Detecting an immune signature of measles using Population Data

Michael Mina, PhD

June 9, 2015

Off-Target effects of Vaccination

Fondation Merieux

Background

- Large reductions in mortality following rollout of measles vaccines in multiple countries.
- Aaby (and numerous others): convincing evidence that live vaccines reduce infectious disease mortality
- Few mechanistic studies to explain this
- Could anything else help explain (at least some of) these large reudctions?

Immunosuppressive effects of measles well recognized

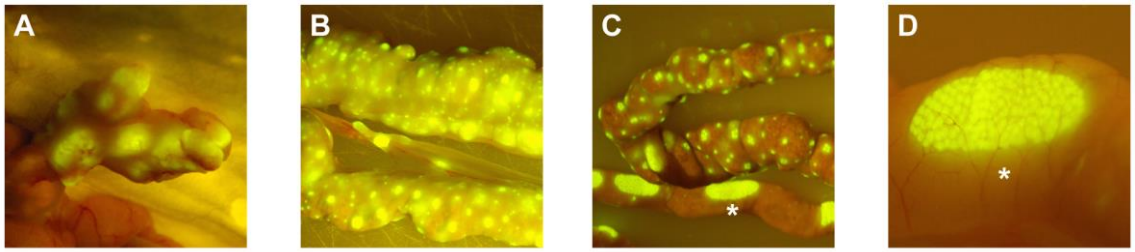
- Clinical
- Immunologic
  - Early depletion
  - Reduced proliferation
  - Lymphocytes return to (roughly) full *numbers* in weeks – months
  - **Frequency / Repertoire unknown**

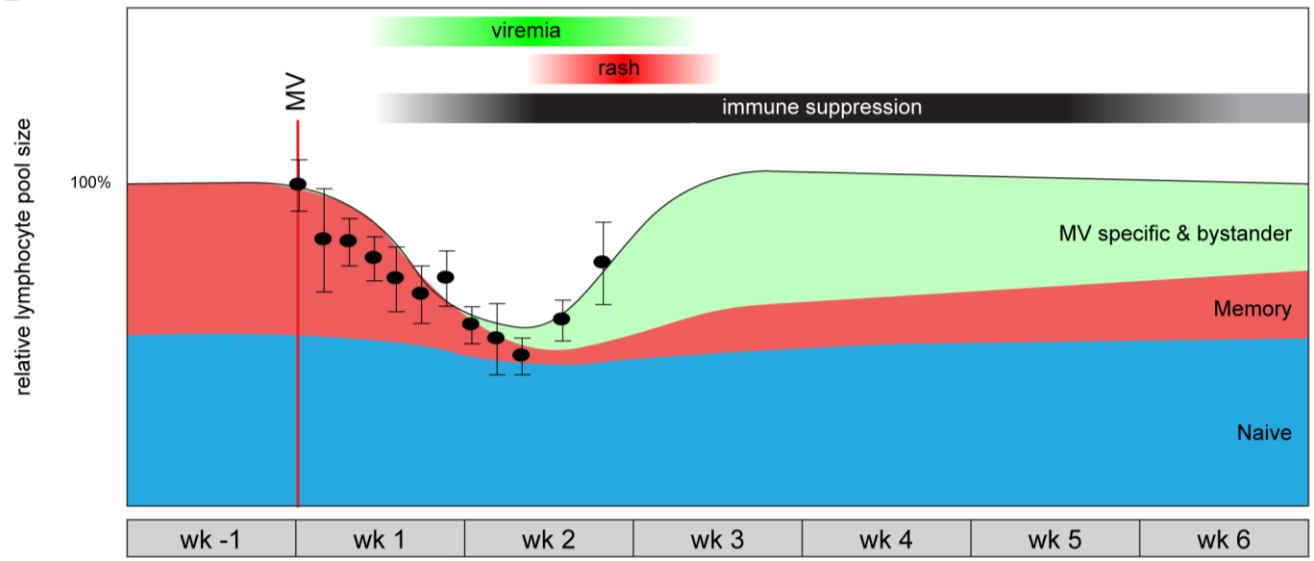
Measles specifically depletes memory lymphocytes

Measles Immune Suppression: Lessons from the Macaque Model

Rory D. de Vries, Stephen McQuaid, Geert van Amerongen, Selma Yüksel, R. Joyce Verburgh, Albert D. M. E. Osterhaus, W. Paul Duprex, Rik L. de Swart

