Vaccinating against influenza A

Jonathan Dushoff

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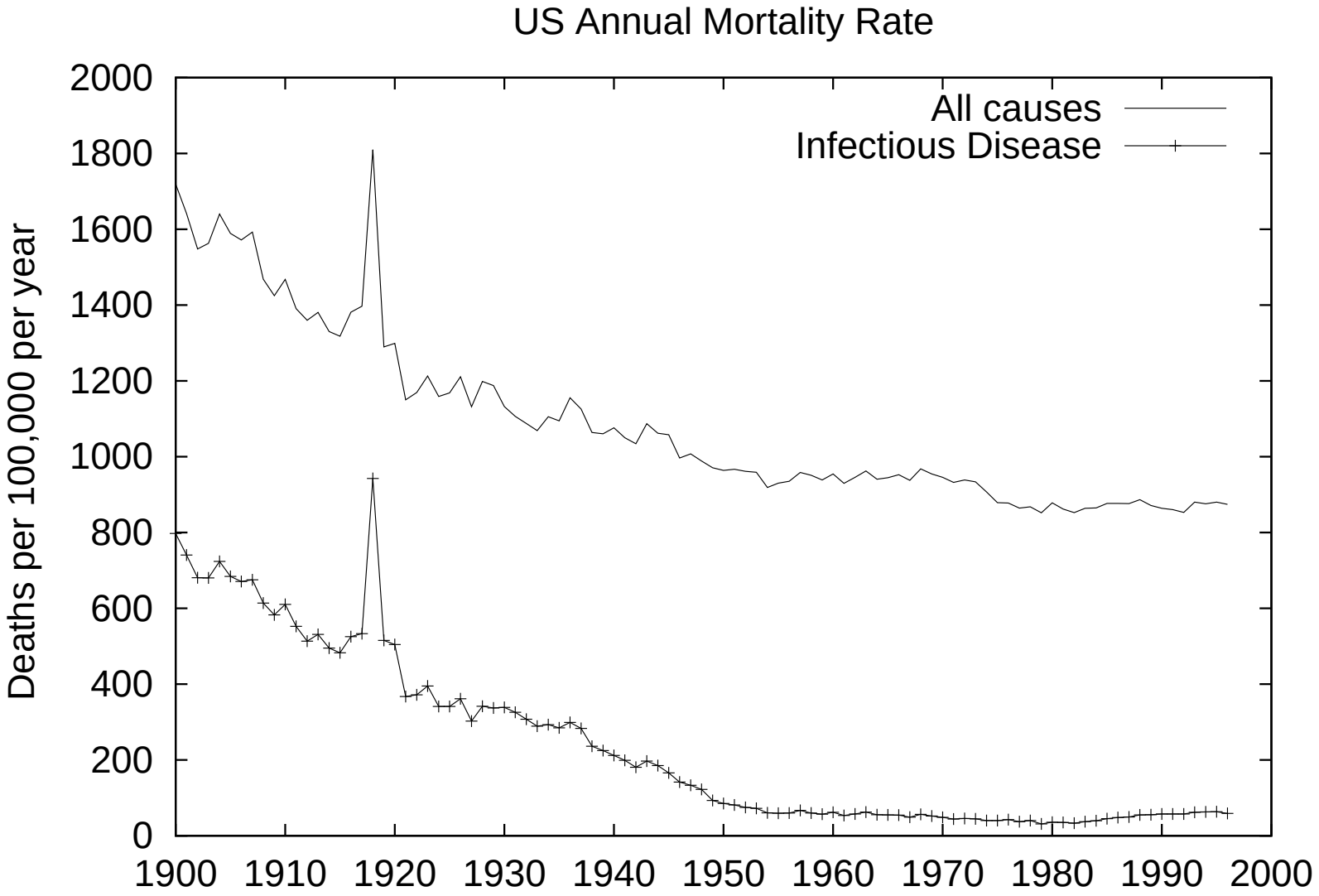
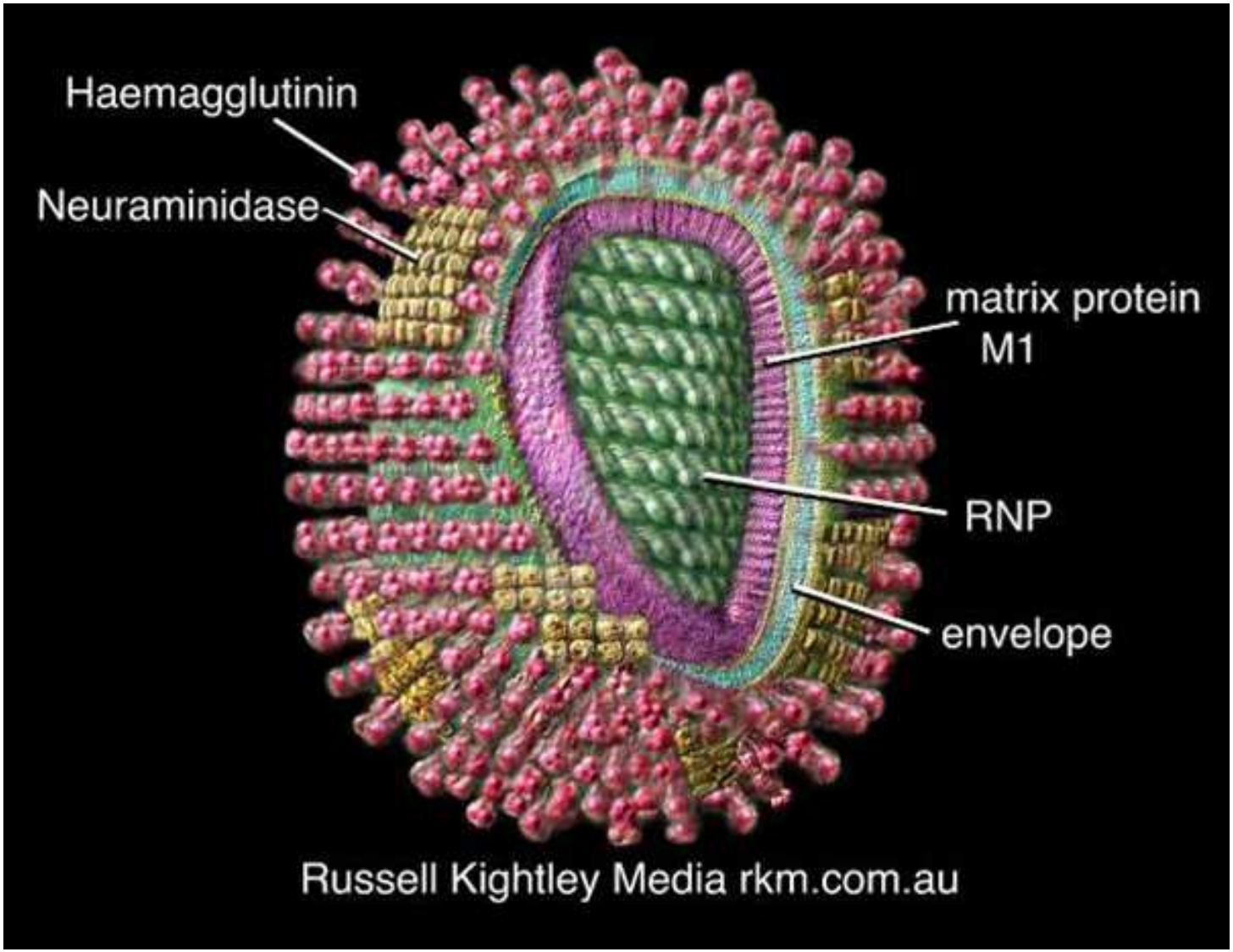

US Annual Mortality Rate
Deaths per 100,000 per year
All causes
Infectious Disease
2000
1800
1600
1400
1200
1000
800
600
400
200
0
1900
1910
1920
1930
1940
1950
1960
1970
1980
1990
2000

