Vaccinating against influenza A

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DIMACS Jun 2005
US Annual Mortality Rate

Deaths per 100,000 per year

- All causes
- Infectious Disease
**Influenza A viruses**

- An important cause of morbidity and mortality on an annual basis.

- Cause occasional pandemics, with extremely high infection rates, and sometimes extremely high mortality.

- Endemic in many mammal and bird populations, with tremendous, stable antigenic diversity in wild waterfowl populations.

- A remarkable capacity for antigenic evolution.

- Epidemiologically more significant than influenza B and C viruses, which circulate primarily in humans.
An influenza virion
A human host (juvenile)
Shift evolution

Major antigenic change caused by reassortment between human and avian virus segments.
ウイルスA

vRNA

宿主の細胞

遺伝子分節の交換によるハイブリッドウイルス
Shift evolution

Major antigenic change caused by reassortment between human and avian virus segments.

- 1918 Spanish flu (H1N1) replaces earlier strain.
- 1957 H2N2 replaces H1N1.
- 1968 H3N2 replaces H2N2.
- 1977 H1N1 mysteriously reappears.

It is estimated that there have been roughly 10 influenza pandemics (presumably caused by shifts) in the last 250 years.
Drift Evolution

- Each influenza subtype undergoes gradual, antigenically significant mutations to HA. After a few years, descendants of an infecting ‘strain’ will have changed enough to re-infect most individuals.

- Unusual phylogenetic pattern generated: a great deal of diversity, but a dominant main trunk.

- Influenza B viruses show a similar, but less dramatic, pattern.
The Hemagglutinin (HA) Monomer

Receptor Binding Site

C HA1

N HA1

N HA2

C HA2
HIV-1

Rambaut, et al., 2001

Influenza A

Fitch, et al., 1997
Overview

- Drift evolution
  - How to vaccinate
  - Whom to vaccinate

- Shift evolution
  - How to vaccinate
  - Whom to vaccinate
Overview

• Drift evolution
  – How to vaccinate
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• Shift evolution
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Quasispecies structure and the antigenic evolution of Influenza A

- What do modelers mean by a ‘strain’?
- What does strain space look like?
- Do influenza viruses cluster into ‘quasispecies’?
Clusters through time

- Quasispecies have limited temporal range
- Dominant quasispecies replace each other on a time scale of 2–5 years
- Evolution is linear over this time span in amino-acid space
Geographic location by cluster

Number of sequences

China
Other

Within-cluster variation

Mean dist. betw. seqs.

Epitope A (19 sites)
B (22)
C (27)
D (41)
E (22)
Other sites (198)
Mean dist. betw. seqs.

Epitope A (19 sites)  
B (22)  
C (27)  
D (41)  
E (22)  
Other sites (198)  

Dist. betw. cluster centroids

Clustering summary

- Sequences are clustered in amino-acid space, forming natural ‘quasispecies’.
- Clusters replace each other on a time scale of 2–5 years.
- Clusters display interesting interactions with antibody-combining regions (epitopes).
- Formal clustering methods have potential for predicting the direction of influenza evolution.
Human H3 structures
How to vaccinate against drift strains?

• Can we predict where drift evolution is going?
  – Structure
  – Surveillance

• Can we control where drift evolution is going?

• How long does protective immunity really last?
  – Transmission
  – Illness
    Mortality
Overview

• Drift evolution
  – How to vaccinate
  – **Whom to vaccinate**

• Shift evolution
  – How to vaccinate
  – Whom to vaccinate
Vaccinating high-risk groups against influenza: is it working?

- Yes
  - Cohort studies
  - Official (CDC) line

- No
  - Population studies
  - Vaccine responses
Modeling question: should we vaccinate ‘core’ or ‘victim’ groups?

- Core group:
  - More active at spreading the disease
  - e.g. school children

- Victim group:
  - More likely to be harmed by disease
  - e.g. elderly people
Cartoon model for flu vaccine priorities

Final-size formula (Kermack and McKendrick)

- $V = 1 - \exp(-\beta V)$, where $\beta = R_0 S/N$ is the realized reproductive number, and $V$ is the proportion of susceptibles infected.

- Very broadly applicable (no assumptions about time distributions), as long as:
  - Population mixes randomly
  - Epidemic burns itself out
Cartoon model for flu vaccine priorities

- Two-group version of single-epidemic model with preferred mixing:
  - Each person spends a proportion $p$ of time mixing at random within the group, and $1 - p$ mixing at random in the whole population (including the group).
  - Cheap version of population structure.
Cartoon model for flu vaccine priorities

- Fundamental parameters are $\beta_c$, $\beta_v$, $p$, $T$ (proportion vaccinated).

- Neglected parameters are:
  - subpopulation sizes (set equal)
  - effectiveness of vaccine against transmission, illness, death (set equal and scaled out)
    - Structure of $\beta$ (assumed that difference is in contact rate, not transmission or susceptibility).
Cartoon model for flu vaccine priorities

Predictions:

- Best to vaccinate victims when $\beta$s are similar, core otherwise.

- In well-mixed population, better to vaccinate one group or other.

- In patchy population, maybe an intermediate optimum?
\[ \beta = 2, 1.1; p = 0.1, T = 0.4 \]
Victim group incidence

$\beta = 2, 1.1; p = 0.5, T = 0.4$
Victim group incidence

$\beta = 2, 1.1; p = 0.9, T = 0.4$
Victim group incidence

\[ \beta = 4, 1.5; p = 0.1, T = 0.4 \]
$\beta = 4, 1.5; p = 0.5, T = 0.4$
Victim group incidence

\[ \beta = 4, 1.5; p = 0.9, T = 0.4 \]
Victim group incidence

$\beta = 1.6, 0.8; p = 0.1, T = 0.4$
Victim group incidence

\[ \beta = 1.6, 0.8; \ p = 0.5, \ T = 0.4 \]
$\beta = 1.6, 0.8; p = 0.9, T = 0.4$
Cartoon conclusions

- Things can get worse when we start moving in the right direction
- Things can get worse if we move too far in the right direction
- Until more is understood, efforts to vaccinate school children must not come at the expense of vaccination of at-risk groups
- This is even more true when inter-annual effects are considered
  - If victims are protected indirectly, susceptibility will accumulate!
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Vaccinating against pandemic influenza

- HA vaccine unlikely to be available

- Other targets
  - Will not stop spread of new subtype
  - But can vaccines against other targets save lives?

- Antivirals

- Antibiotics!
Overview

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• Shift evolution
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Facing a pandemic

Can a pandemic be stopped?

- Example of SARS
- Flu quicker, more cryptic (is infectious before symptoms, similar to many other diseases)

Will decision makers use resources:

- To treat those first affected?
- To try to stop or control spread?
- To protect the powerful (i.e. developed countries)?
Is the new subtype vulnerable \textit{after} the pandemic? (David Earn)

- Little immune pressure $\rightarrow$ little antigenic drift
- Epidemic burnout
- Develop a quick test, vaccine, isolation measures and try to stamp out the subtype the second year?
  - Can we really finish human influenza A?
  - What about existing subtypes?
Thanks

- David Earn, Hunter Fraser, Sergey Kryazhimskiy, Catherine Macken, Ben McMahon, Walt Mankowski, Ellis McKenzie, Joshua Plotkin, Tom Reichert, Peter Palese, Lone Simonsen, David Smith, Cecile Viboud.
- National Institutes of Health (NIGMS, Fogarty Int’l Center)
- Academy of Motion Picture Arts and Sciences
- Conference organizers
- This audience