Antigenic Drift of Influenza A

related to vaccination and pandemic planning

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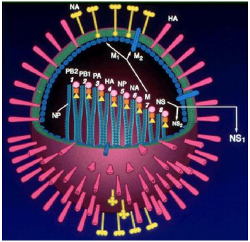
DIMACS June 29, 2005

Contents

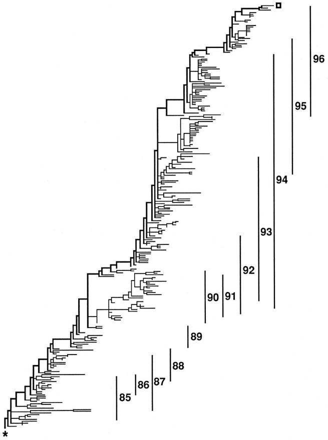
Virus characteristics



- RNA virus, family *Orthomyxoviridae*
- 3 *types*: A, B, C
- Waterfowl (ducks, geese) are a natural reservoir for type A
- Influenza A: antigenic *subtypes*, corresponding to surface proteins haemagglutinin (H), neuraminidase (N)
- 15 H- and 9 N- subtypes
- Variation within subtypes: *strains*
- Rapidly evolving . . .

Antigenic drift and phylogenetics

Example: phylogeny of HA1 domain of A/H3N2



Fitch et al. (1997)

- Less viral diversity than expected
- Antigenic drift
- Serial replacement of predominant strains
- *'Slender trunk' with short branches*
- 'Competitive exclusion'

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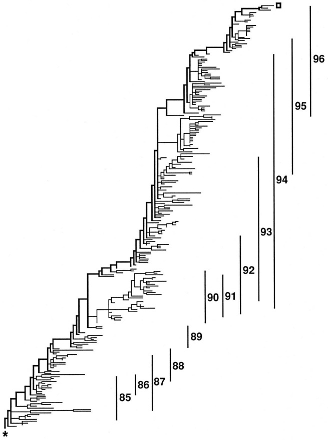

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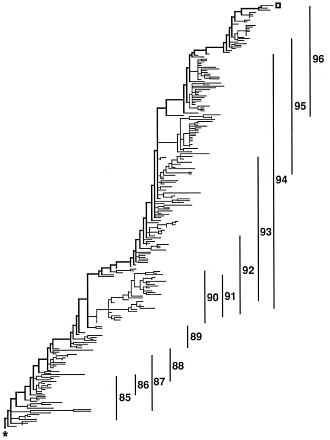

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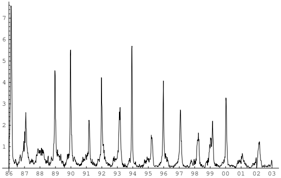
Immune response

- Low cross-immunity between strains
- *Strain-specific long-lived* immunity
  - Host memory of viral epitopes
  - $\approx$ (life)long
- *Strain-aspecific short-lived* immunity
  - Large amounts of antibodies/CTLs still present
  - $\approx$ weeks (months)

Epidemics

Annual 'winter epidemics' in temperate regions



- 5–15 % of population infected
- Fatalities mainly in risk groups due to secondary infections
- Antigenic *drift*:
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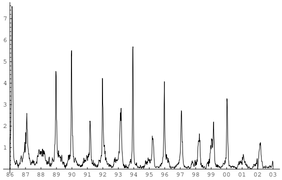

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Pandemics

Worldwide epidemics of new influenza A subtypes

1918	**H1N1**	*Spanish flu*
1957	**H2N2**	*Asian flu*
1968	**H3N2**	*Hong-Kong flu*

- 30–50 % of population infected
- Massive demand for health care
- Antigenic *shift*:
  novel subtype (viral reassortment, gradual adaptation?)
- Majority of population susceptible

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Interventions

Potentially powerful

Influenza characteristics:

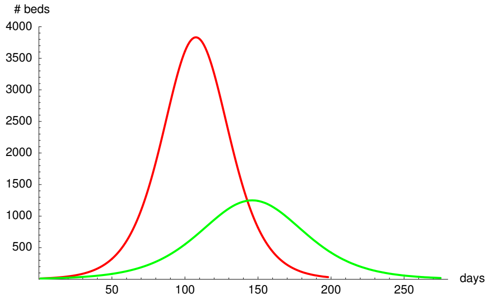
Generation interval	*short*	≈ 3.5 days
R_0	*low*	$\approx [1.5, 3.5]$

Intervention measures:

- Vaccination
- Antivirals (prophylactic, therapeutic, . . .)
- Hygienic measures (masks, . . .)
- Contact rate minimization (school closure, . . .)

