

Strain replacement following vaccination: the example of pneumococcus

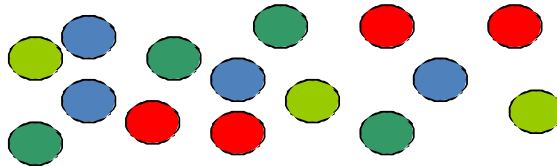
Dan Weinberger
Fogarty International Center, National Institutes of Health
Bethesda, MD, USA

In collaboration with Marc Lipsitch (Harvard) and Krzysztof Trzcinski (UMC Utrecht)

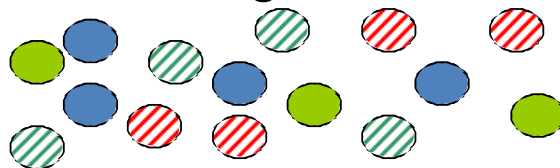


Strain replacement following vaccination

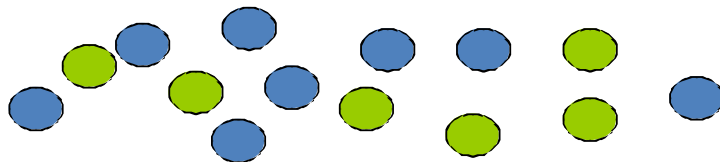
- Pathogens with multiple antigenic types



- Some vaccines target subset of the types



- Non-vaccine strains can “replace” vaccine strains

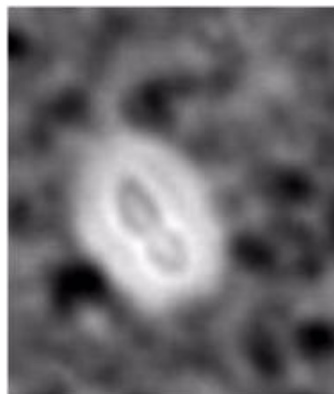


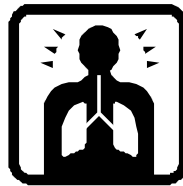
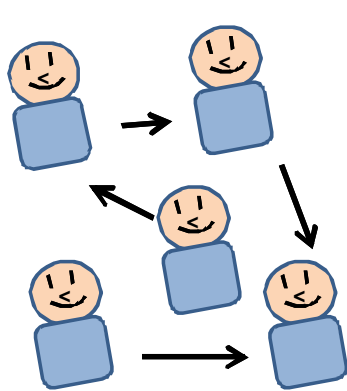
Outline

- Strain replacement in **pneumococcus**
 - Ecology, vaccine impacts
- Implications for HPV

Pneumococcus

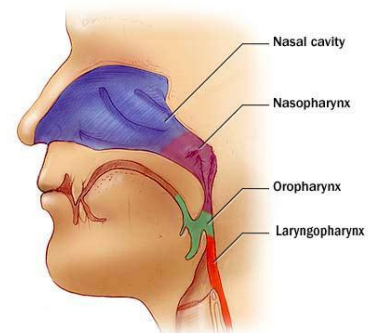
- Gram-positive bacterium
- Pneumonia, meningitis, septicemia, otitis media, conjunctivitis
- Capsule polysaccharide defines **92+ serotypes**



