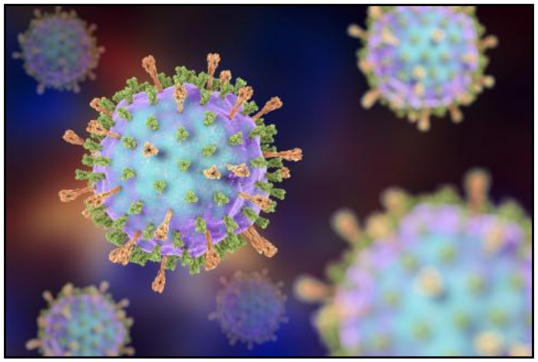
Inferring the ecological and evolutionary determinants of pathogen re-emergence

Pejman Rohani

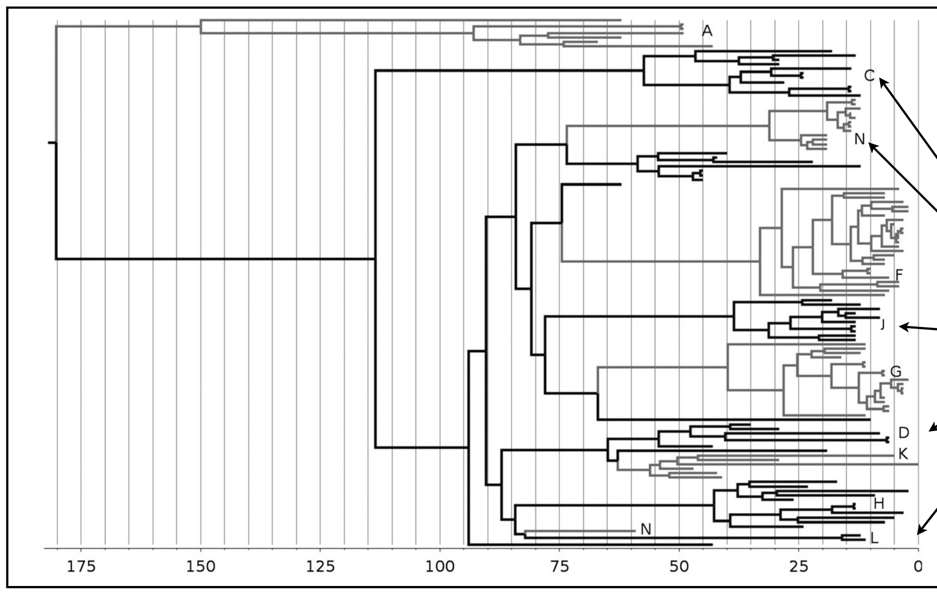
Gokhale *et al.* (2023; *PNAS* 120: e2207595120)