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

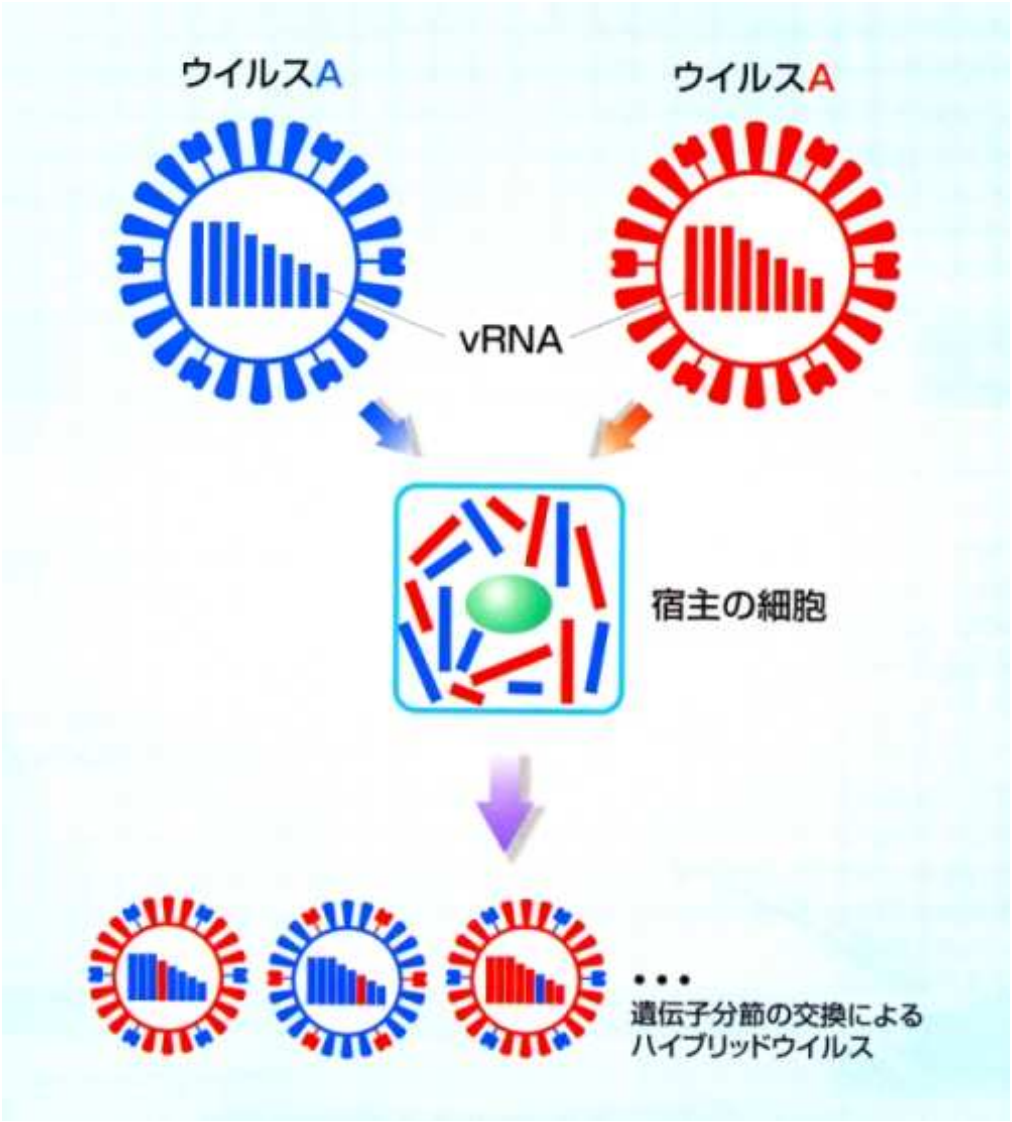


A human host (juvenile)

Shift evolution

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

http://homepage2.nifty.com/yamasaki-clinic/



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.

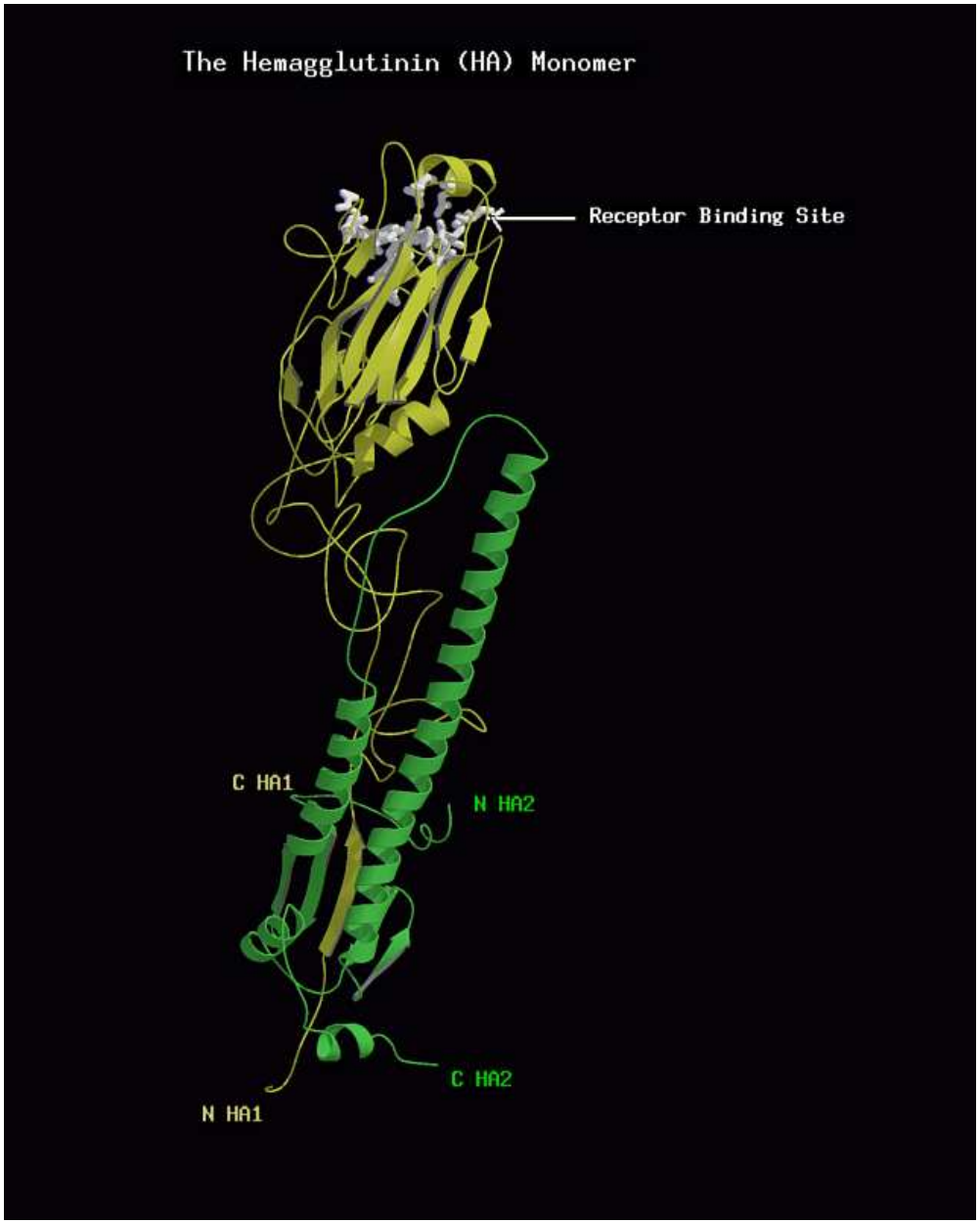
Drift Evolution

- Each influenza subtype undergoes gradual, antigenically significant mutations to HA.

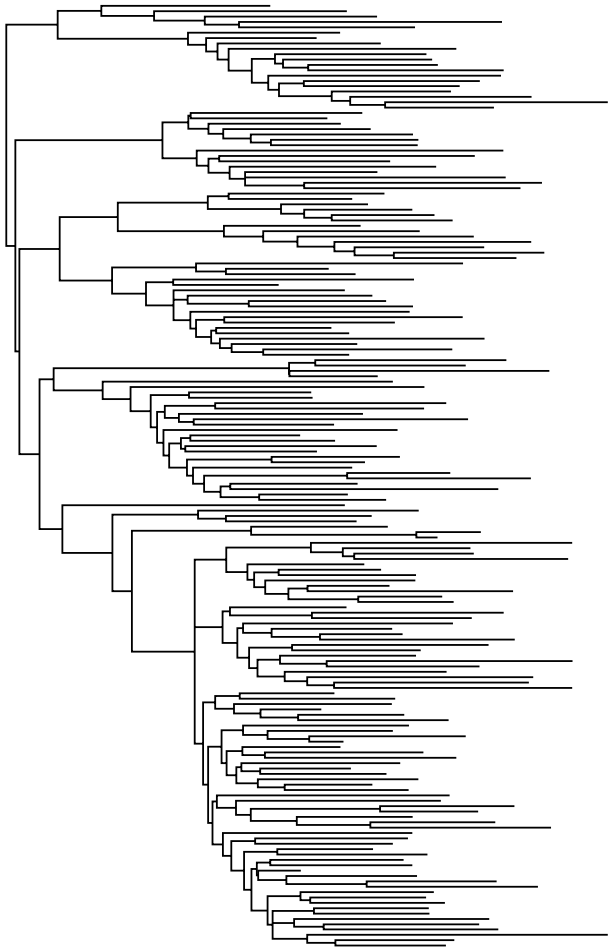
  After a few years, descendants of an infecting 'strain' will have changed enough to re-infect most individuals.

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

- Influenza B viruses show a similar, but less dramatic, pattern.