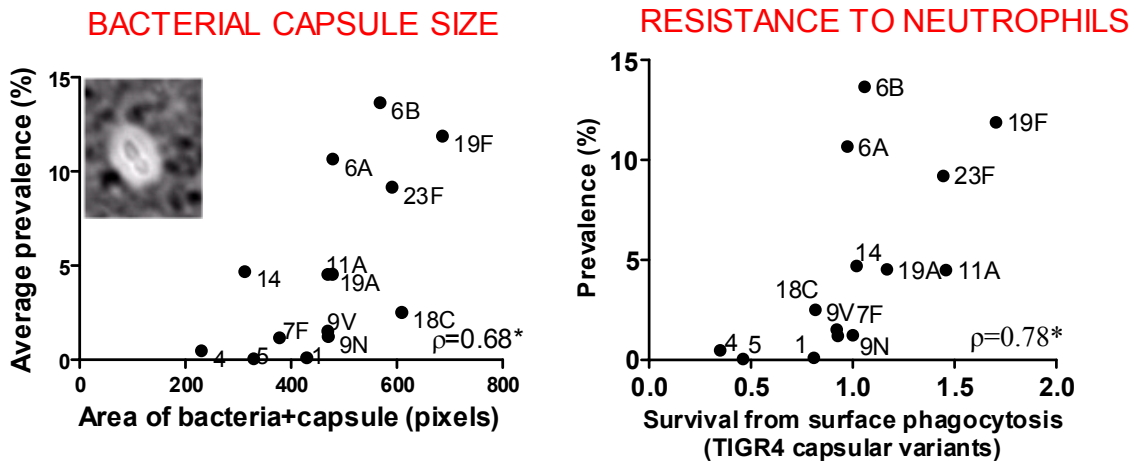


Carriage and ecology

- Required for transmission, precedes disease
- 2-8 week duration
- Many strains and species

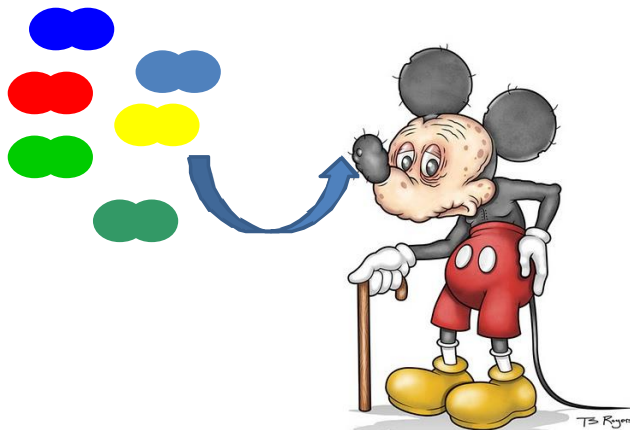


Why are some serotypes more prevalent in carriage?



Prevalence/competition is related to the **biological properties of each serotype

Why are some serotypes more common in carriage?

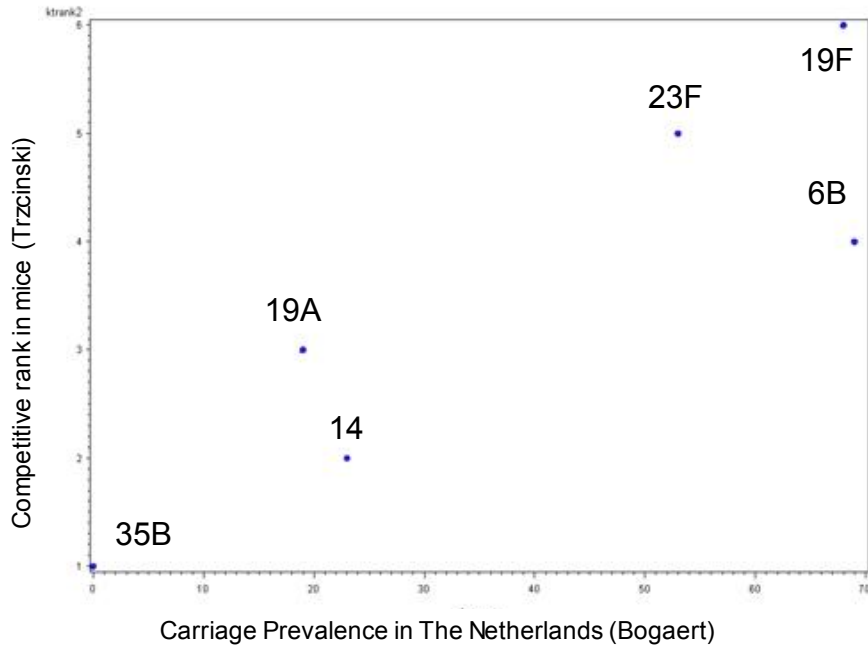


Teassare Illustration and Design

- Successively remove top competitor, see which serotype wins
- Strains are identical except for surface polysaccharides

