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Departments of Biology and Entomology
www.thereadgroup.net

EEID-NSF-NIH-USDA
R01 GM105244 (PI: Read)
BBSCR (PI: Nair)
RAPIDD Fogarty

Can vaccines create hot viruses? Lessons from Marek's disease

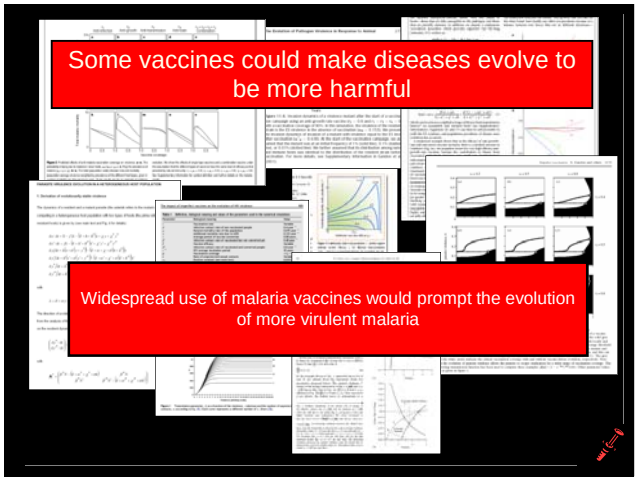
Andrew F. Read

Will vaccines favour more or less virulent strains?

vaccines protect virulent pathogens from themselves

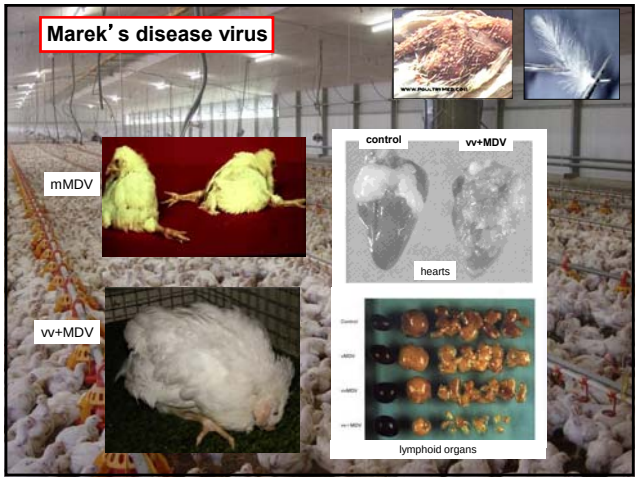
vaccines allow more virulent strains to circulate

Gandon, Mackinnon, Nee, Read (2001) *Nature*



Some vaccines could make diseases evolve to be more harmful

Widespread use of malaria vaccines would prompt the evolution of more virulent malaria



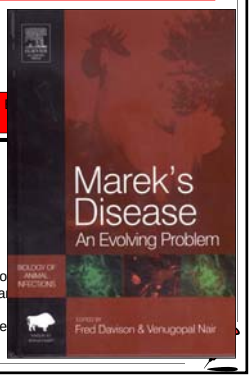
Virus evolution undermined 1st and 2nd generation Marek's disease vaccines

HVT

HVT failure

Bivalent

1940 1950 1960 1970 1980

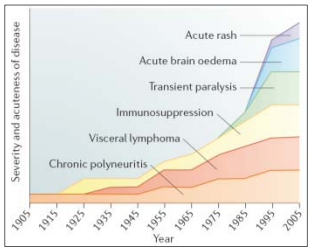


- Two generations of vaccine have failed in the face o
- This evolution played-out in US, Europe, Australia a

Virus evolution led to the failure of vaccines that were

Vaccine failure was not due to antigenic change

The only virus phenotype which has changed is virulence



Intensive farming made the virus more virulent

Did vaccination drive this evolution?