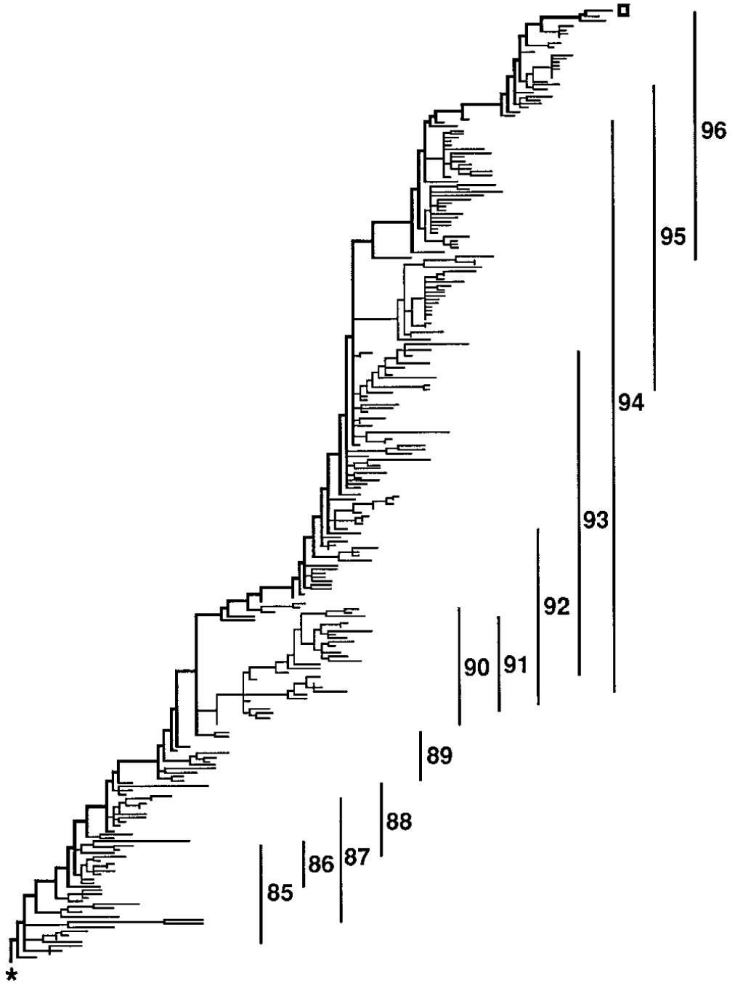

The Hemagglutinin (HA) Monomer
Receptor Binding Site
C HA1
N HA2
C HA2
N HA1

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

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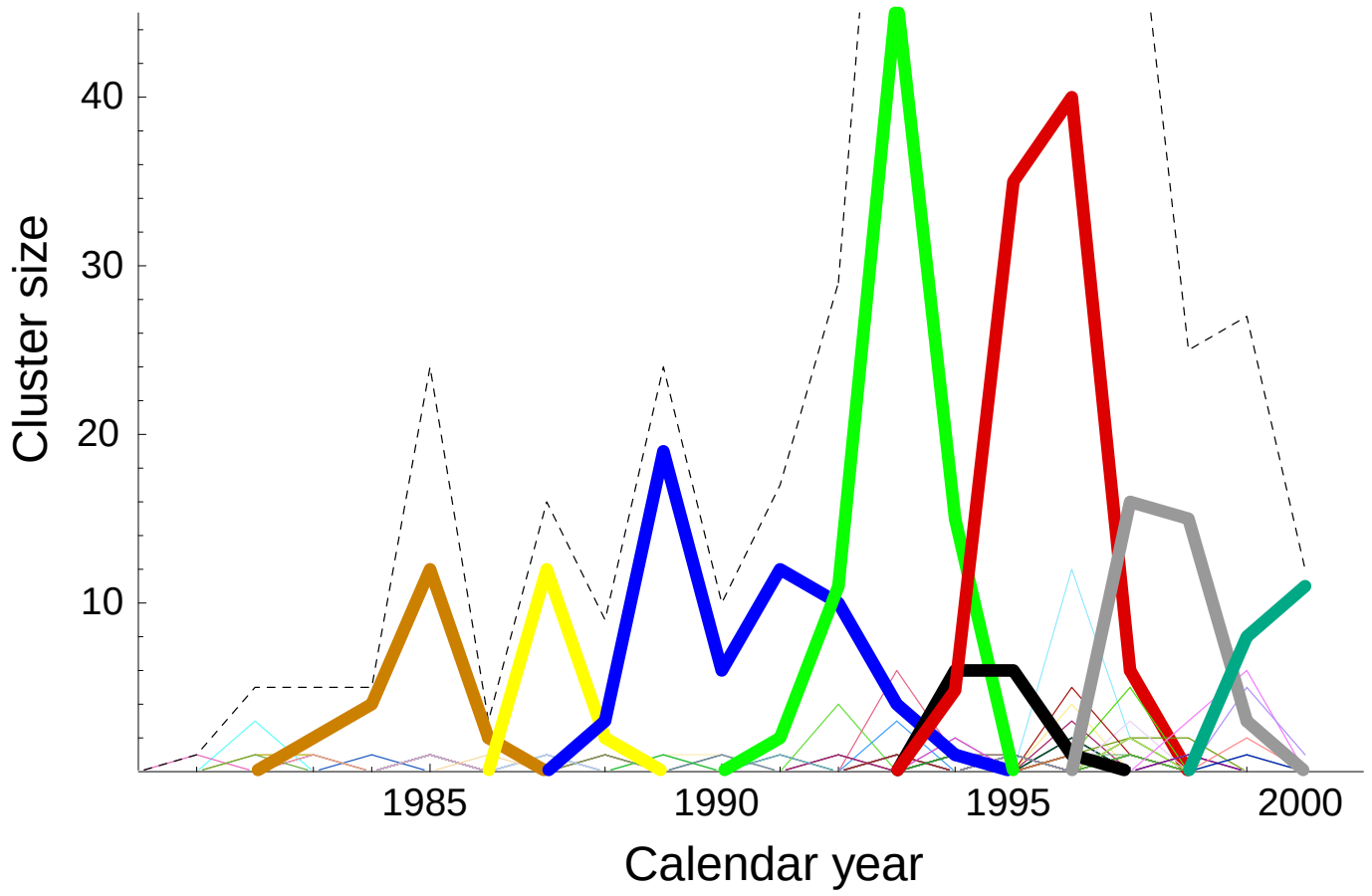
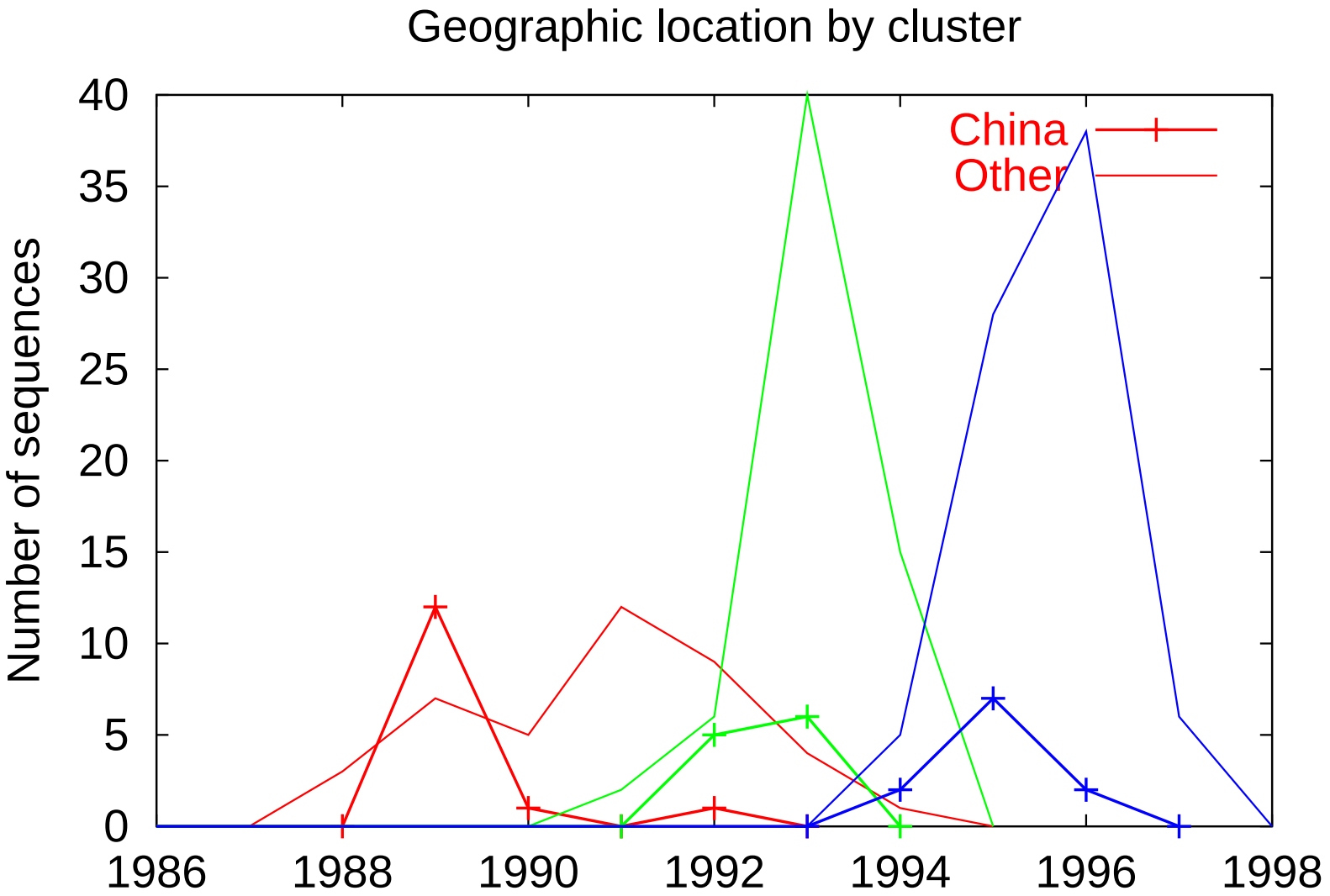
Quasispecies structure and the antigenic evolution of Influenza A

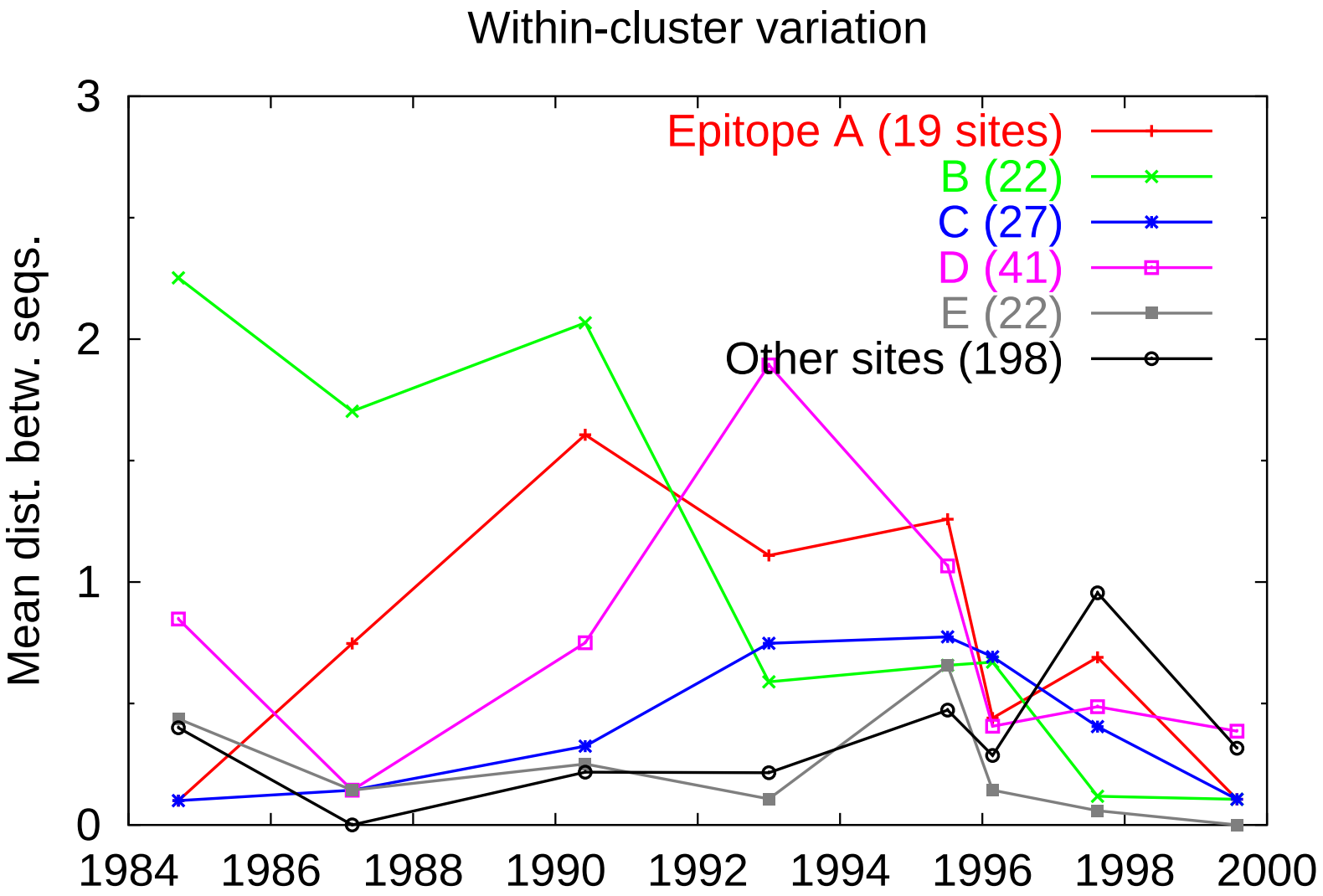
- What do modelers mean by a 'strain'?
- What does strain space look like?
- Do influenza viruses cluster into 'quasispecies'?