19F > 23F > 6B > 19A > 14 > 35B

More competitive serotypes are more prevalent in humans

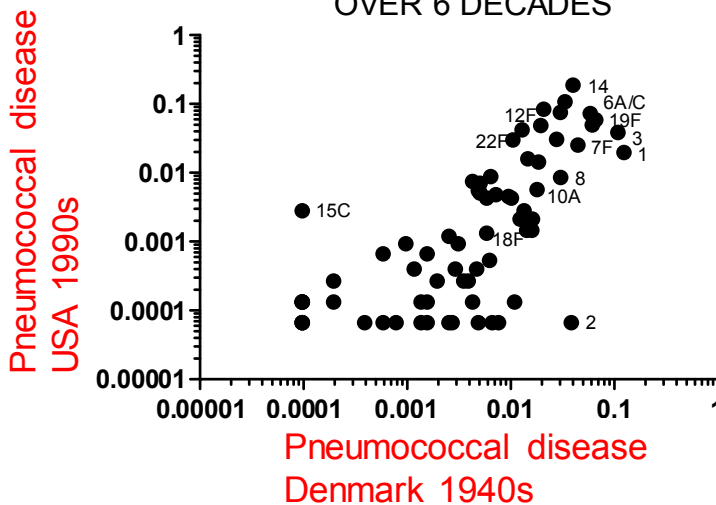


K. Trzcinski, unpublished

Stable hierarchy in disease



STABLE HIERARCHY IN DISEASE
OVER 6 DECADES



USA data from CDC, Danish data from Morch

Summary of pneumococcal ecology

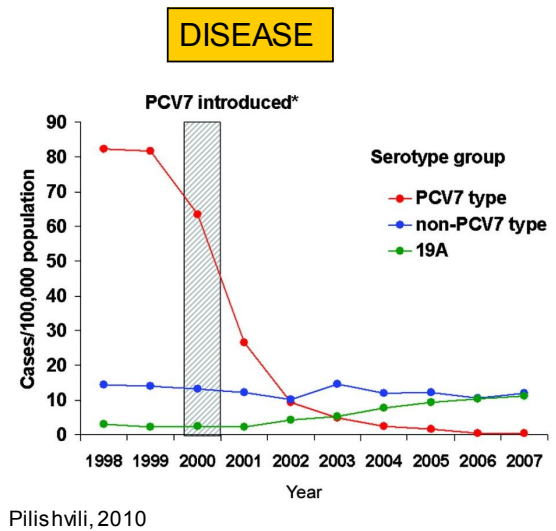
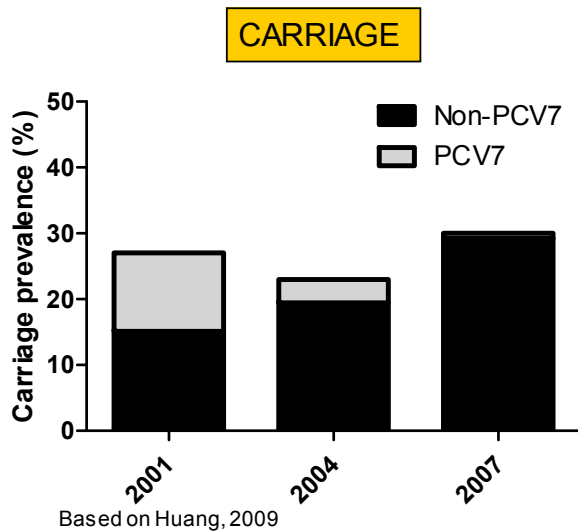
- Active competition between serotypes
- Biological properties of serotype determine competition
- Stable patterns in carriage and disease

Disrupting the pattern: vaccination



- Antibodies against 7, 10, or 13 serotypes
- Affects carriage and disease
- Herd-immunity benefits the unvaccinated elderly
- Ecological hole for remaining 80+ serotypes