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NSF-EEID: R01 GM105244 (PI: Read)
RAPIDD, Fogarty International

1. Where is the evolutionary action? (natural history)
2. How does vaccination affect viral fitness?

Penn State

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Sue Baigent
Claire Powers
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Lydia Kgosana
Lorraine Smith

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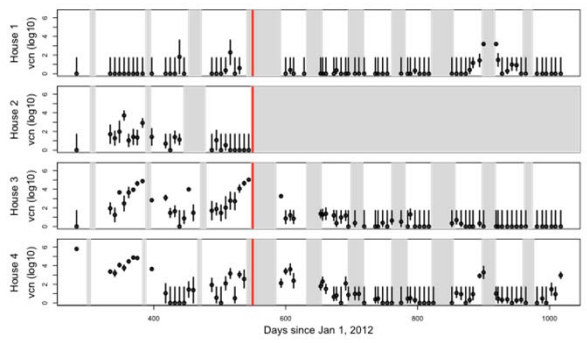
Queens, Canada
Troy Day

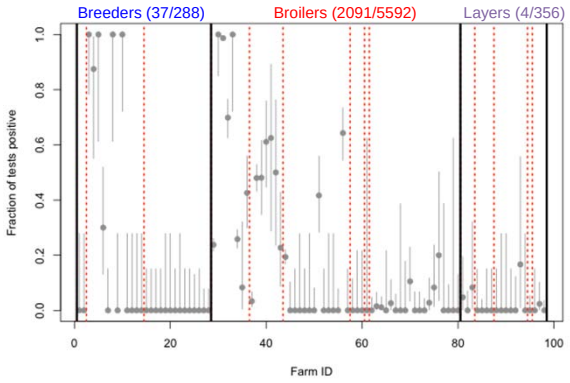
U. New England, Australia
Steve Walkden-Brown

Long term surveillance on one broiler farm



Kennedy, Dunn, Jones, Cairns, Read in prep

Prevalence of positive dust samples across farms



Kennedy, Dunn, Jones, Cairns, Read in prep

MDV Natural History: where is the virus?

Observations so far

Wild type virus is mostly in broiler operations

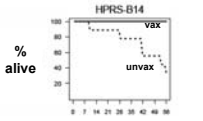
Viral densities vary:
- between houses on the same farm
- between cohorts on the same farm
- between farms and companies

Kennedy, Dunn, Jones, Cairns, Read in prep

MDV experimentation: viral fitness under vaccination

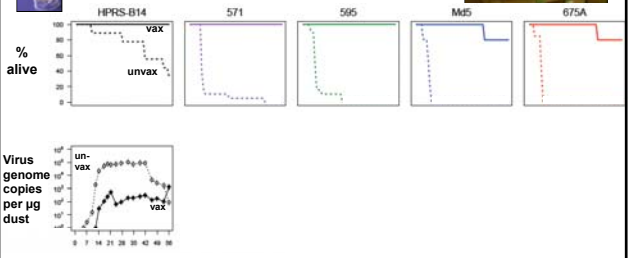
THE Pirbright INSTITUTE Preventing and controlling viral diseases

Virus strain differences in virulence

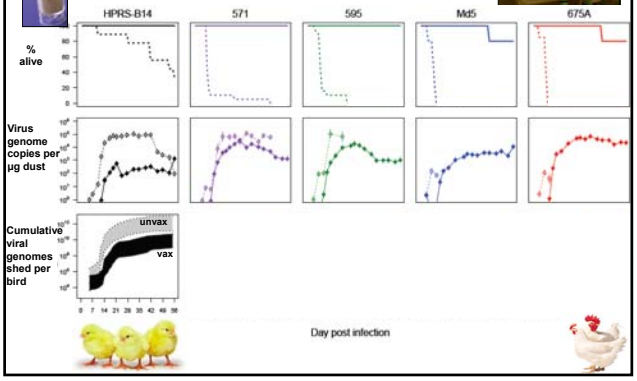


How does 'natural' selection act on this sort of variation?

Viral concentration in the dust



Viral strain 'fitness': shedding



Viral strain 'fitness': actual transmission

populations of 20 birds

Conclusion
Vaccination makes possible the persistence/spread of hyper-pathogenic strains

experimentally infected birds

10/10 dead
(by day 10)

naïve sentinels

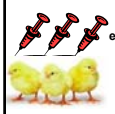
all alive

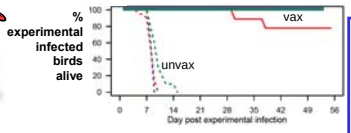
all alive

675A

10/10 dead
Started dying d28, all dead by d47

Viral strain 'fitness': actual transmission





Conclusion

- Vaccination enhances the transmission of hot strains
- Vaccination kills the unvaccinated