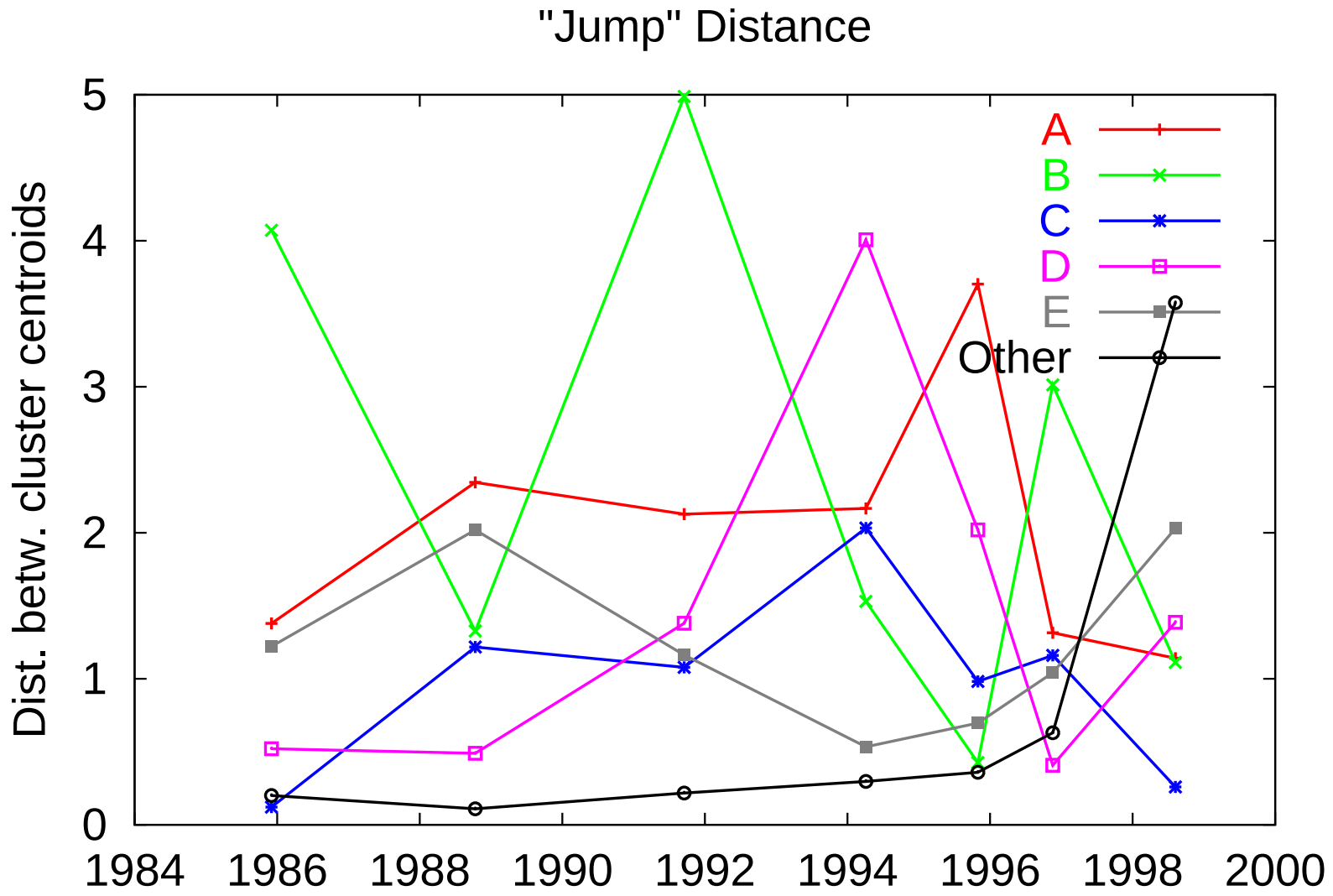

Cluster size
40
30
20
10
1985
1990
1995
2000
Calendar year

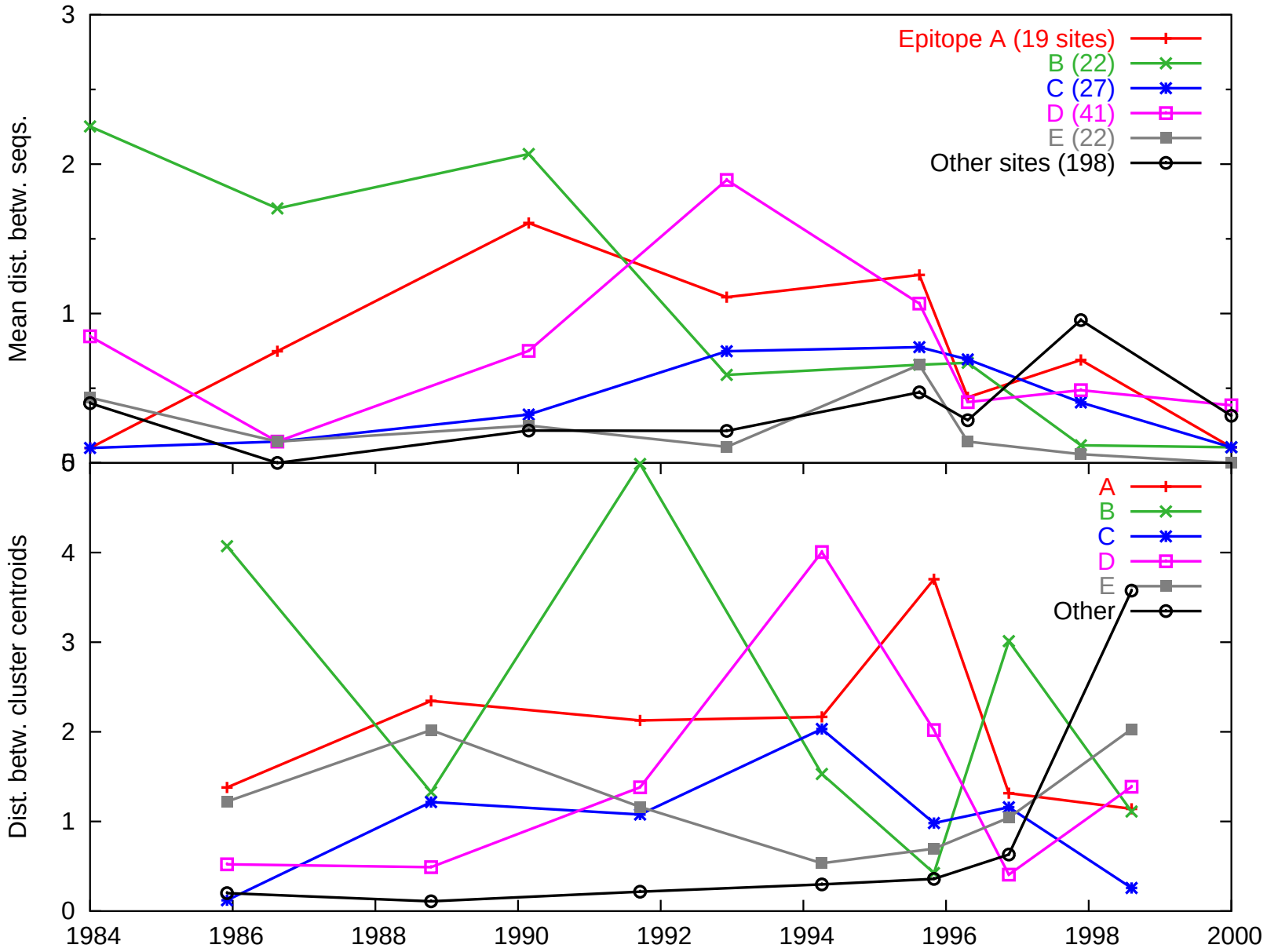
Clusters through time

- 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
40
35
30
25
20
15
10
5
0
1986
1988
1990
1992
1994
1996
1998
China
Other


Within-cluster variation
Mean dist. betw. seqs.
0
1
2
3
1984
1986
1988
1990
1992
1994
1996
1998
2000
Epitope A (19 sites)
B (22)
C (27)
D (41)
E (22)
Other sites (198)