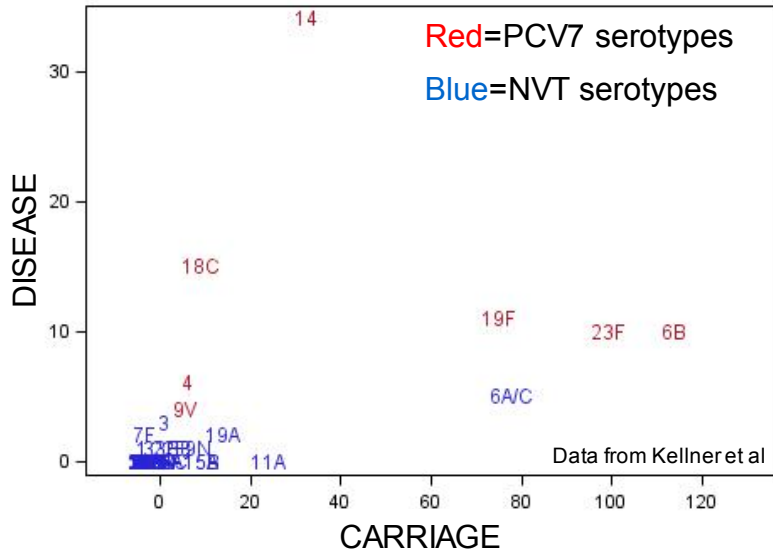
Disrupting the pattern: vaccination



Complete replacement in carriage but not in disease
New equilibrium with 5-7 years

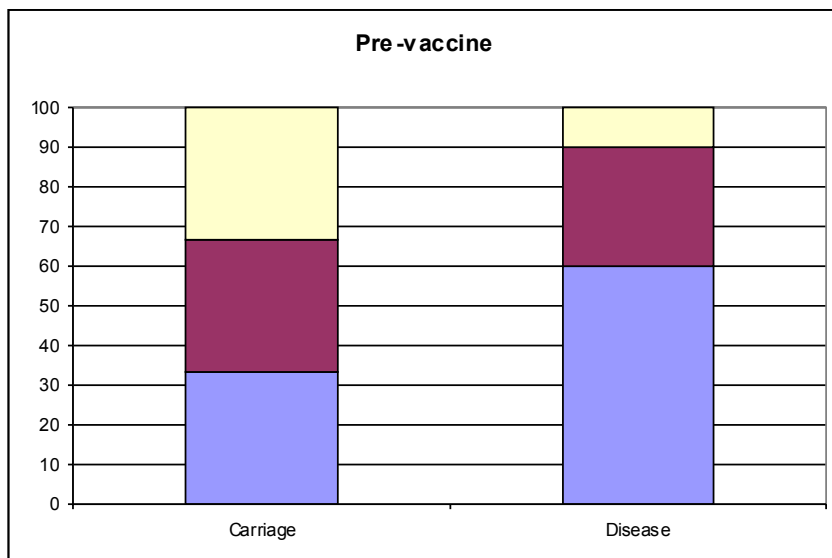
Why does 'replacement' have a different impact on carriage and disease?

“Invasiveness”