Vaccination of mothers

experimentally infected birds

all dead
by day 11

naïve sentinels

all alive

675A

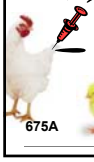
Vaccination of mothers

experimentally infected birds

all dead
by day 11

naïve sentinels

all alive



675A

Vaccination of mothers

Conclusion
Vaccination of mothers makes possible the persistence/spread of hyper-pathogenic strains

experimentally infected birds

all dead
by day 11

naïve sentinels

all alive

all dead
started dying d11,
all dead by d32

all dead
started dying d21,
all dead by d32

675A

Modern commercial broilers

Maternal antibodies
More resistant
Vaccinated

Rhode Island Red

Cobb broiler

Modern commercial broilers

Populations
of 20 birds

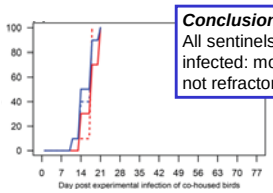
Experimentally infected birds:
- maternal antibody +ve
- vaccinated

Sentinels:
- Maternal antibody +ve

675A

Modern commercial broilers: transmission

% sentinels infected

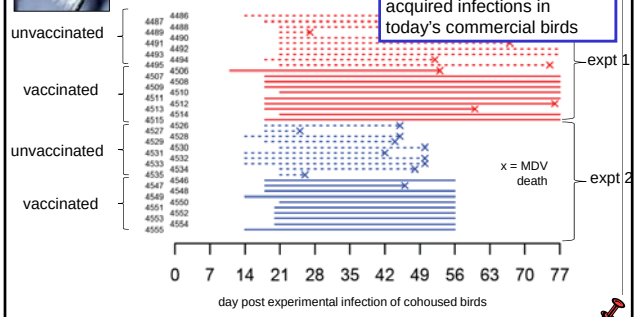


Conclusion
All sentinels became infected: modern birds are not refractory

675A

modern commercial broilers: infectious periods of sentinels

Conclusion
Vaccination prolongs the infectious period of naturally acquired infections in today's commercial birds



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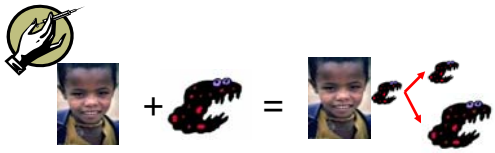
Will vaccines favour more or less virulent strains?



vaccines protect virulent pathogens from themselves

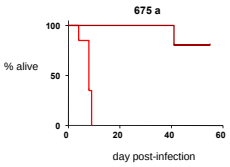
vaccines allow more virulent strains to circulate

Gandon, Mackinnon, Nee, Read (2001) *Nature*

Did vaccination make Marek's so virulent?

mMDV

vv+MDV



Vaccination is sufficient to explain the persistence of hot strains

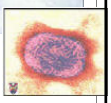
Could this happen in other contexts?

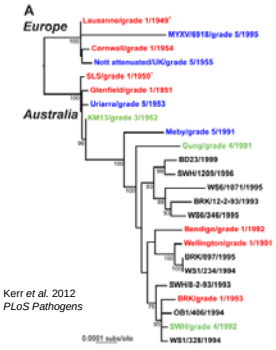
Feline calicivirus

- Hypervirulent strains spreading in high density vaccinated cat populations
- Two apparently independent evolutionary events (CA, Liverpool)
- Vaccine-protection negligible
- Burnt out

Hurley *et al.* 2004, Coyne *et al.* 2006, Radford *et al.* 2006

Myxoma virus virulence in Australia





Kerr *et al.* 2012
PLoS Pathogens

R01 AI093804 (PI: Read)
Kerr (CSIRO), Cattadori (PSU), Holmes (Sydney), Ghedin (Pitt), Hudson (PSU)