"Jump" Distance
Dist. betw. cluster centroids
0
1
2
3
4
5
1984
1986
1988
1990
1992
1994
1996
1998
2000
A
B
C
D
E
Other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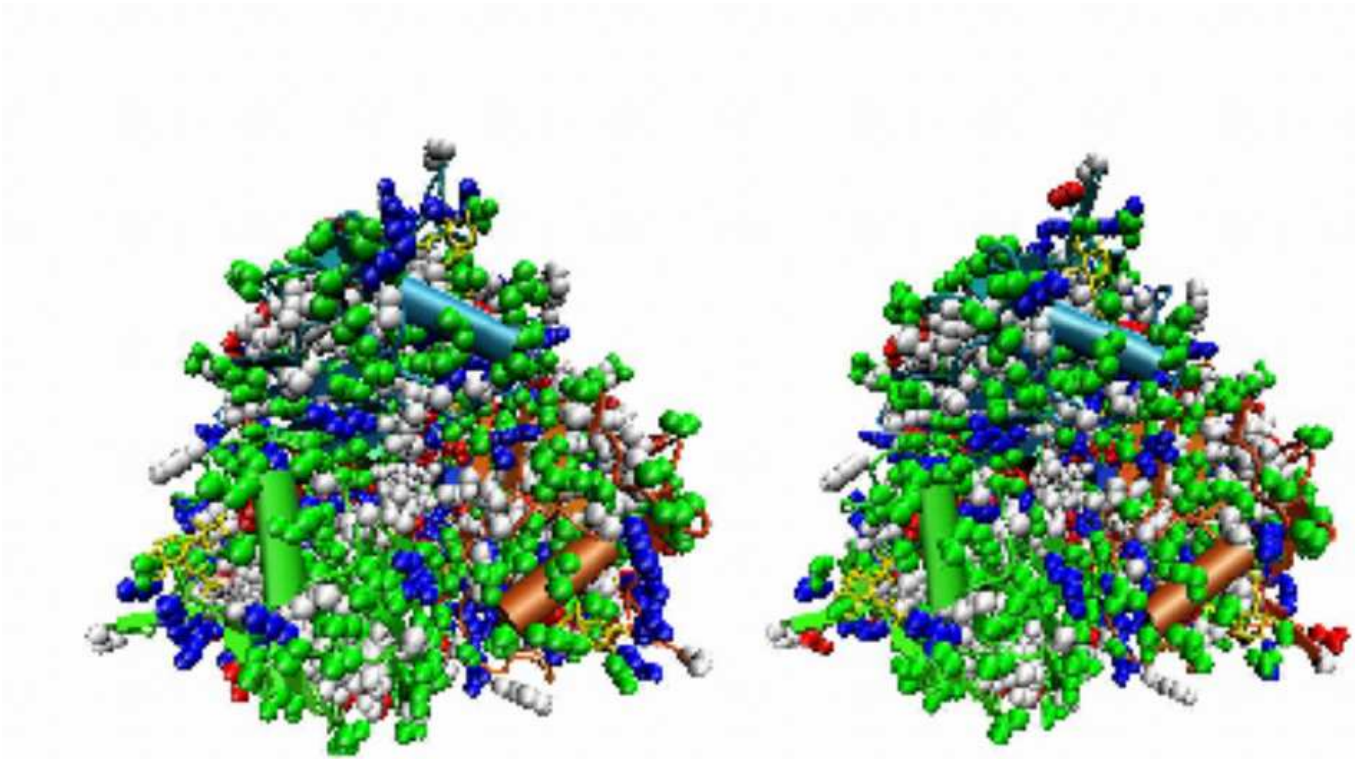
Dist. betw. cluster centroids
A
B
C
D
E
Other
0
1
2
3
4
1984
1986
1988
1990
1992
1994
1996
1998
2000

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
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  - **Whom to vaccinate**
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  - 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 β_c, β_v, p, T (proportion vaccinated).
- Neglected parameters are:

  subpopulation sizes (set equal)

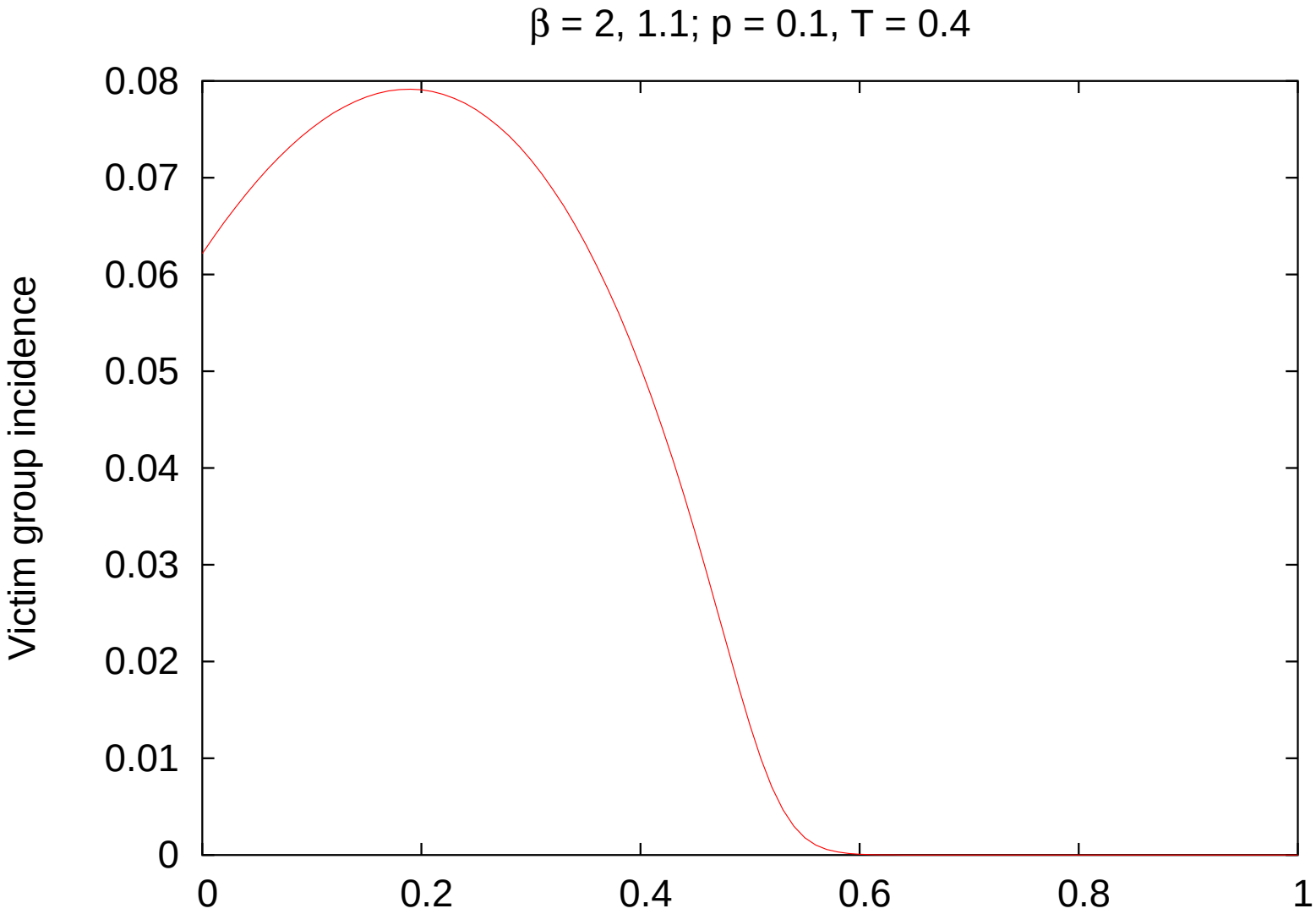
  effectiveness of vaccine against transmission, illness, death (set equal and scaled out)

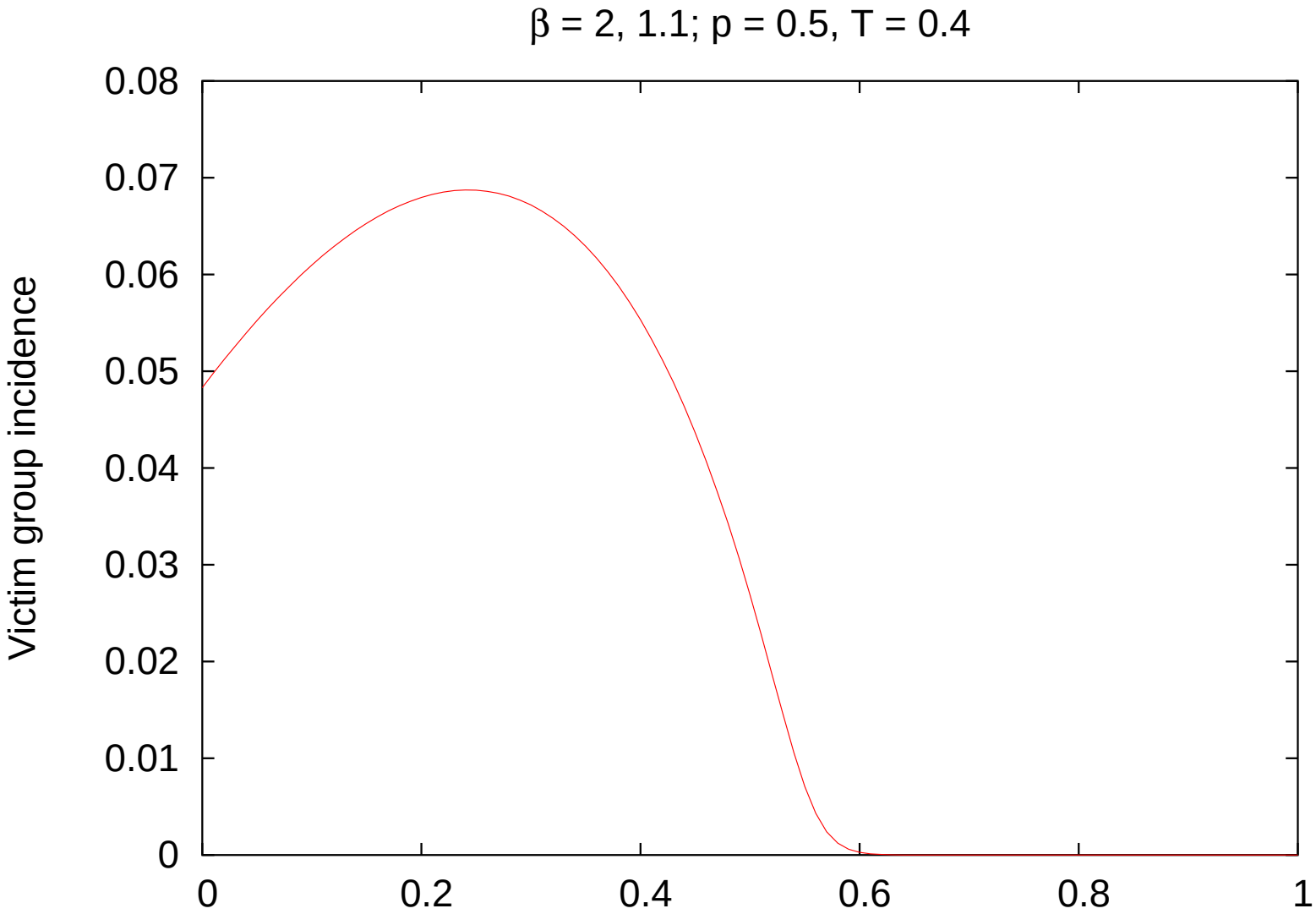
  - Structure of β (assumed that difference is in contact rate, not transmission or susceptibility).