Mumps

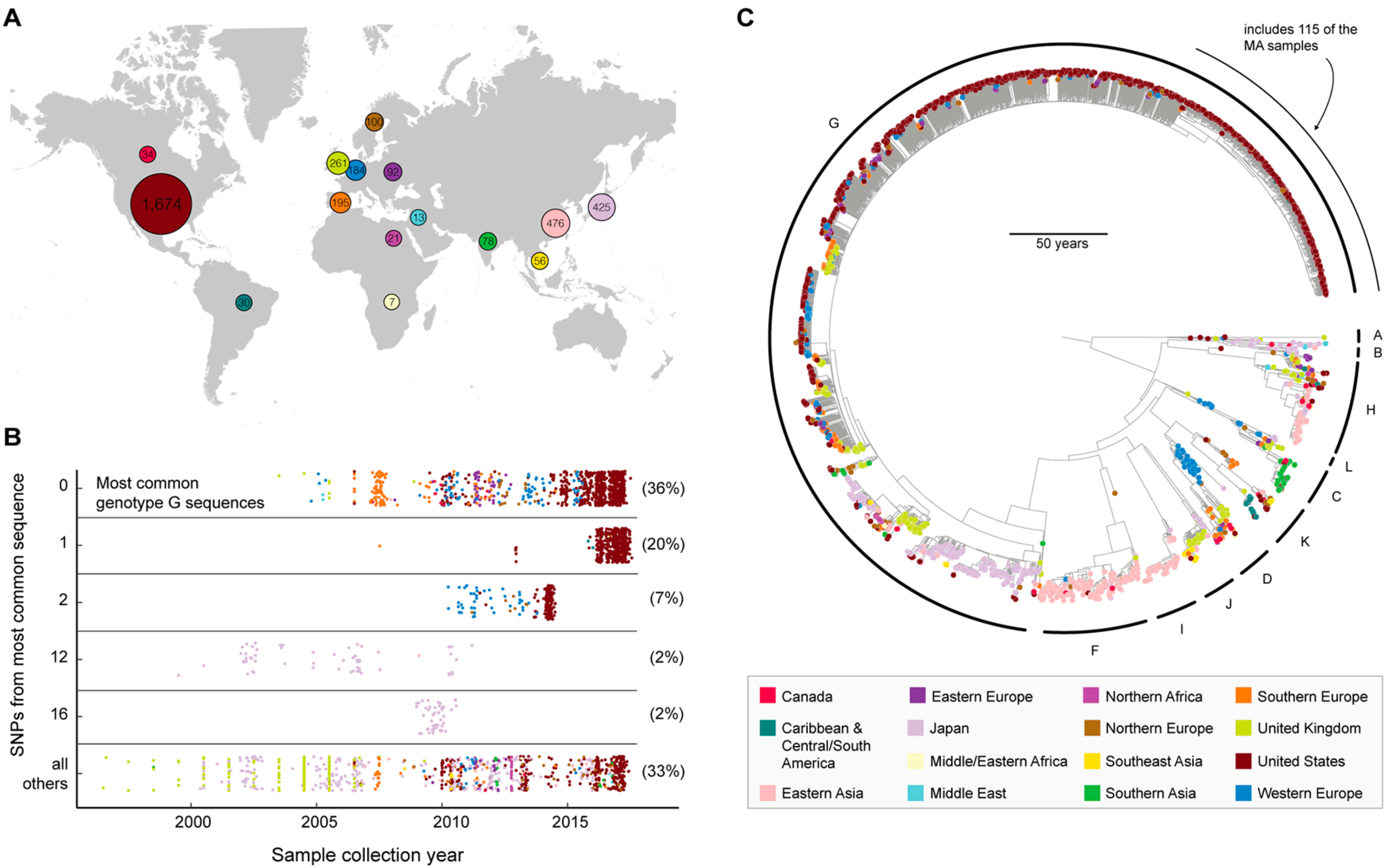
RNA virus — *Paramyxoviridae*

150,000 cases annually



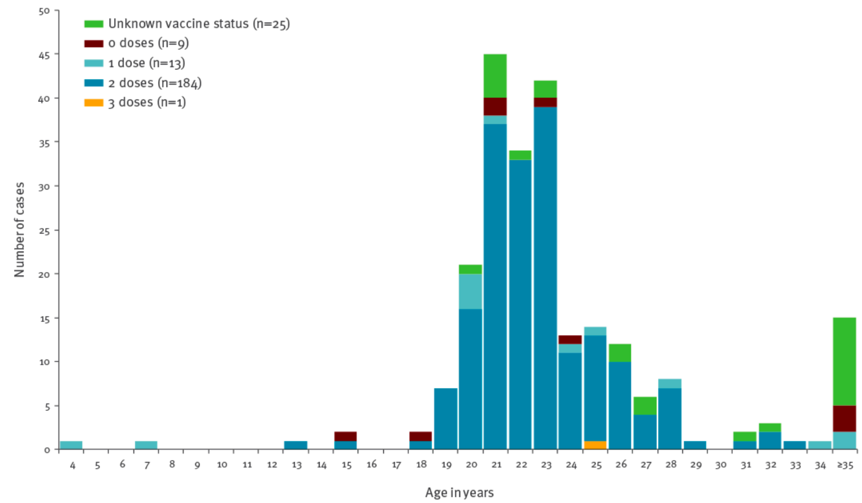
Genotypes

Jin et al., Reviews Medical Virology 2015



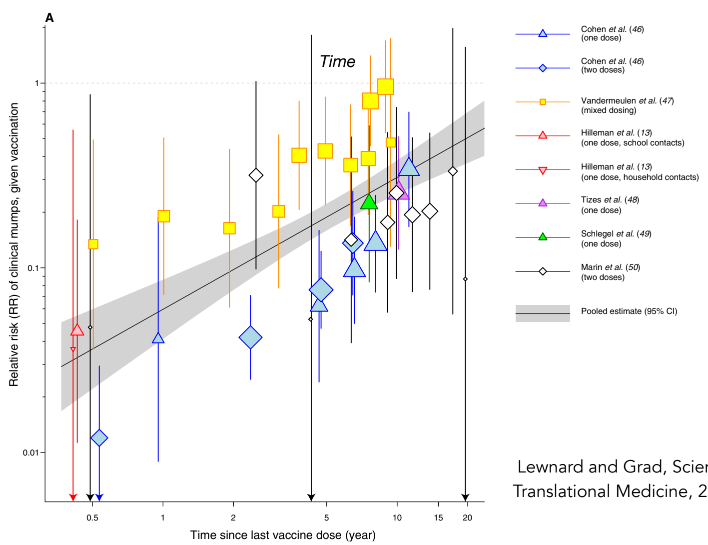
A
34
1,674
30
100
261
184
92
195
13
21
7
78
476
425
56
B
SNPs from most common sequence
0
Most common
genotype G sequences
(36%)
1
(20%)
2
(7%)
12
(2%)
16
(2%)
all
others
(33%)
2000
2005
2010
2015
Sample collection year
C
includes 115 of the
MA samples
G
50 years
A
B
H
L
C
K
D
J
I
F
Canada
Eastern Europe
Northern Africa
Southern Europe
Caribbean &
Central/South
America
Japan
Northern Europe
United Kingdom
Middle/Eastern Africa
Southeast Asia
United States
Eastern Asia
Middle East
Southern Asia
Western Europe

Veneti *et al.*, Eurosurveillance, 2018



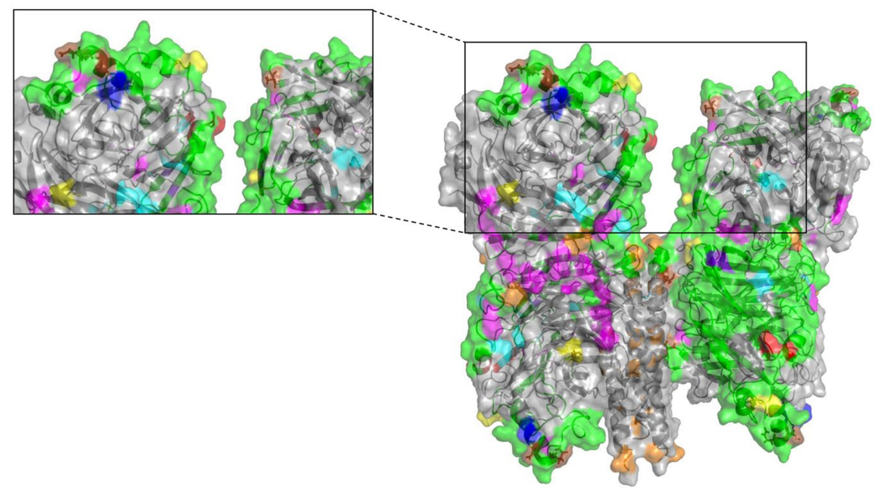
Competing explanations for mumps re-emergence

