

The evolution of seasonal influenza strains

Gavin JD Smith

State Key Laboratory of Emerging Infectious Diseases
& Department of Microbiology
The University of Hong Kong



Introduction

- Provide historical perspective
- Recent developments in evolutionary methods & their application to infectious diseases
- Summary of the current state of knowledge



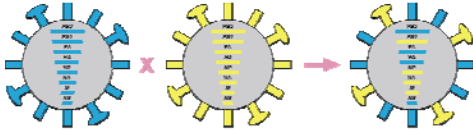
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Influenza A evolutionary strategies

Antigenic drift: mutation

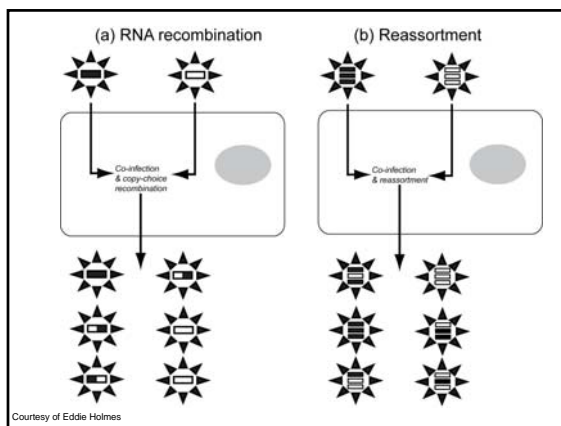


Antigenic shift: reassortment



What is reassortment?

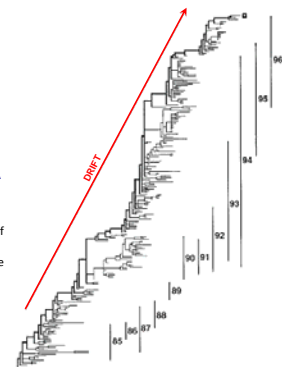
- Term seemingly specific to influenza and its segmented genome
- Occurs frequently and is detectable by phylogenetic analysis
 - variants referred to as “genotypes”



“Pre-genomic” era

- Sequencing labor intensive & expensive
- Concentrated on HA gene
 - Relevant to vaccine strain selection
- In the late 1990’s a series of studies investigated the evolution of the H3-HA
- Key findings included
 - Dramatic visualization of antigenic drift
 - Viral lineages with the greatest number of mutations in positively selected amino acids (AAs) were the progenitors of future seasonal strains
 - AAs under positive selection were associated with antigenic or receptor binding sites

Fitch et al. 1997. PNAS 94:7712–7718
Bush et al. 1999. Science 286:1921–1925
Bush et al. 1999. Mol Biol Evol 16:1457–1465



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"Genomic" era

- Inexpensive (relatively!) high-throughput sequencing
- Full genome sequencing of (initially) mostly avian influenza viruses
- Provides information on drug resistance, host adaptation signatures & reassortment
- Corresponding developments in analytical methodologies
- Development of "phylodynamics"

Reassortment diagram

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Phylodynamics

- Behavior of infectious diseases that arises from the combined effects of evolutionary and ecological processes

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Grenfell et al. 2004. Science 303:327-332

Analytical developments (1)

- Greatly aided by increased computer processing power
- More robust statistical methods available
 - Molecular clocks:** A statistical model that describes the relationship between time & the genetic distance among nucleotide sequences
 - Coalescent theory:** Describes the shape & size of genealogies over time, allowing detection of changes in population diversity over time

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Analytical developments (2)

- Allows us to address key biological questions, such as:
 - When did a newly emergent epidemic begin?
 - From which population/species did it emerge?
 - The order & timing of transmission events & viral adaptations (natural selection)
 - Changes in virus population behavior/diversity following interspecies transmission

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The NIAID Influenza Genome Sequencing Project

<http://www.niaid.nih.gov/dmid/genomes/mcsc/influenza.htm>

<http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html>

- 3410 genomes sequenced to date (from current planned total of 5020)
- Majority are human influenza A virus (1731 H3N2, 831 H1N1)
- Growing data base of avian influenza viruses

Courtesy of Eddie Holmes

NCBI Influenza Virus Resource
Information, Search and Analysis

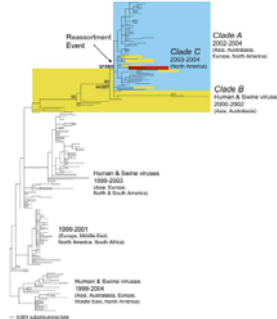
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Current knowledge

A summary of findings from series of studies since 2005

Reassortment of H3N2

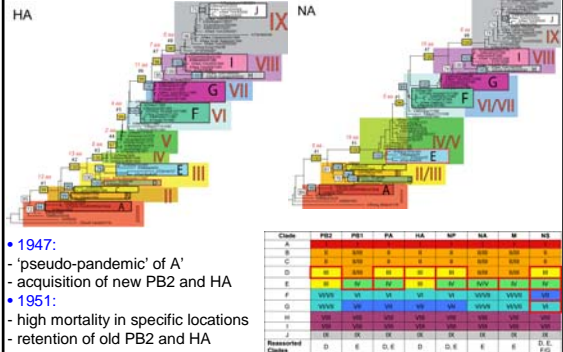
- Phylogenetic analysis of 156 complete genomes of human H3N2 influenza A viruses
- Collected between 1999 and 2004 from New York State
- Demonstrated that multiple lineages of H3N2 can co-circulate, persist, and reassort in epidemiologically significant ways
- Reassortment produced the progenitor of the antigenically variant influenza A/Fujian/411/2002-like epidemic in 2003–2004