Cartoon model for flu vaccine priorities

Predictions:

- Best to vaccinate victims when βs are similar, core otherwise.
- In well-mixed population, better to vaccinate one group or other.
- In patchy population, maybe an intermediate optimum?


β = 2, 1.1; p = 0.1, T = 0.4
Victim group incidence
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0
0.2
0.4
0.6
0.8
1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0.01
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0.2
0.4
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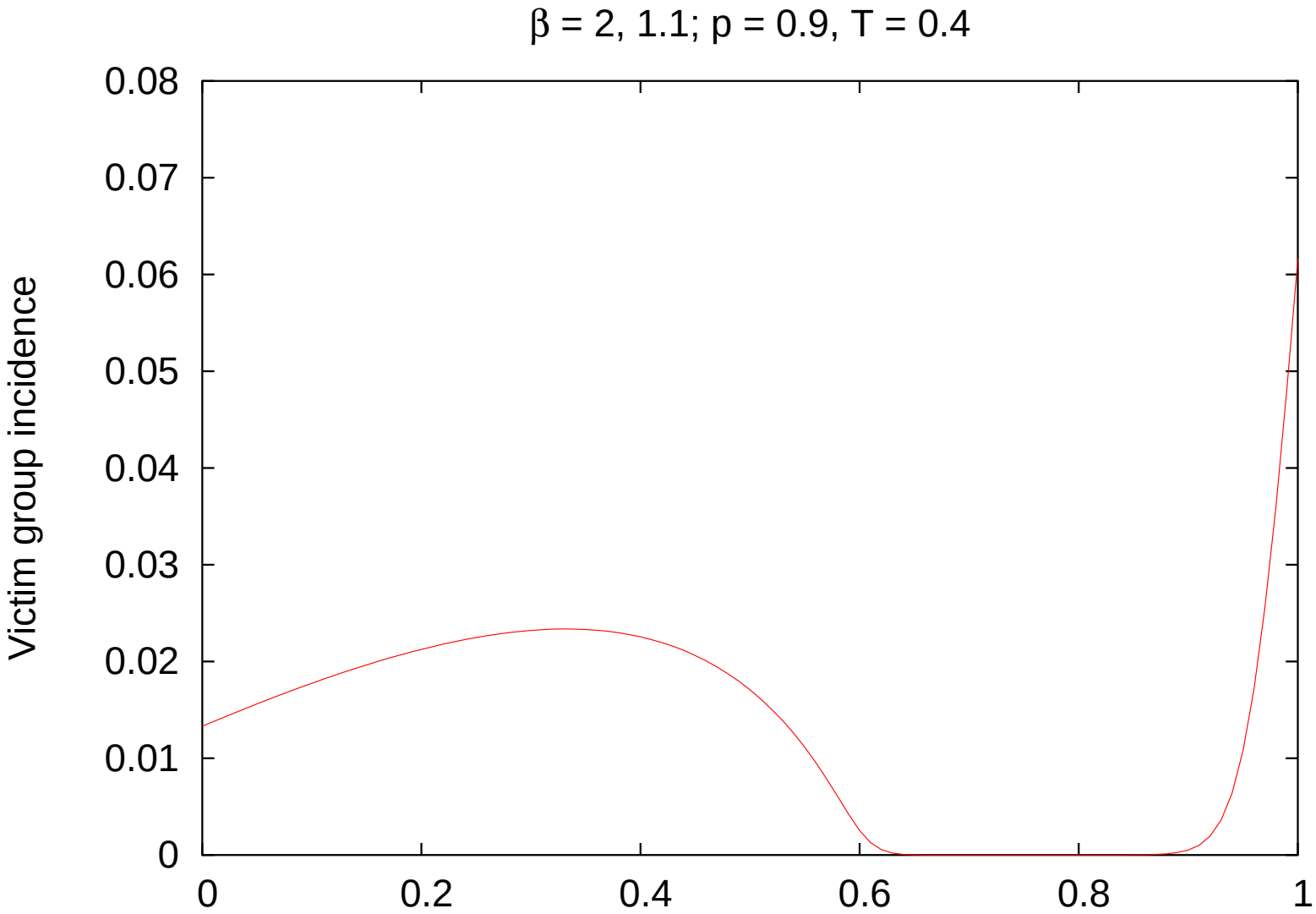
1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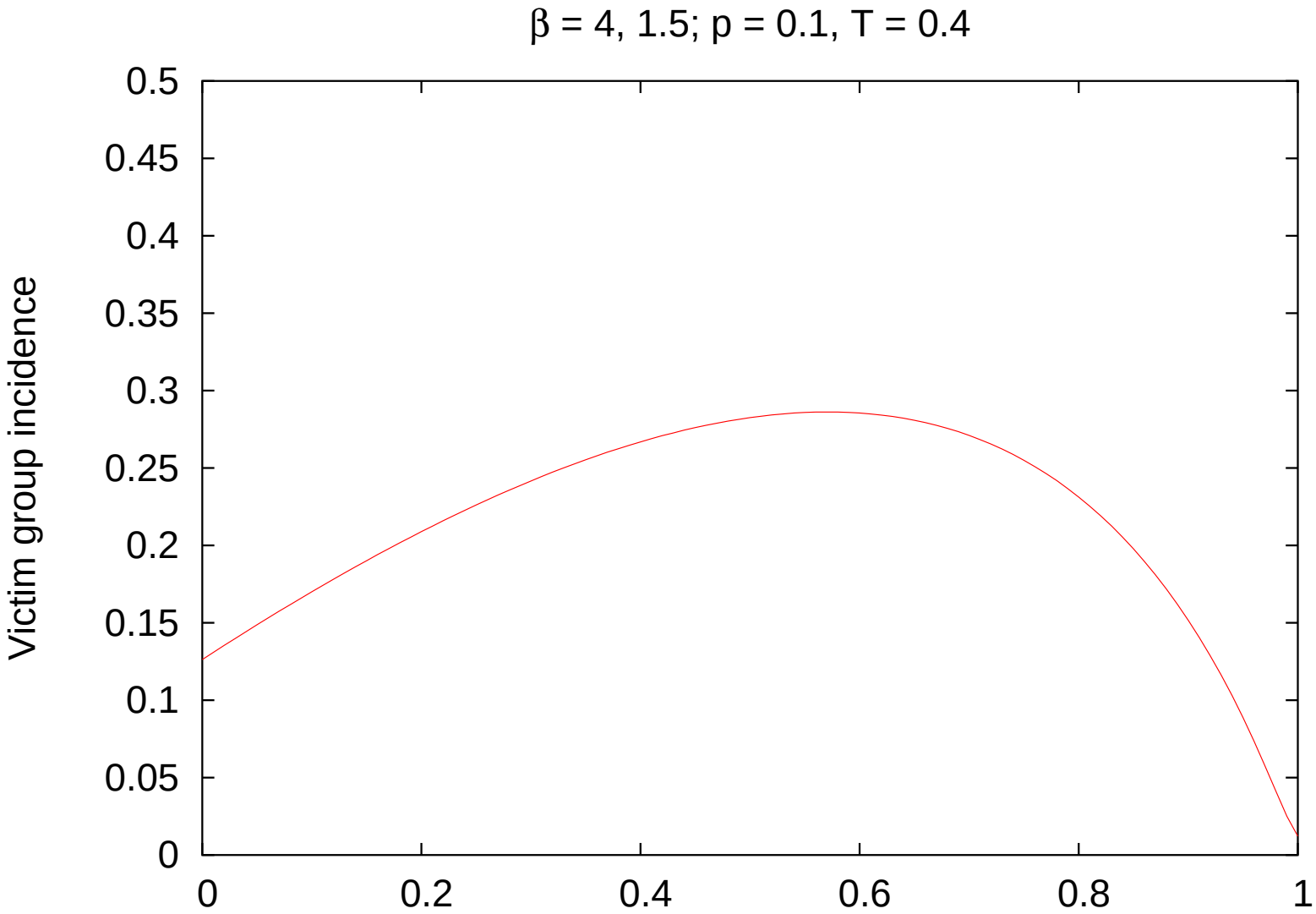
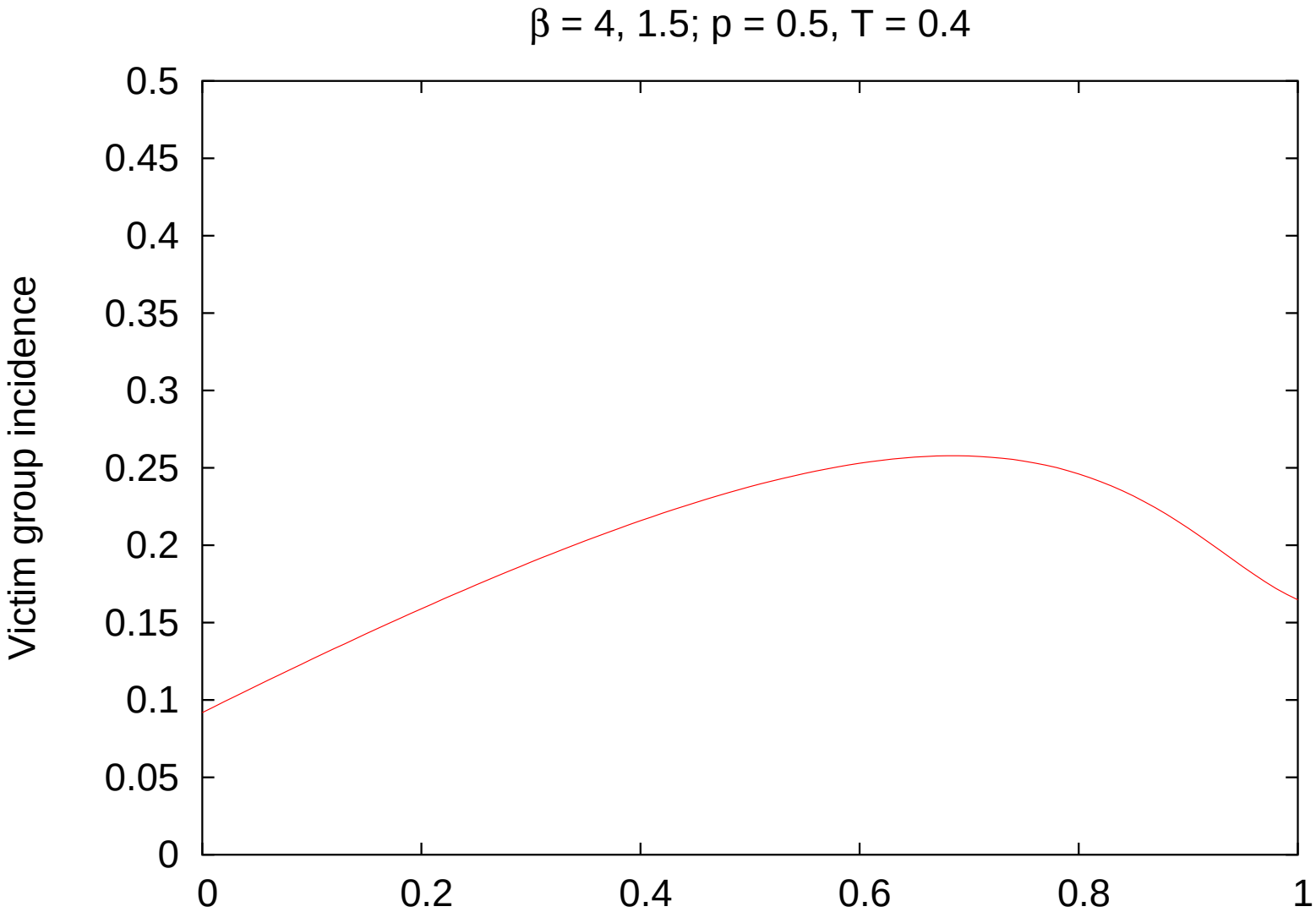
Victim group incidence
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0
0.2
0.4
0.6
0.8
1