Waning



Lewnard and Grad, Science Translational Medicine, 2018

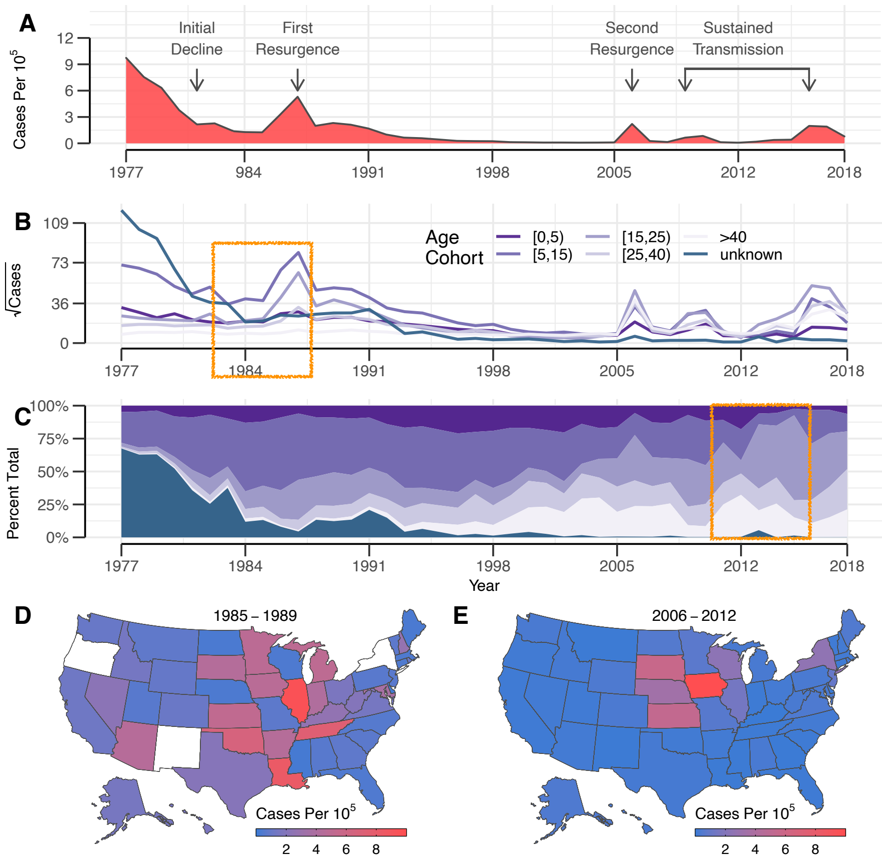
Evolution/strain mismatch



Gouma et al., Scientific Reports, 2018

Vaccine licensure and roll out in 1968

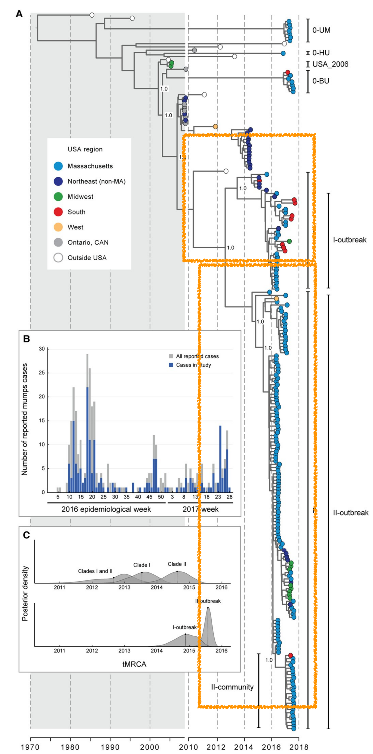
Booster introduced 1989



99% incidence reduction

Dynamical shifts in age-distribution

Spatial aggregation of cases in mid-western US

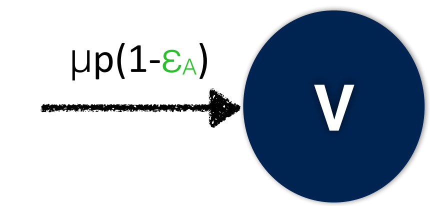


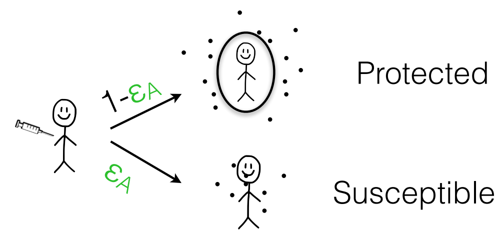
Wohl et al., PLOS Biology 2020

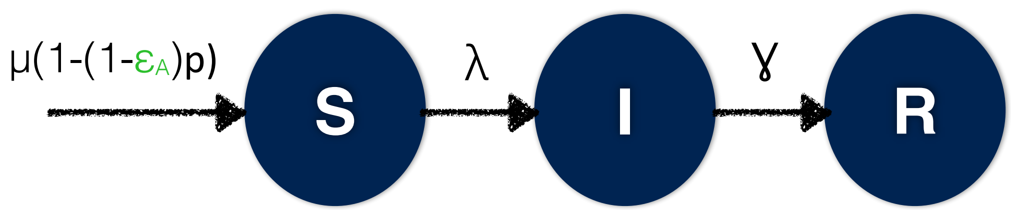
Phylogenetic turnover of the dominant genotype in circulation

Modes of vaccine failure

<u>"Primary" failure</u>: each dose associated with probability **ε**$_A$ of failure (Halloran *et al.* 1992; Am. J. Epid.; McLean & Blower 1993; *Proc R Soc* B)



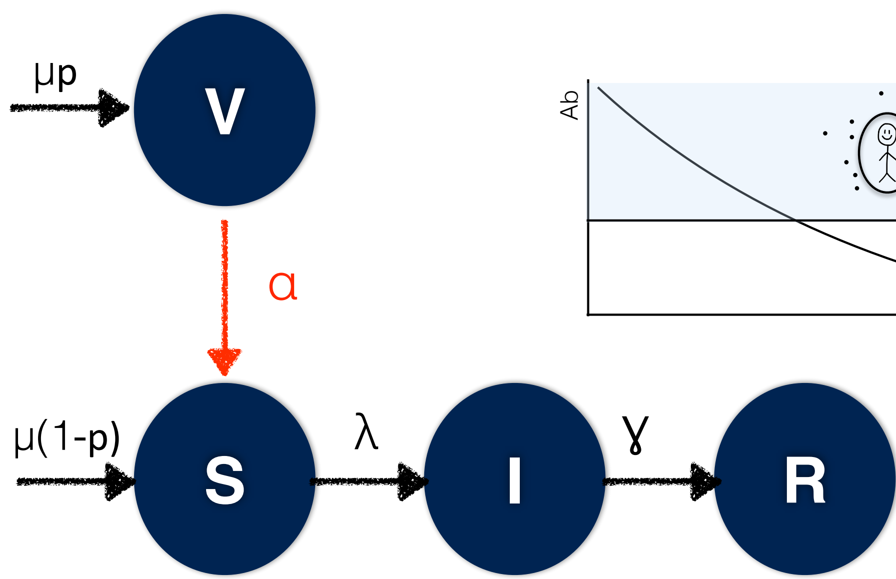


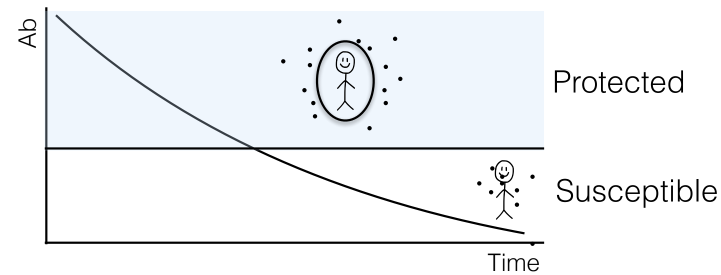


Magpantay et al. (2014) *SIAM J Appl Math*

Modes of vaccine failure

"Waning" vaccine: perfect but transient protection





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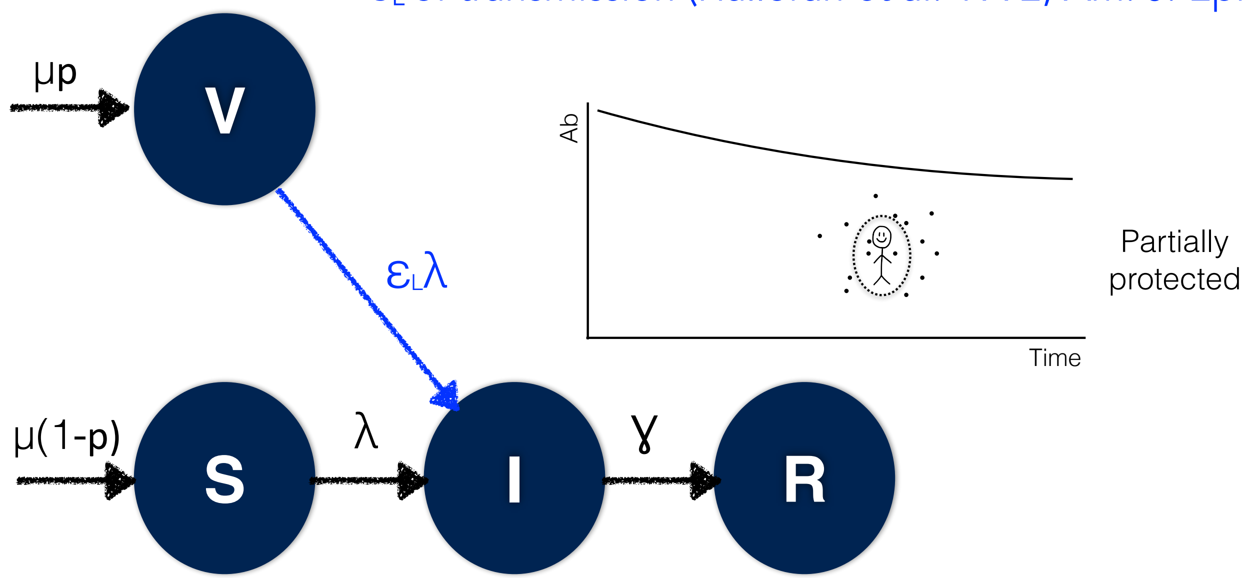
Modes of vaccine failure

"Leaky" vaccine: each exposure associated with probability ε_L of transmission (Halloran *et al.* 1992; Am. J. Epid.)