Holmes et al. 2005. *PLoS Biol* 3:e300
Nelson et al. 2008. *PLoS Path* 4:e1000012

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Reassortment in A/H1N1 Virus (1918-2007)

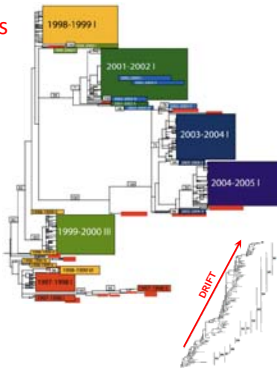


- 1947: 'pseudo-pandemic' of A'
- acquisition of new PB2 and HA
- 1951: high mortality in specific locations
- retention of old PB2 and HA

Courtesy of Eddie Holmes

Single location epidemics

- Dated phylogenetic analysis of 413 complete genomes of human H3N2 influenza A viruses
- Collected between 1997 and 2004 from New York State
- Showed viral evolution within a single epidemic season in a single location is dominated by the random importation of genetically different viral strains from other geographic areas (e.g. the yellow boxes)
- Contrasts with antigenic drift model seen when viruses are studied over years from multiple locations & years



Nelson et al. 2006. *PLoS Path* 2:e125

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Country-wide epidemics

- Genetic Diversity of A/H1N1 in the 2006-7 Season
- Multiple introductions, no cross-season persistence, no spatial structure
- Little persistence of viral lineages between seasons (i.e. influenza is not latent in the summer off-season)

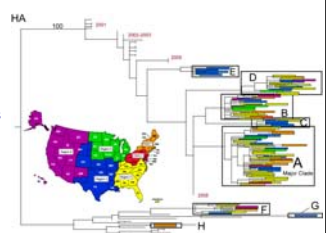


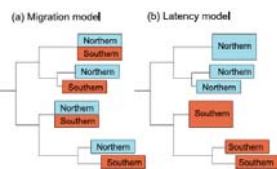
Figure 3

Nelson et al. 2008. *PLoS Path* 4:e1000133

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Global migration

- Dated phylogenetic analysis of 487 complete genomes of human H3N2 influenza A viruses
- Collected between 1999 and 2005 from Australia & New Zealand (plus NY)
- Rejected latency model for influenza epidemics
- Showed global viral migration (with no clear directional pattern) contributes significantly to the seasonal emergence of influenza A epidemics
- Highlighted the need for sampling from tropical regions and during non-epidemic periods

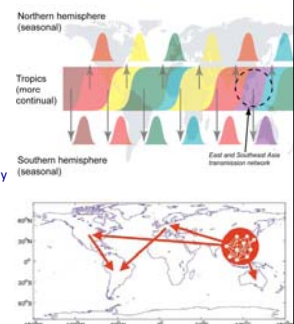


Nelson et al. 2007. *PLoS Path* 3:131

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The source-sink model

- New lineages are seeded from a persistent influenza reservoir hypothesized to be in the tropics
- Russell *et al.* showed continuous circulation in east and Southeast Asia via a region-wide network of temporally overlapping epidemics
- Epidemics in the temperate regions were seeded from this network each year
- Rambaut *et al.* showed complex interplay between frequent reassortment and periodic selective sweeps of H3N2



Rambaut et al. 2008. *Nature* 453:615–619
Russell et al. 2008. *Science* 320:340–346

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Global aviation network



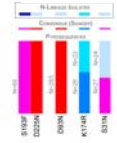
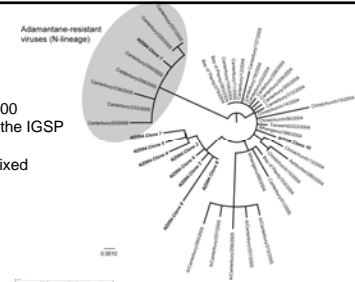
10 25000 19
Russell et al. 2008. Science 320:340-346

How Frequent is Mixed Infection in Influenza Virus?

- Examined trace files of ~3000 sequences generated under the IGSP
- ~3% contain evidence of mixed infection

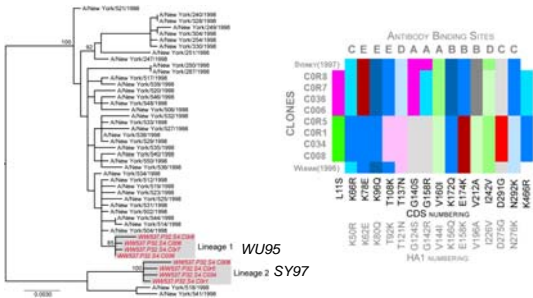
Mixed infections of:

- Influenza A and influenza B virus
- H1N1 and H3N2, including those that differ in adamantane resistance status and those that are antigenically distinct



Courtesy of Eddie Holmes

Antigenic Variation within a Single Individual



Courtesy of Eddie Holmes

Future challenges

- "The explosion in viral genomic data is outpacing our ability to develop methods that fully exploit the potential of these data"
 - Pybus & Rambaut 2009. Nat Rev Gen 10:540-550
- New generation sequencing methodologies (e.g. 454, Solexa) will exacerbate this problem

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Options for the Control of Influenza VII

A major international event held every three years

3-7 September, 2010
Hong Kong SAR, China

Dr. Malik Peiris
Conference Chair
Professor
Department of Microbiology
The University of Hong Kong
Hong Kong SAR, China
and
Scientific Director
H&J-Factor Research Center
Hong Kong SAR, China

Dr. Yi Guan
Conference Scientific Chair
Director
State Key Laboratory of
Emerging Infectious
Diseases, Department
of Microbiology
The University of Hong Kong
Hong Kong SAR, China

for more information, please visit
www.controlinfluenza.com