β = 4, 1.5; p = 0.1, T = 0.4
Victim group incidence
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
0.2
0.4
0.6
0.8
1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0.35
0.3
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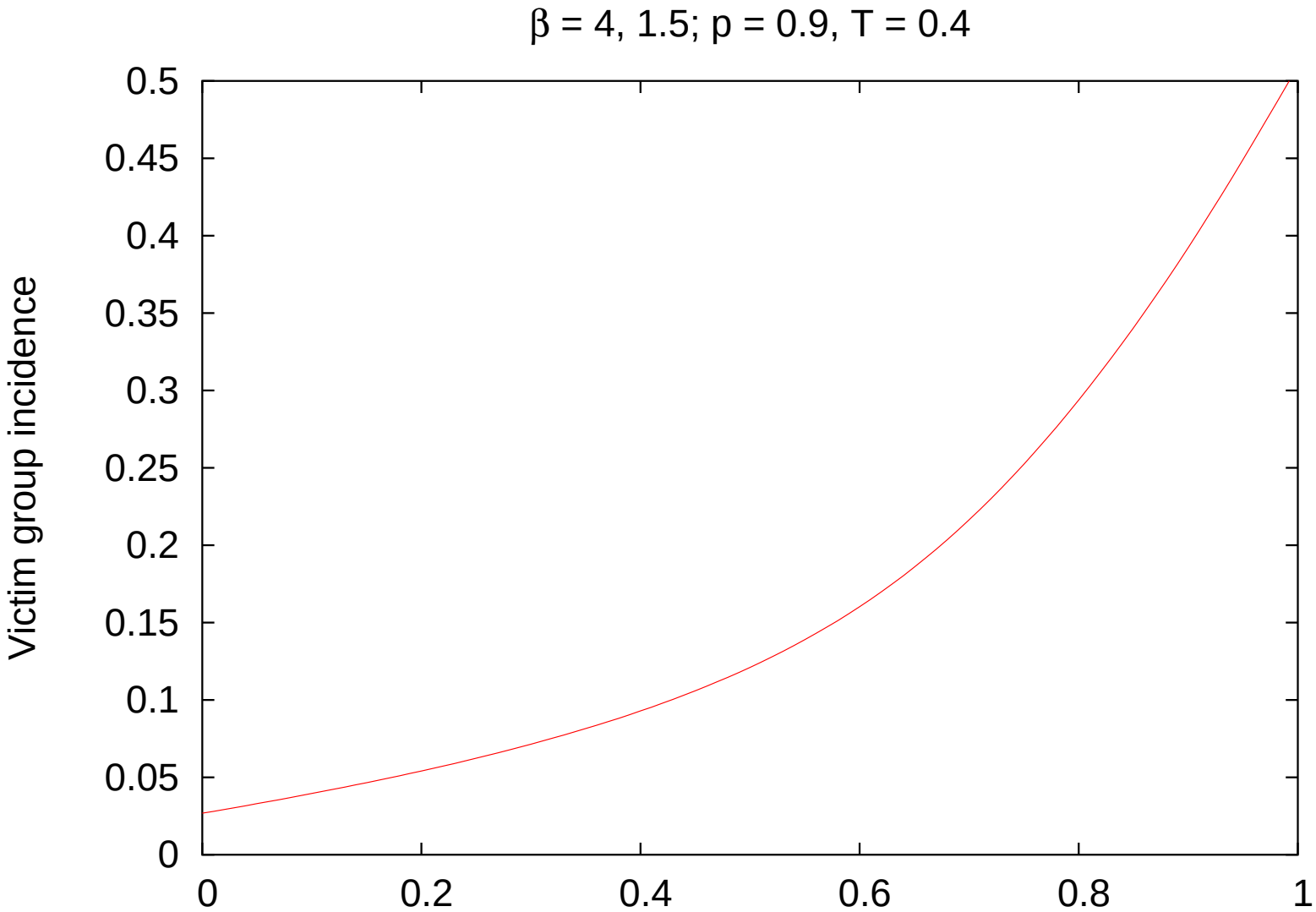
0.2
0.15
0.1
0.05
0
0
0.2
0.4
0.6
0.8
1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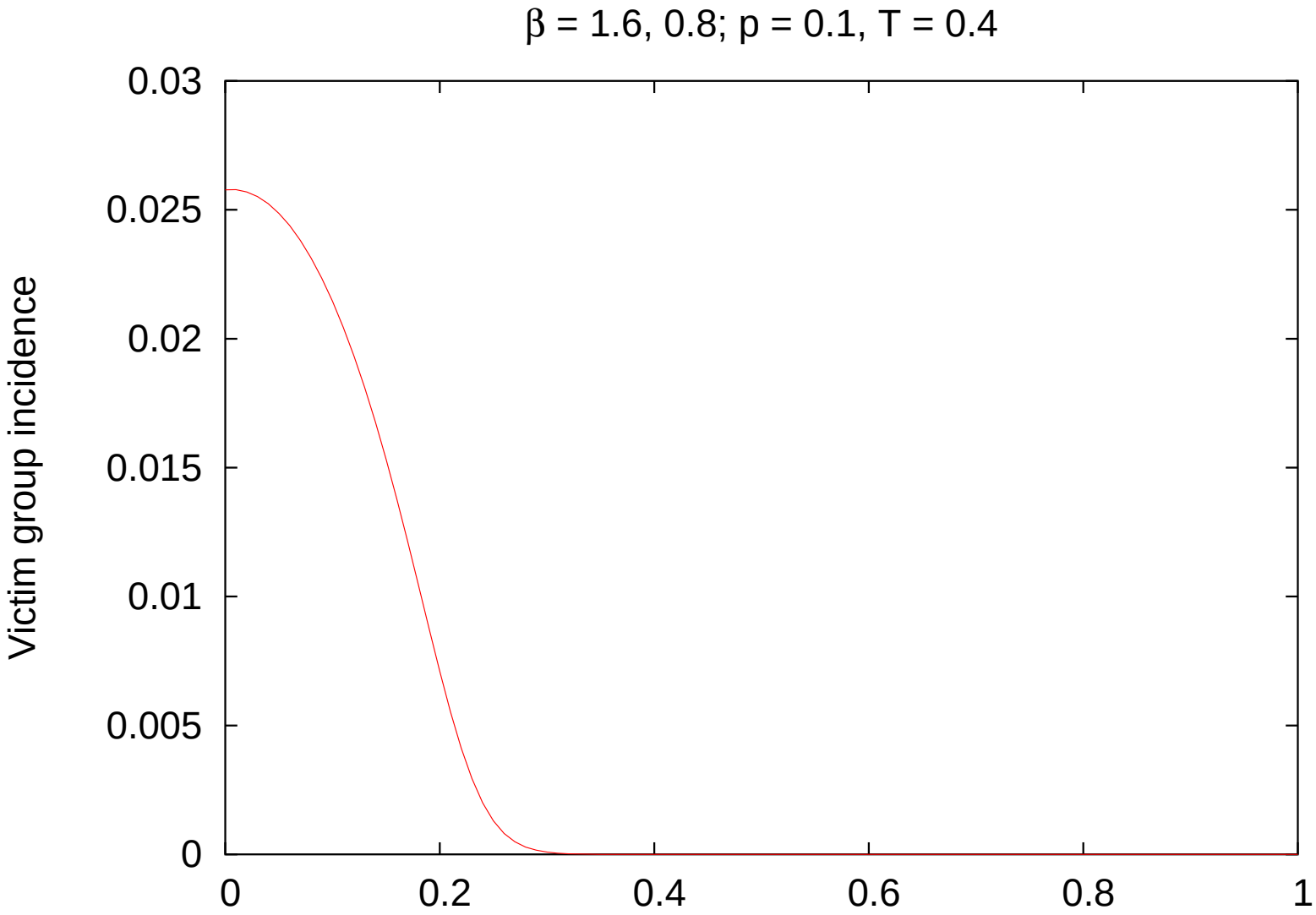
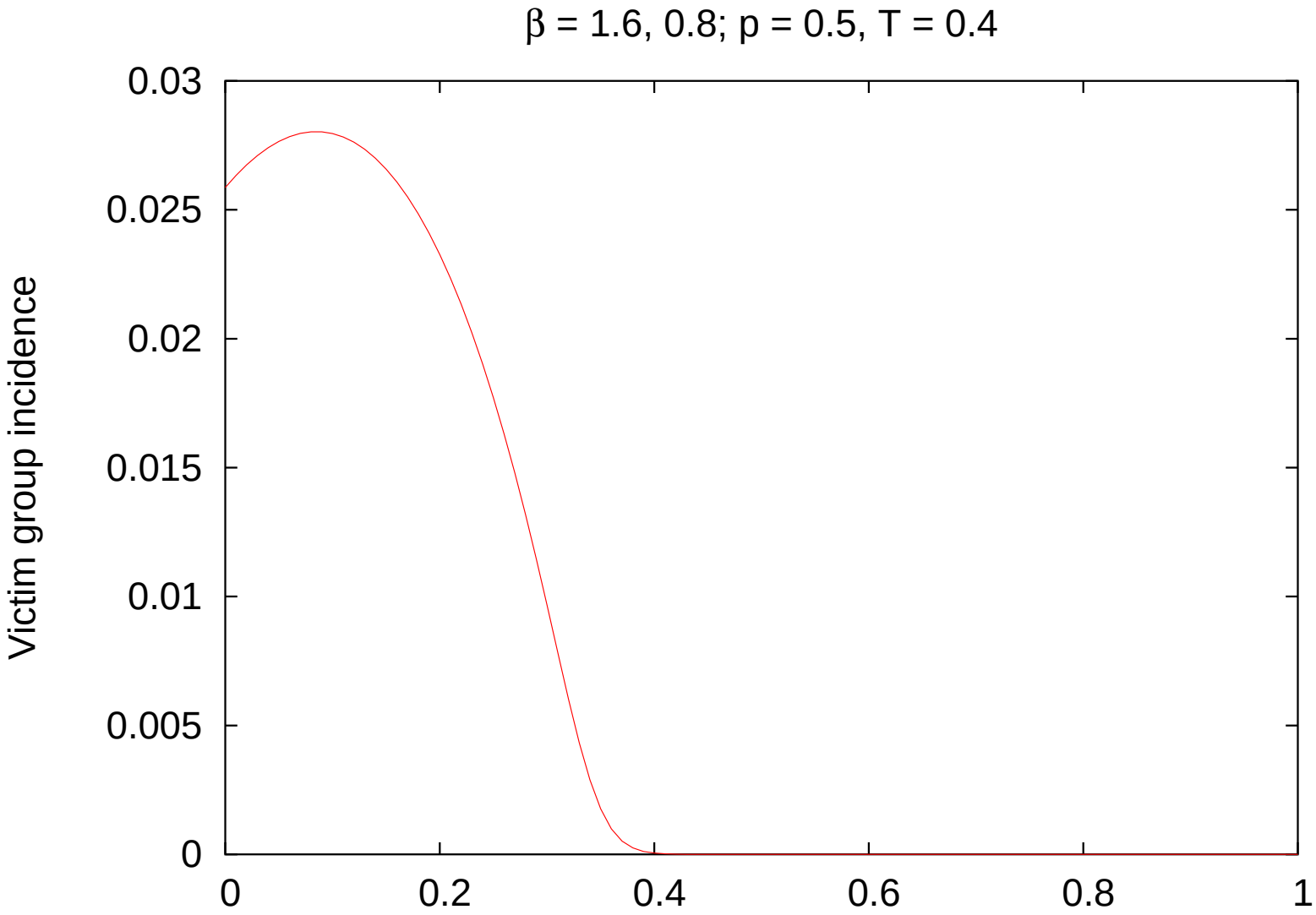
1