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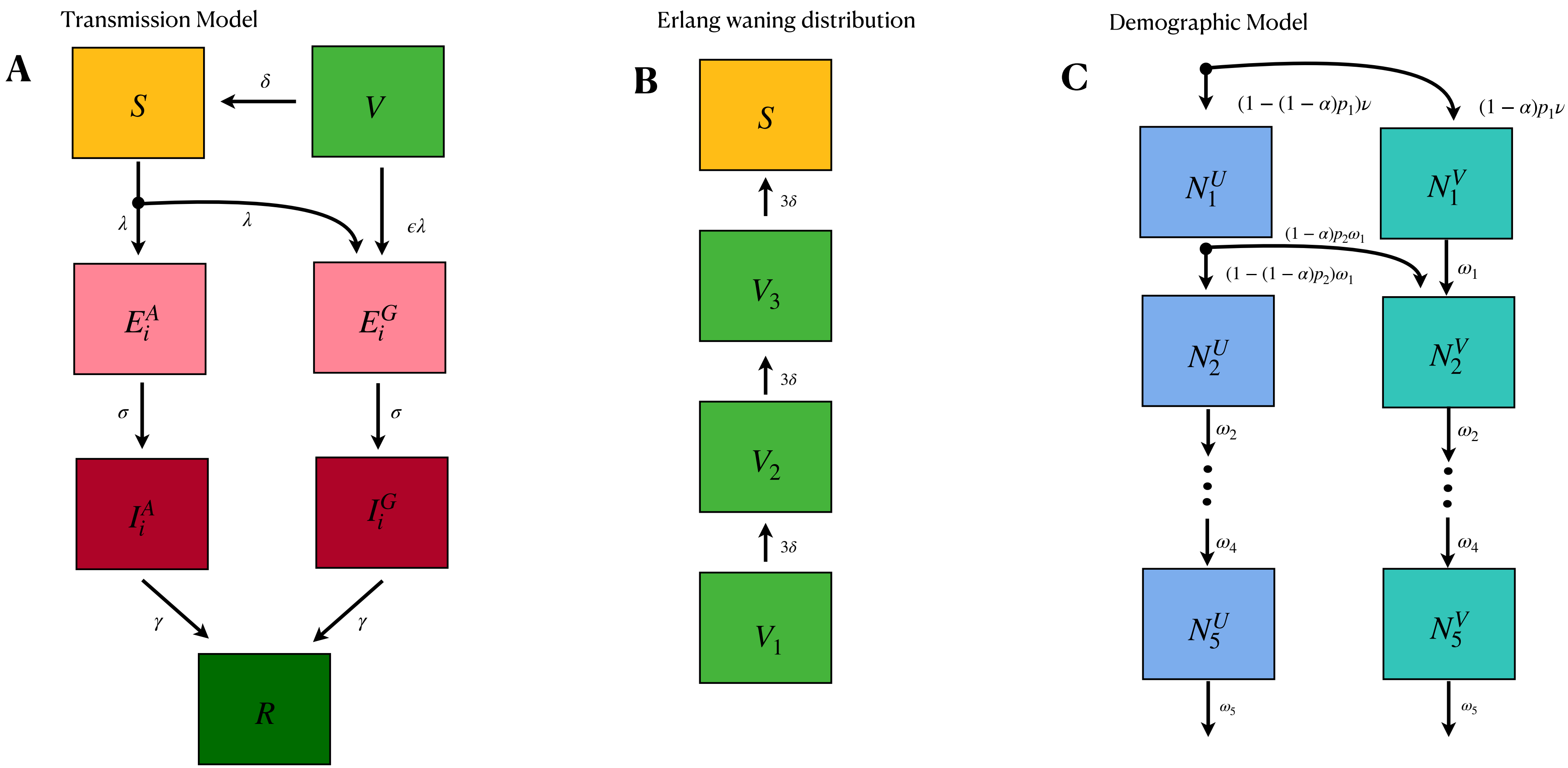
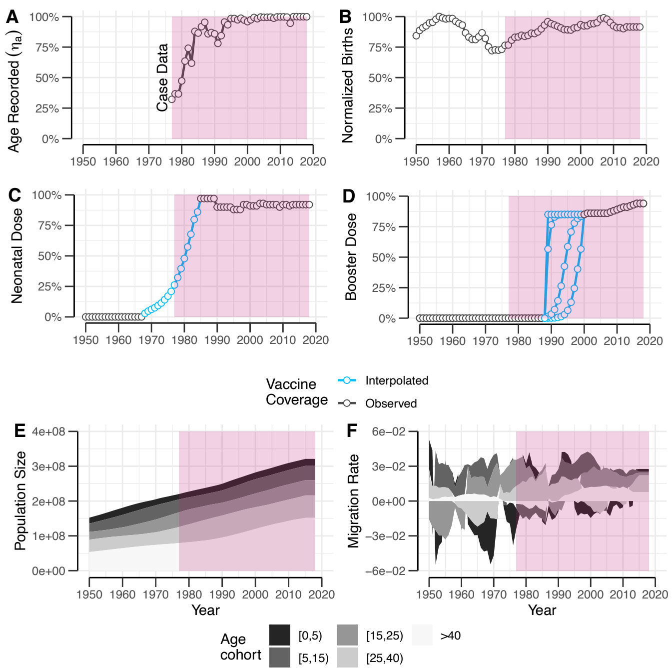
Developing latent-state models and testing hypotheses of vaccine failure


Transmission Model
A
S
V
δ
λ
λ
ϵλ
E_i^A
E_i^G
σ
σ
I_i^A
I_i^G
γ
γ
R
Erlang waning distribution
B
S
3δ
V_3
3δ
V_2
3δ
V_1
Demographic Model
C
$(1-(1-\alpha)p_1)\nu$
$(1-\alpha)p_1\nu$
N_1^U
N_1^V
$(1-\alpha)p_2\omega_1$
$(1-(1-\alpha)p_2)\omega_1$
ω_1
N_2^U
N_2^V
ω_2
ω_2
ω_4
ω_4
N_5^U
N_5^V
ω_5
ω_5

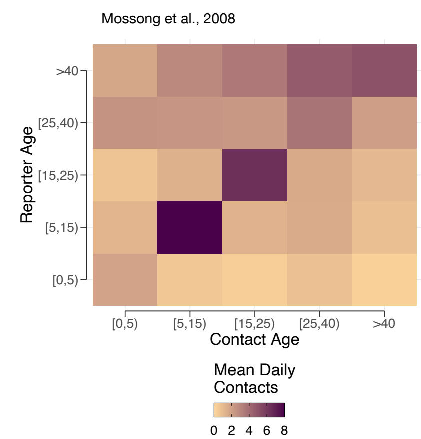
Model Co-variates

Booster shapes
sub-hypotheses



Inferred migration rates

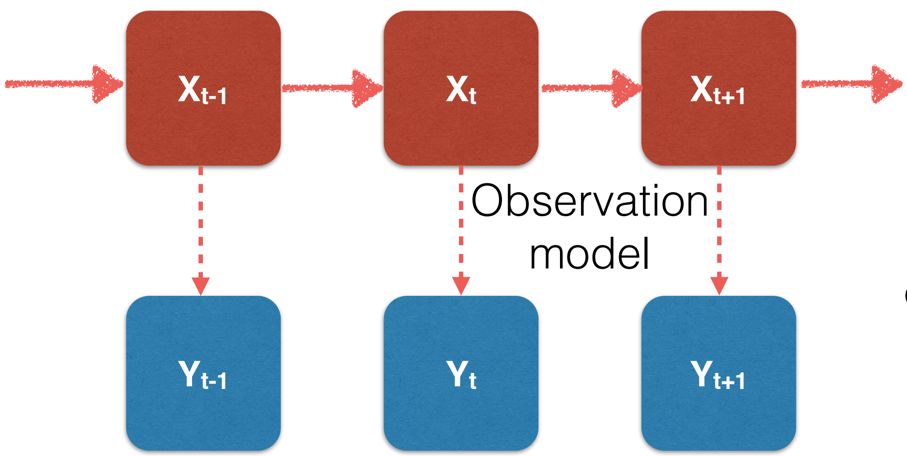
Calibrated to
US population



POMP

- Partially Observed Markov Process

Process model



We know $\mathbb{P}(X_t \mid X_{t-1})$ and $\mathbb{P}(Y_t \mid X_t)$

Was the age of the case documented?