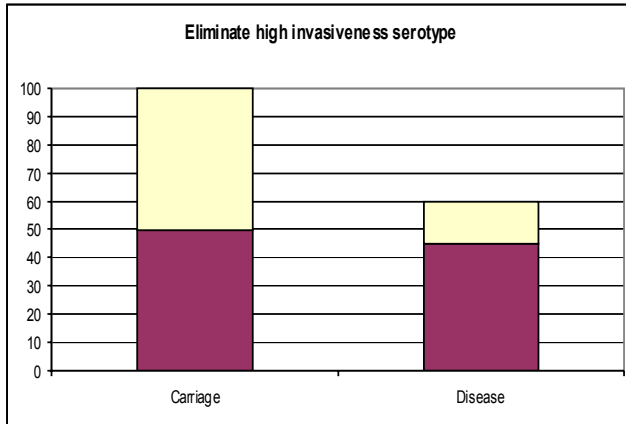


- Pediatric case/carrier ratio is **stable**

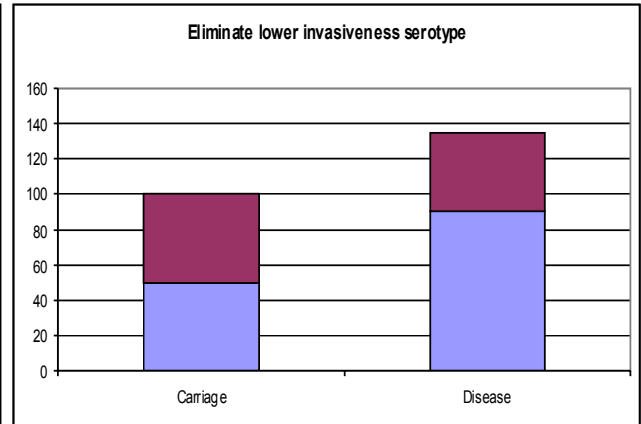
Implications for vaccination: A simplified example:



A simplified example:



Example: serotype 14

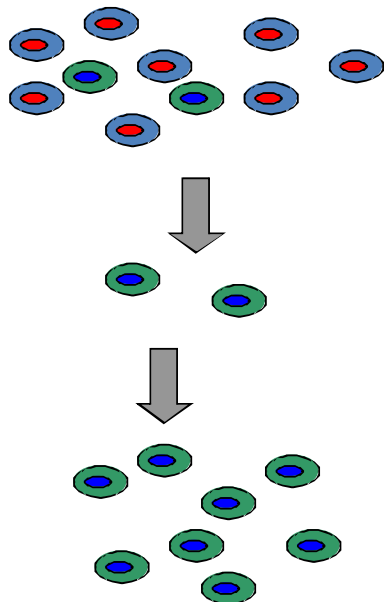


Example: serotype 6B

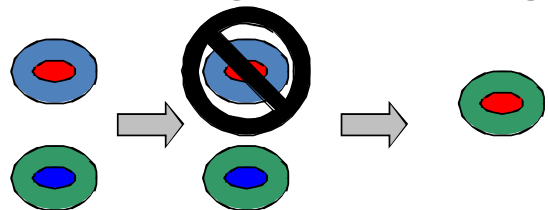
- Targeting high prevalence, low invasiveness serotypes might result in more serotype replacement

Mechanisms for pneumococcal serotype replacement

Expansion of existing clones

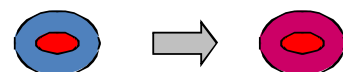


Antigenic switching



Red strain "acquires" the green capsule biosynthesis cassette

Mutation



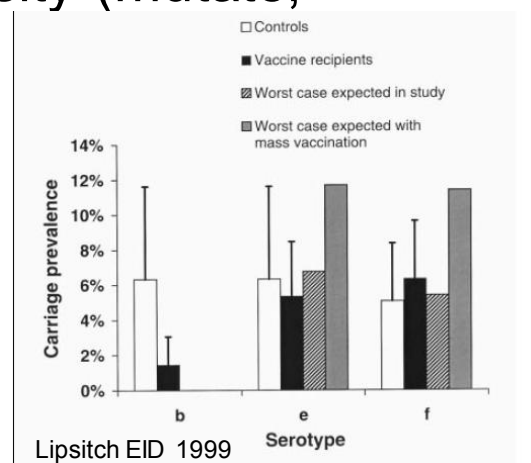
Point mutation or deletion in the biosynthesis cassette

Summary of pneumococcal serotype replacement

- Competition among serotypes
- Stable patterns before vaccination
- Complete serotype replacement in carriage, incomplete in disease
- Invasiveness of remaining strains is critical

Characteristics that promote replacement

- Competition
 - Immune mediated
 - Saturation of host targets
- Ability to generate diversity (mutate, recombine)
- High vaccine coverage



Comparing HPV and pneumococcus

PNEUMOCOCCUS

Respiratory transmission

Active competition among all strains and between species

Serotypes vary in likelihood of invasion given carriage

HPV

Sexual transmission

Possibly competition among some subtypes

Subtypes vary in likelihood of causing Severe outcomes

Does strain replacement matter?

- Does replacement occur?
 - Does prevalence of carriage change?
- Are the replacing strains as virulent?
- What level of strain replacement is acceptable?

Acknowledgements

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