaths in Norway & Ukraine

Swine flu: What next?
Will the virus mutate and give rise to more severe illness?

- US CDC & AFIP researchers have recovered 1918 virus from corpses
- HA does not have a series of basic AAs @ cleavage site
- Put into H1N1 Texas 1991 does not enhance lethality to mice
- Inserting 5/8 genes into H1N1 Tx91 enhances lethality (100%@9 days) BUT less than wild type 1918 virus (100%@5 days)

Swine flu: What next?
Will the virus mutate and give rise to more severe illness?

In 1918 both US & British army pathologists showed zary bacterial pneumonias in c80% of post mortems

Brudage: TLID 2006;6:303-12

Swine flu: What next?
Will oseltamivir resistance become more widespread?

- Yes
  - Point mutation
    - H274Y (Histidine-Lysine)
    - R292Y (Arginine-Lysine)
  - Common in seasonal flu
  - First reported in Norway
    - (>60% in 2007-08)

Outbreak of Oseltamivir Resistant H1N1v Influenza A, Cardiff: Summary

- The outbreak occurred on a haematology unit amongst patients who were immuno-suppressed.
- 8 cases of infection due to resistant virus were detected.
- Resistance developed on oseltamivir treatment in at least two cases.
- There was evidence of person to person spread.
- Treatment was changed to zanamivir
- Isolation precautions were put in place.
- One patient remains on critical care, the others are all improving.
- The incident remains under investigation, but currently there is no evidence of further spread.

Influenza A H1N1v: “Swine flu”: what next?

- When will the pandemic finish?
  - Christmas
- Will the virus return?
  - Yes, as seasonal flu, next winter
- Will the virus mutate and give rise to more severe illness?
  - Yes but no
- Will oseltamivir resistance become more widespread?
  - Yes
- What is to be done?
Swine flu: What is to be done?

- Rebuild/diversify stockpiles
  - Zanamavir
- Research
- Retain engagement of “usual” health providers
- Immunisation
  - China
  - Ontario, Canada