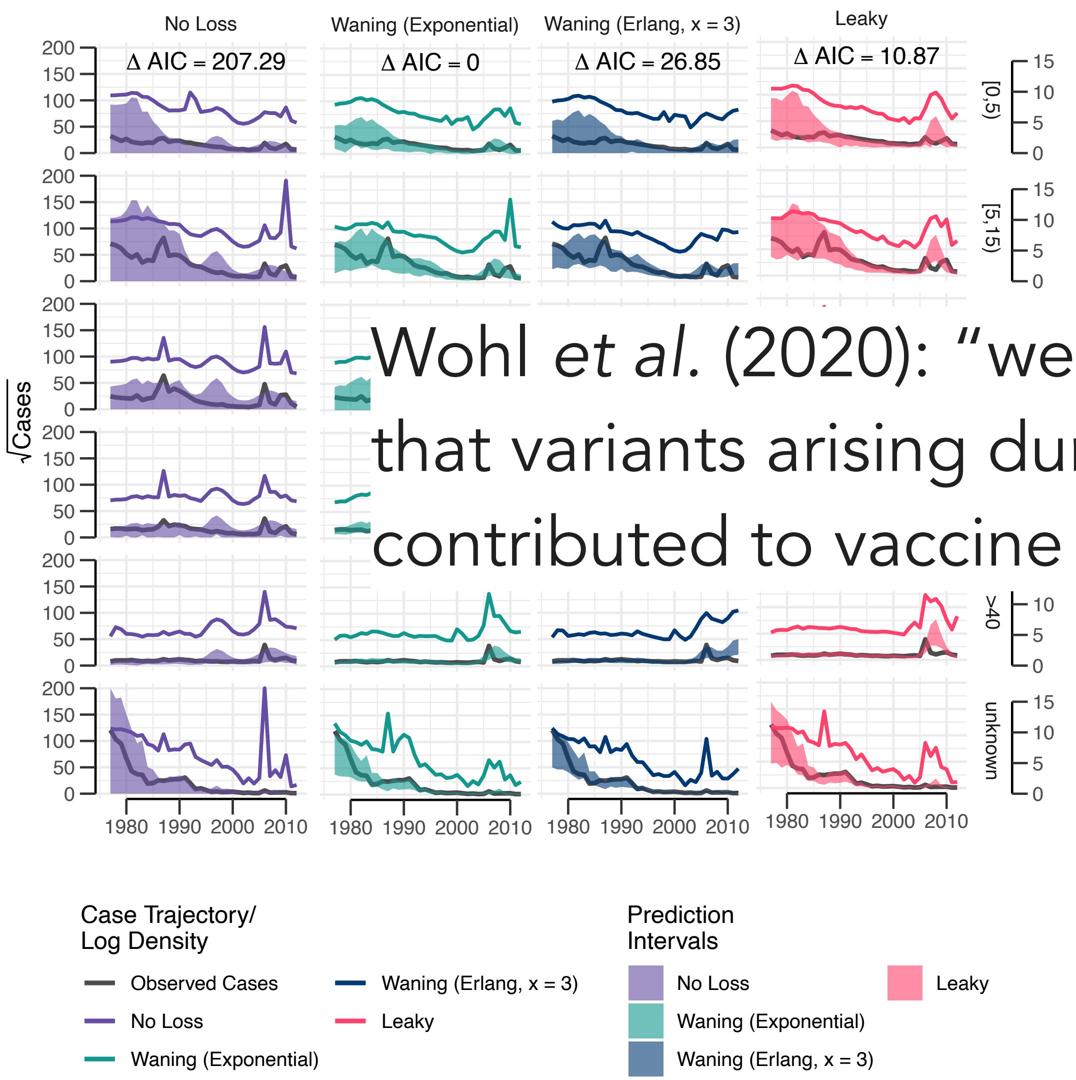
Was the case reported?

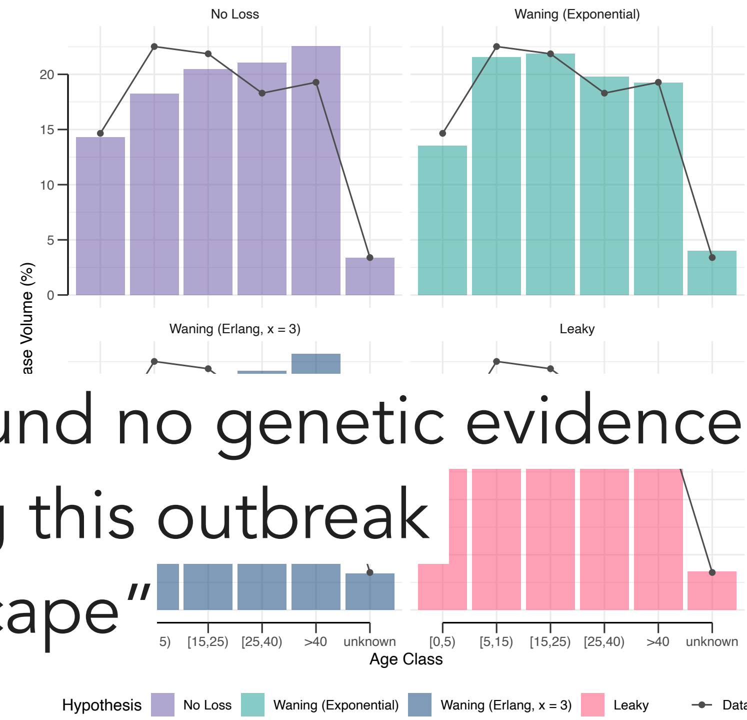
Observation Process

$$\mathscr{L}(\theta) = \prod_{i=1}^{5}\left(\prod_t P(D_i(t) \,|\, \rho_i \eta_a C_i(t;\theta)\right) \times \left(\prod_t P(D^u(t) \,|\, \rho_u (1-\eta_a)\sum_{i=1}^{5} C_i(t;\theta)\right)$$

$$P\left(\cdot|\rho_i^s C_i,\ \sqrt{\rho_i^s C_i(1-\rho_i^s+\psi_i^2 C_i)}\right)$$

How do the models perform?





Wohl *et al.* (2020): "we found no genetic evidence that variants arising during this outbreak contributed to vaccine escape"