Diphtheria in Delhi

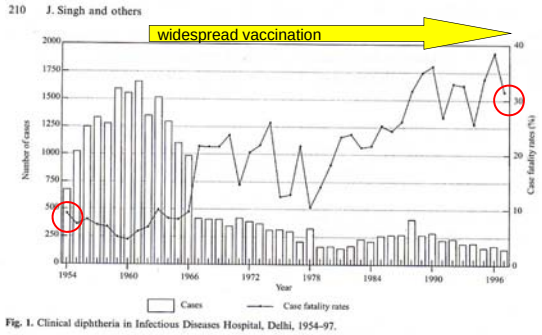
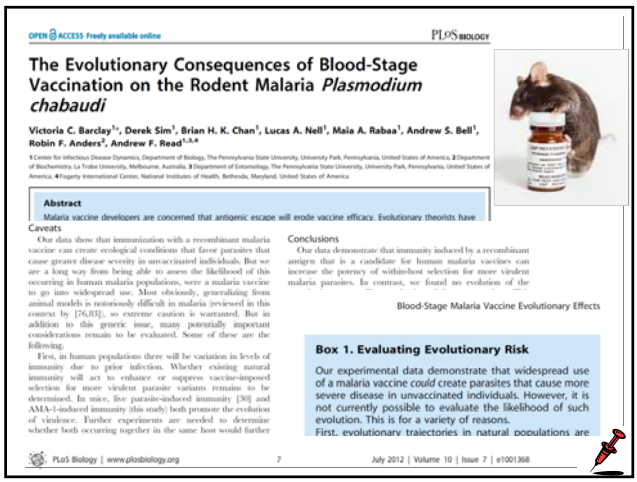


Fig. 1. Clinical diphtheria in Infectious Diseases Hospital, Delhi, 1954-97.

From Singh *et al.* 1999



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The Evolutionary Consequences of Blood-Stage Vaccination on the Rodent Malaria *Plasmodium chabaudi*

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Abstract

Malaria vaccine developers are concerned that antigenic escape will erode vaccine efficacy. Evolutionary theorists have

Caveats

Our data show that immunization with a recombinant malaria vaccine can create ecological conditions that favor parasites that cause greater disease severity in unvaccinated individuals. But we are a long way from being able to assess the likelihood of this occurring in human malaria populations, were a malaria vaccine to go into widespread use. Most obviously, generalizing from animal models is notoriously difficult in malaria [reviewed in this context by [76,83]], so extreme caution is warranted. But in addition to this generic issue, many potentially important considerations remain to be evaluated. Some of these are the following.

First, in human populations there will be variation in levels of immunity due to prior infection. Whether existing natural immunity will act to enhance or suppress vaccine-imposed selection for more virulent parasite variants remains to be determined. In mice, live parasite-induced immunity [30] and AMA-1-induced immunity (this study) both promote the evolution of virulence. Further experiments are needed to determine whether both occurring together in the same host would further

Conclusions

Our data demonstrate that immunity induced by a recombinant antigen that is a candidate for human malaria vaccines can increase the potency of within-host selection for more virulent malaria parasites. In contrast, we found no evolution of the

Blood-Stage Malaria Vaccine Evolutionary Effects

Box 1. Evaluating Evolutionary Risk

Our experimental data demonstrate that widespread use of a malaria vaccine *could* create parasites that cause more severe disease in unvaccinated individuals. However, it is not currently possible to evaluate the likelihood of such evolution. This is for a variety of reasons.

First, evolutionary trajectories in natural populations are

Could this happen in other contexts?

Vaccine-preventable diseases

Diphtheria
Measles
Monkeypox
Mumps
Pertussis (Whooping Cough)
Poliomyelitis (Polio)
Rubella (German Measles)
Smallpox

Anthrax
Hepatitis A
Hepatitis B
Haemophilus influenzae type b (Hib)
Human Papillomavirus (HPV)
H1N1 Flu (Swine Flu)
Influenza (Seasonal Flu)
Japanese Encephalitis (JE)
Lyme Disease

Meningococcal disease
Pneumococcal diseases
Rabies
Rotavirus
Shingles (Herpes Zoster)
Tetanus (Lockjaw)
Tuberculosis
Typhoid Fever
Varicella (Chickenpox)
Yellow Fever

+ many more veterinary vaccines

Feline calicivirus
Bird flu
Next gen vaccines:
Malaria, HIV, Ebola

Assessing the evolutionary risk of vaccines

Does the vaccine allow transmission of wild-type pathogens?

Are hyperpathogenic strains possible?

What stopped them spreading in the pre-vaccine era?

Will vaccination relax that?

Will hyperpathogenic strains have a fitness advantage in vaccinated hosts?

Take home messages

1. Vaccines can fail in the face of pathogen evolution.
2. Vaccine-driven evolution can be about more than antigens. Vaccine-induced immunity can favor more virulent pathogens.
3. Vaccination can enable the circulation of strains otherwise too lethal to persist
4. Assessing and managing evolutionary risk is a challenging problem