β = 1.6, 0.8; p = 0.1, T = 0.4
Victim group incidence
0.03
0.025
0.02
0.015
0.01
0.005
0
0
0.2
0.4
0.6
0.8
1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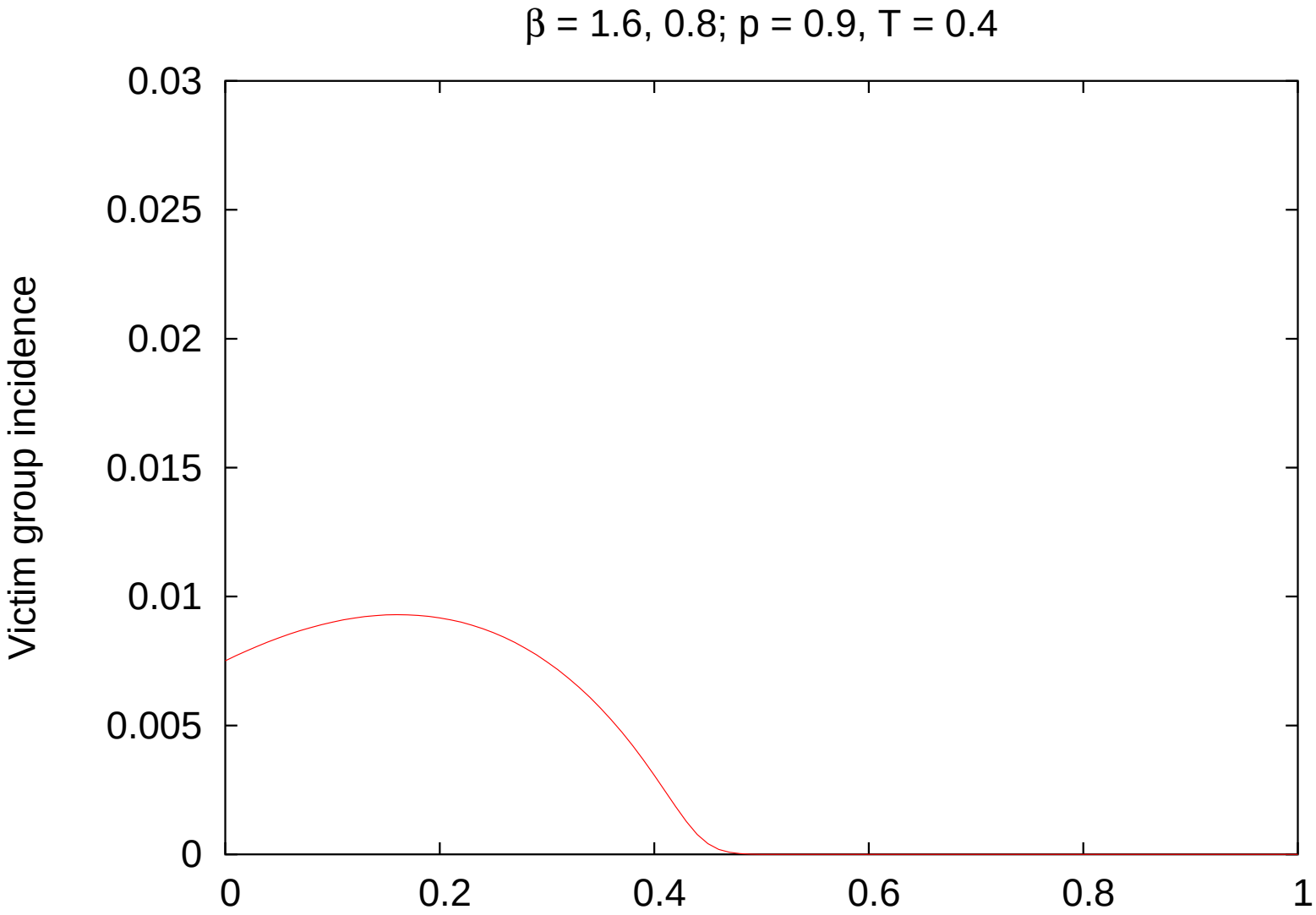
0.025
0.02
0.015
0.01
0.005
0
0
0.2
0.4
0.6
0.8
1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0
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0.8
1

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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- **Shift evolution**
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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!

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  - **Whom to vaccinate**

Facing a pandemic

Can a pandemic be stopped?

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

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 *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.
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- This audience