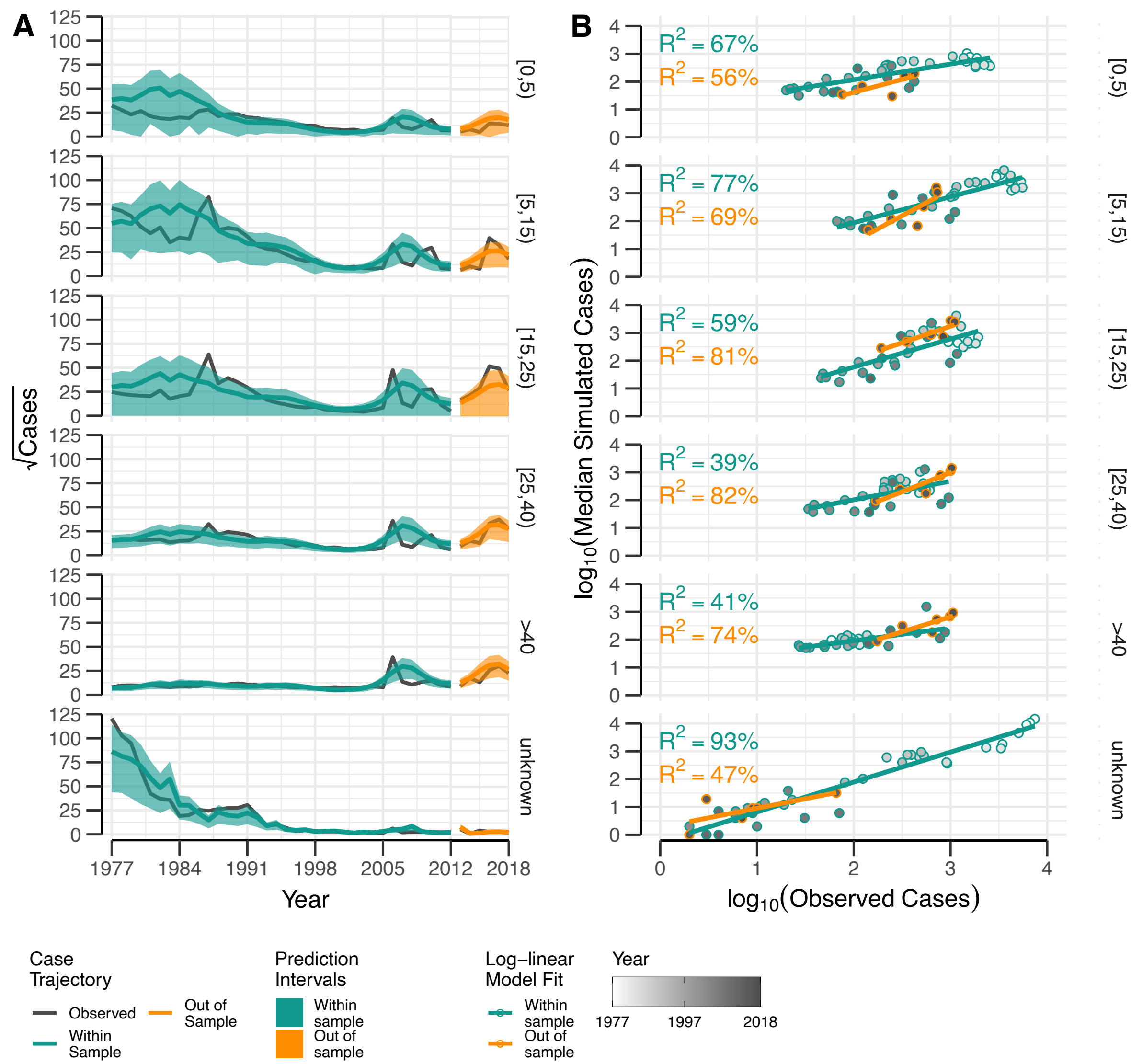
	Model			
Parameter/Quantity	No Loss	Waning (Exponential)	Waning (Erlang, N = 3)	Leaky
ΔAIC	207.288	0	26.853	10.87
R_0	42.414	13.992	31.371	22.199
R_p	2.29	6.45	20.211	1.789
ξ	0.946	0.539	0.356	0.919
β_1	0.185	0.036	0.341	0.735
σ^{-1} (Days)	12.022	24.998	16.894	24.999
δ^{-1} (Years)	-	111.456	56.457	-
ϵ	-	-	-	0.028
p_{intro} (Age cohort)	-	-	-	[15, 25)
t_{intro}	-	-	-	2000
Booster shape	Constant	Sigmoid	Sigmoid	Constant

How do we validate the fitted model?

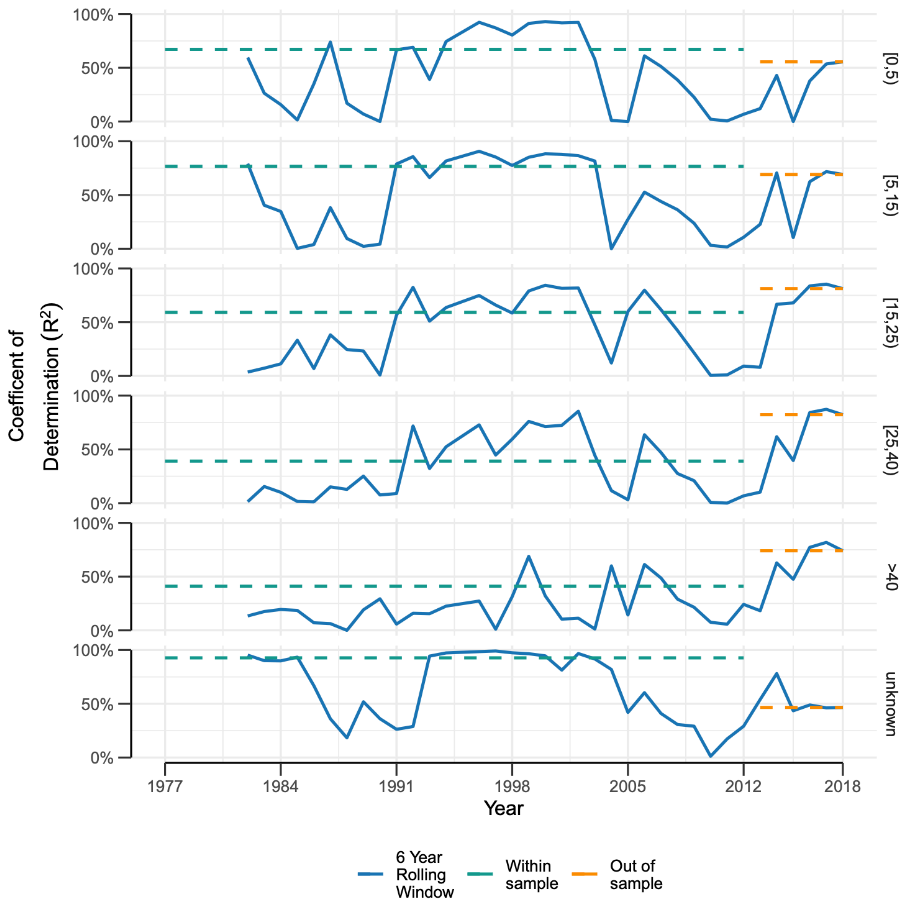
Waning model reasonably recapitulates observed dynamics

Fits for younger age-cohorts better, relative to older population

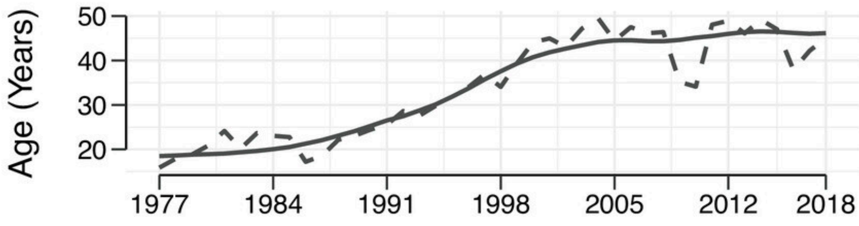
On an average, simpler dynamics in test epochs result in better fits than training epoch



Why is the out of fit R^2 better?

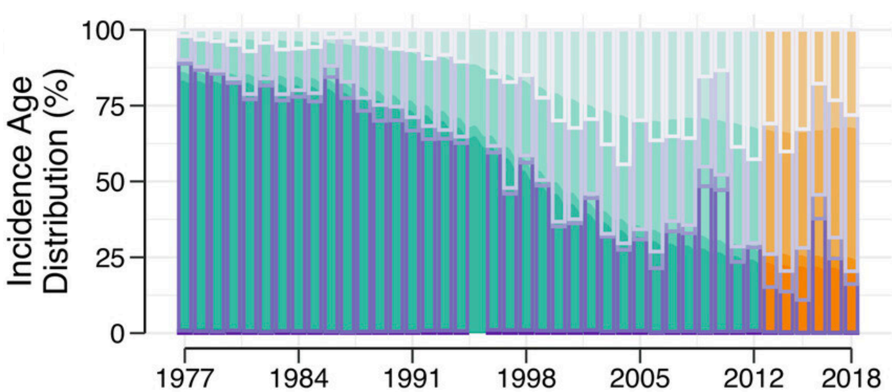


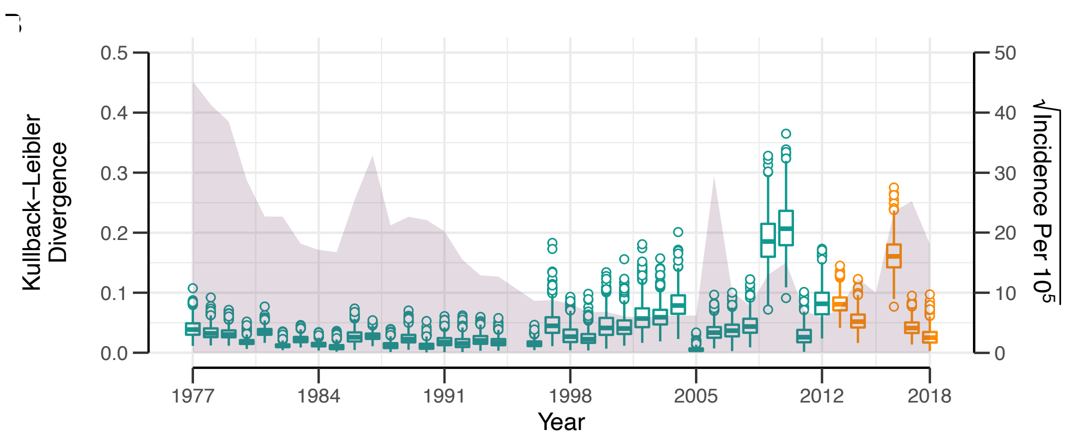
Straightforward to observe similarly good R2 values for other 6-year segments of in-sample fit