Antivirals

Example scenario: pandemic with 50 % infected



Number of Dutch hospital beds occupied,
without (red) and with (green) early therapeutic use of oseltamivir
for 80 % of all people with ILI

Vaccination
and its problems

- Long production delay ($\approx$ 0.5 yr) $\Rightarrow$
- *Epidemics* (antigenic drift):
  - Every year predict which strains to incorporate
  - Mismatch
- *Pandemics* (antigenic shift):
  - Probably too late
  - Not successful yet for every subtype
- Additional selection pressure on virus $\Rightarrow$?

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Model
Goal

Question:

How are the influenza A ‘slender trunk’ phylogeny, immune response, and seasonal dynamics related?

Starting point

Ferguson et al. (2003) [1]

- Multiple-strain model with mutation
- Individual-based, stochastic
- Spatially structured (patch dynamics, N/S hemispheres)
- Long-lived and short-lived immune response

- *Short-lived strain-transcending immunity essential to restrict viral diversity*

[1] N.M. Ferguson, A.P. Galvani and R.M. Bush, 2003.
Ecological and immunological determinants of influenza evolution,
Nature 422(6930): 428–433

Another model
Ingredients 1

- Multiple-strain 'hybrid' simulation model:
- Deterministic 'high-R_0' SIR-model in winter
- Stochastic 'low-R_0' in summer

- Renewal (births and deaths) once a year
- Constant population size
- Homogeneous mixing
- Small, constant import of infectious hosts in summer

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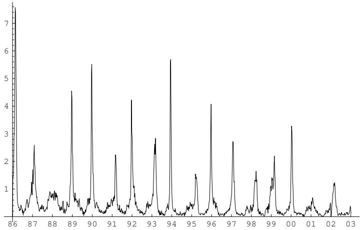
Another model
Ingredients 2

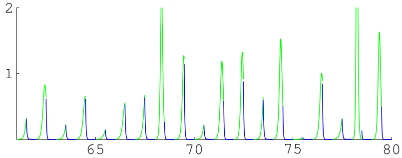
- Cross-immunity between mutant and parent strain exponentially distributed
- Cross-immunity between arbitrary strains multiplicative by descent
- Polarized immunity & reduced transmission (Gog & Grenfell, 2002)
- Number of mutants descending from each strain Poisson-distributed
(cumulative infection days $\times$ per-host mutation prob.)

Results

Annual outbreaks: % infected

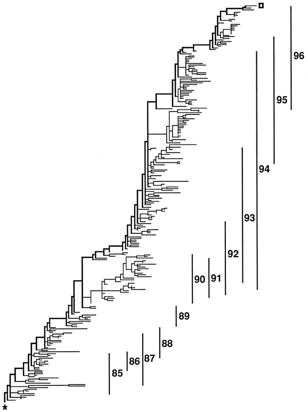


Data



Model

Results
Phylogenetic tree



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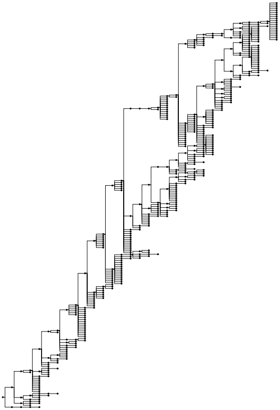
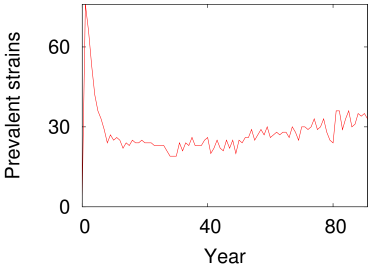


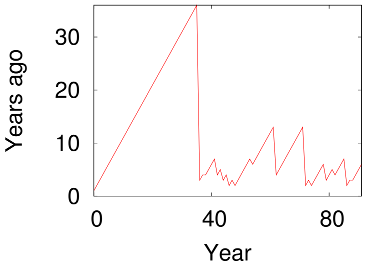
Model

Results

Number and ancestry of strains



Number of prevalent strains in each year



Most recent common ancestor of all prevalent strains

Conclusions

Also without explicit spatial structure
and with a different implementation:
Annual epidemics and ‘slender-trunk’ phylogenetic tree

Necessary conditions:

- Short-lived immunity
- Low-transmission (stochastic) summer period

Robust result . . .

Remarks

- Specific, hybrid model
- Duration of short-lived immunity needed is rather long
- Sensitive to initial conditions; large population size needed
- Import necessary during summer period

Conclusions and Questions
Immune response

Epidemiological dynamics guides evolutionary dynamics . . .

Specificity and *waning* of immune response rather important, both for model behavior and for vaccination:

Data ?!?

- Immune response after re-infection with influenza A?
- After asymptomatic infection (30–50 %)?
- After vaccination?

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Further questions

Interventions and persistence

Immune response governs susceptibility level:

- Implications for R_0 estimation?
- Implications for effectiveness of interventions?

Import needed:

- What makes influenza survive the summer?

Far further questions

Vaccination and evolution

Vaccination poses selection pressure upon virus:

- Directional effects?
- Virulence effects?
- General results possible or not?

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