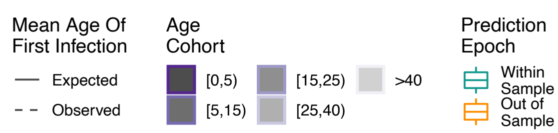


Model captures upward trend in mean age of first infection

Highest discrepancies in relative age-distributions lie in regions of low incidence, but they are also highly variable





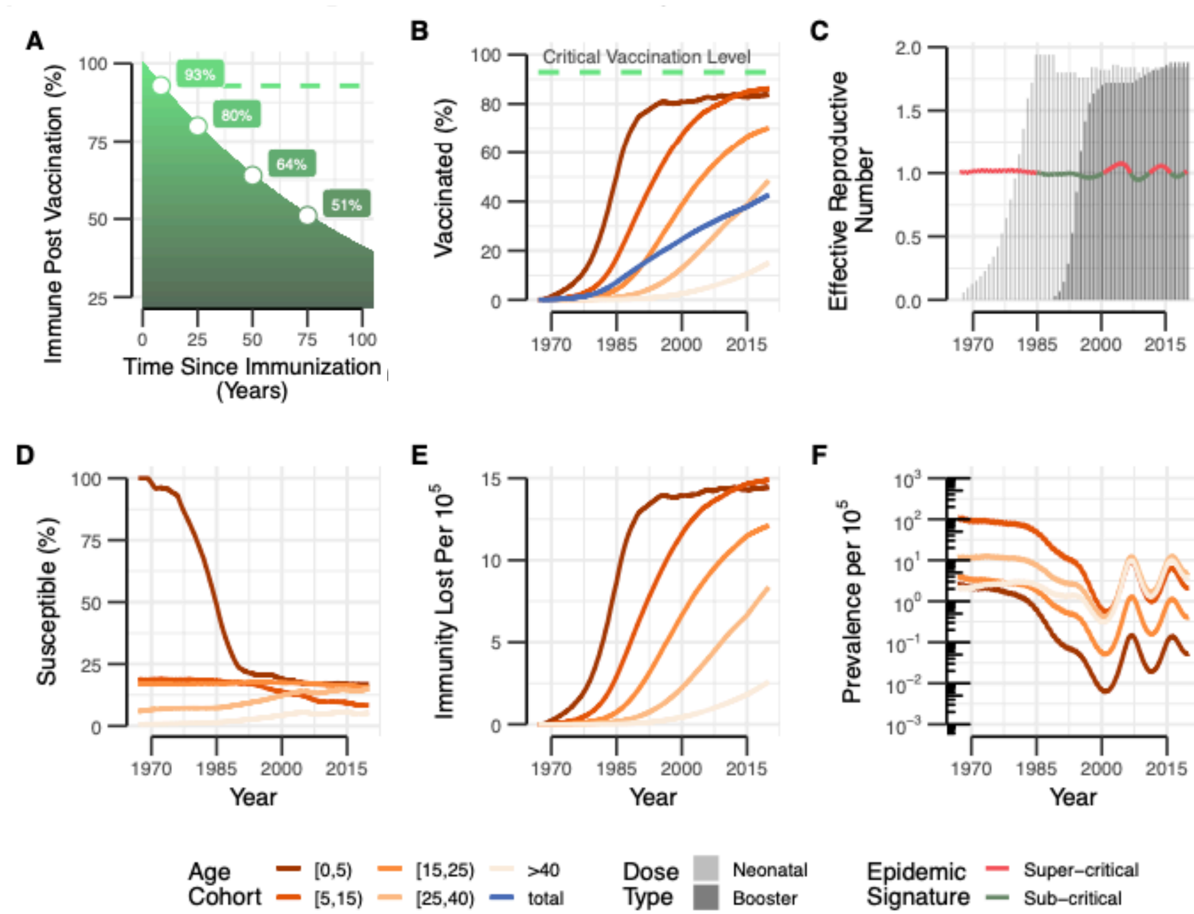


How does fitted model explain mumps resurgence?

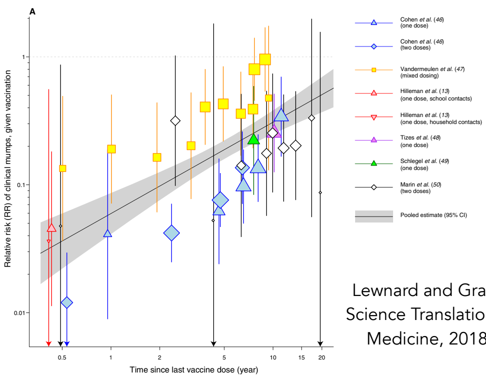
$$P(Immune\ Loss) = e^{-\delta t}$$

Immune loss is proportional to vaccination intensity

Age-shift in susceptibility profile causes shift in incidence age-distribution



Two important points



Lewnard and Grad, Science Translational Medicine, 2018

Leonard & Grad estimated mean duration of immunity of 27.4 y (95% CI, 16.7 to 51.1 y)

For direct comparison with model estimate, need to calculate expected time to loss of immunity (T_L) conditioned on survival of an individual (i.e., $T_L < T_D$, where T_D is time to death)

$$\mathbb{E}\left[T_L \mid T_L < T_D\right] = \frac{1}{\delta} - \frac{\tau e^{-\tau\delta}}{1 - e^{-\tau\delta}} \quad = 35.3 \text{ y}$$

Gokhale *et al.* (2023; *PNAS* 120: e2207595120)

Vaccine impact:

$\phi = (1-\varepsilon_A)(1-\varepsilon_W)(1-\varepsilon_L)$

where $\varepsilon_W = \alpha/(\alpha+\mu)$

⇒ Eradication threshold:

$p_c = (1-1/R_0) \times 1/\phi$

- Individual vaccine impact estimate ~59% (54%, 67%).
- R_0 estimate ~14

⇒routine immunization with current vaccines cannot lead to eradication

Magpantay et al. (2014) *SIAM J Appl Math*

Vaccine effectiveness and waning intensity

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A Mumps Outbreak among Fully Vaccinated People

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By Ekemini Hogan, Akpabio Akpabio, Utibe Effiong on June 24, 2020

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HEALTH NEWS

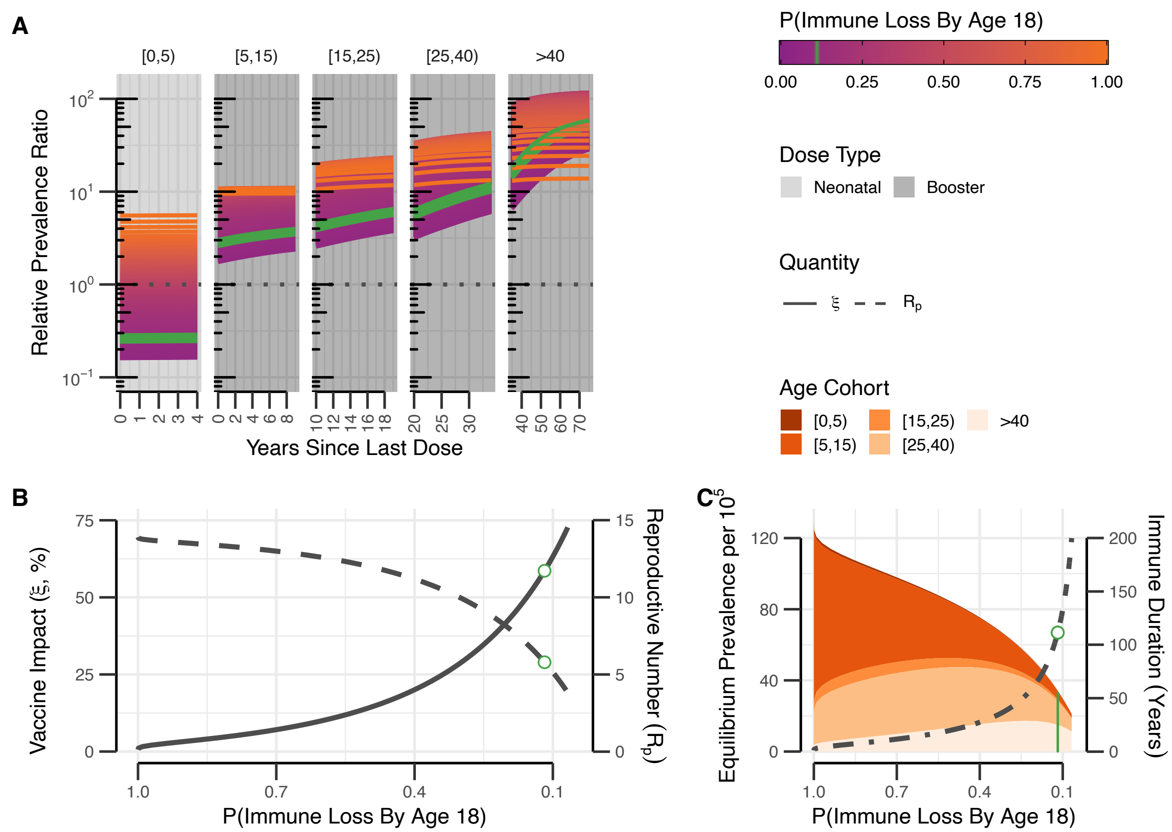
Majority of mumps cases are among the vaccinated, CDC finds

As many as 94 percent of children and adolescents who contracted the highly contagious virus had been vaccinated.

Relative prevalence increases monotonically with age

For older age-classes prevalence is maximized at an intermediate value of waning intensity

Vaccine effectiveness is function of duration of immunity



Gokhale *et al.* (2023; *PNAS* 120: e2207595120)

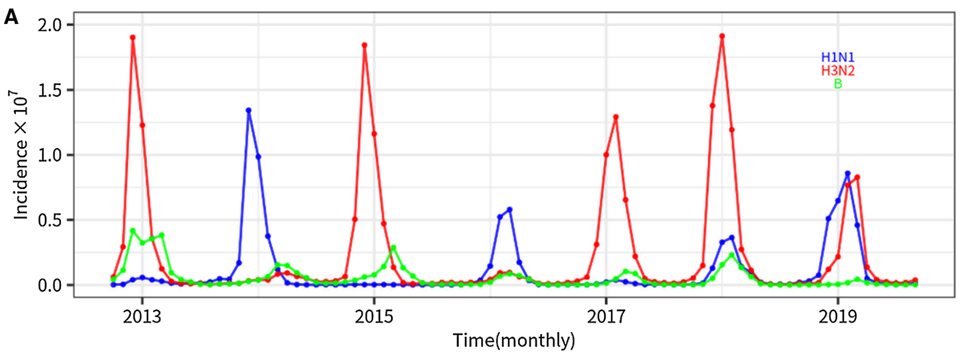
Summary

- Mumps re-emerged in US, despite high estimated vaccine coverage
- At population level, models indicate waning of vaccine-derived immunity drives recent epidemics
- Vaccines with long-lasting immunity can bring about substantial decrease in prevalence of mumps
    - <u>But</u>, in resurgence era, most cases among previously vaccinated
- Validated transmission models can inform age-stratified boosting schedule to maintain high levels of herd immunity

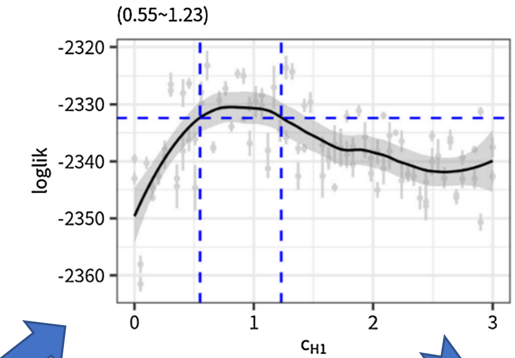
Influenza forecasting

Influenza forecasting

Incidence data

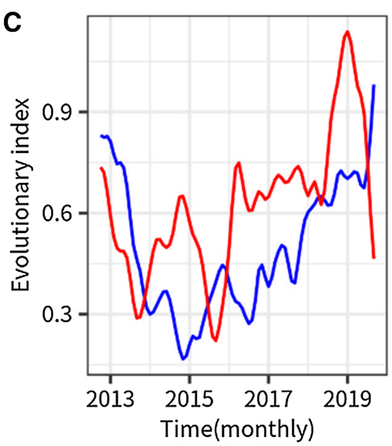


Statistical inference

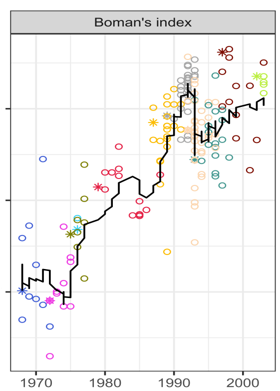


Omid Arhami

Evolutionary covariates

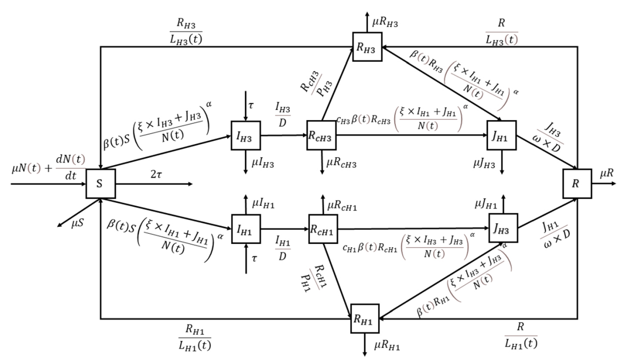


Wang et al. (2022)

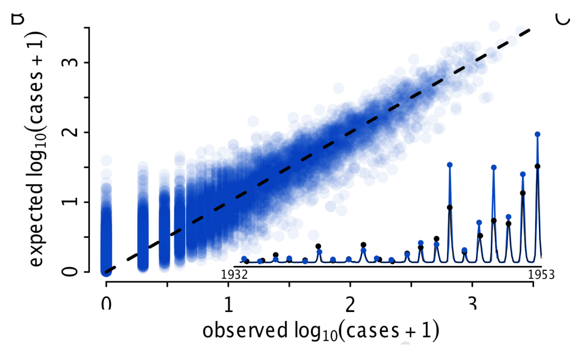


Forna et al. (ms in prep)

Transmission model



Probabilistic forecasts



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A NIAID funded international research network created to study influenza and combat influenza outbreaks.

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