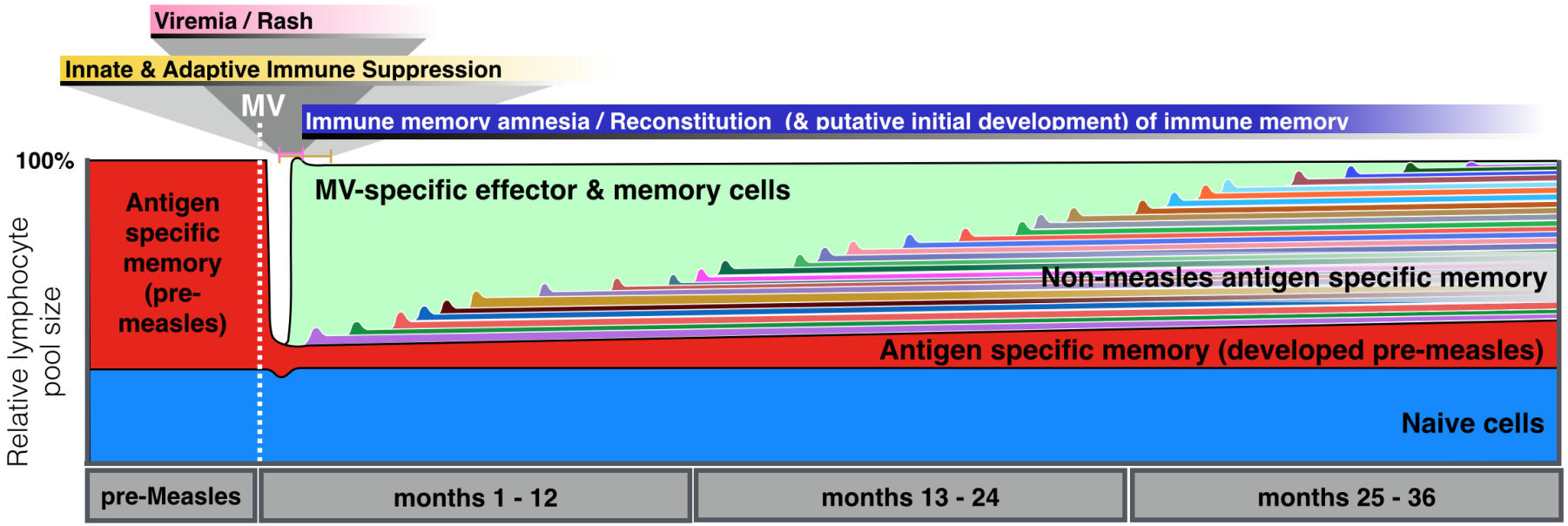
Published: August 30, 2012 • DOI: 10.1371/journal.ppat.1002885





Possible long-term effects?

- Unknown if memory cell frequencies and original repertoire spontaneously return
- Re-stimulation necessary (direct or heterologous)?



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DOI: 10.1126/science.aaa3662

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REPORT

Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality

Michael J. Mina[1,2,*], C. Jessica E. Metcalf[1,3], Rik L. de Swart[4], A. D. M. E. Osterhaus[4], Bryan T. Grenfell[1,3]

How to test (an immunologic phenomenon in population data)?

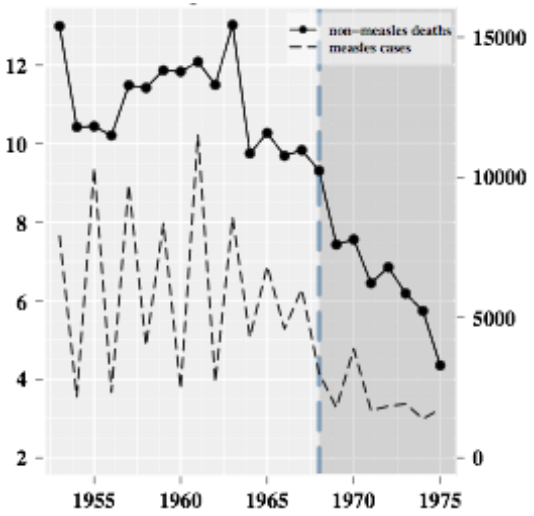
1) Non-measles mortality should be correlated with measles incidence data, especially after onset of vaccination

2) An immune-modulation mechanism should present as a strengthening of the association as measles incidence data are *transformed* to reflect an (age-structured) accumulation of previous measles cases

3) the strength of this association should peak where measles cases are accumulated for the mean duration of suppression

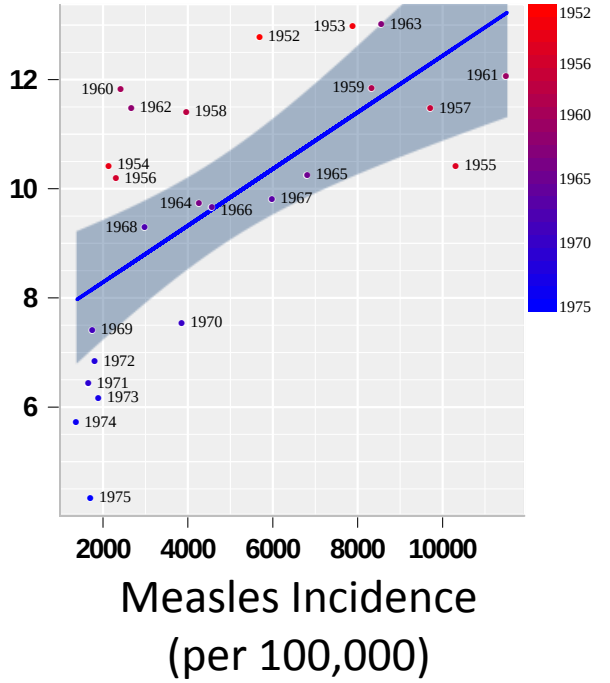
4) this estimated duration should be reasonably consistent with the time required to build a sufficiently protective immune response

England & Wales Data



Measles Incidence (per 100,000)

Non-Measles Infectious Disease Mortality (per 100,000)

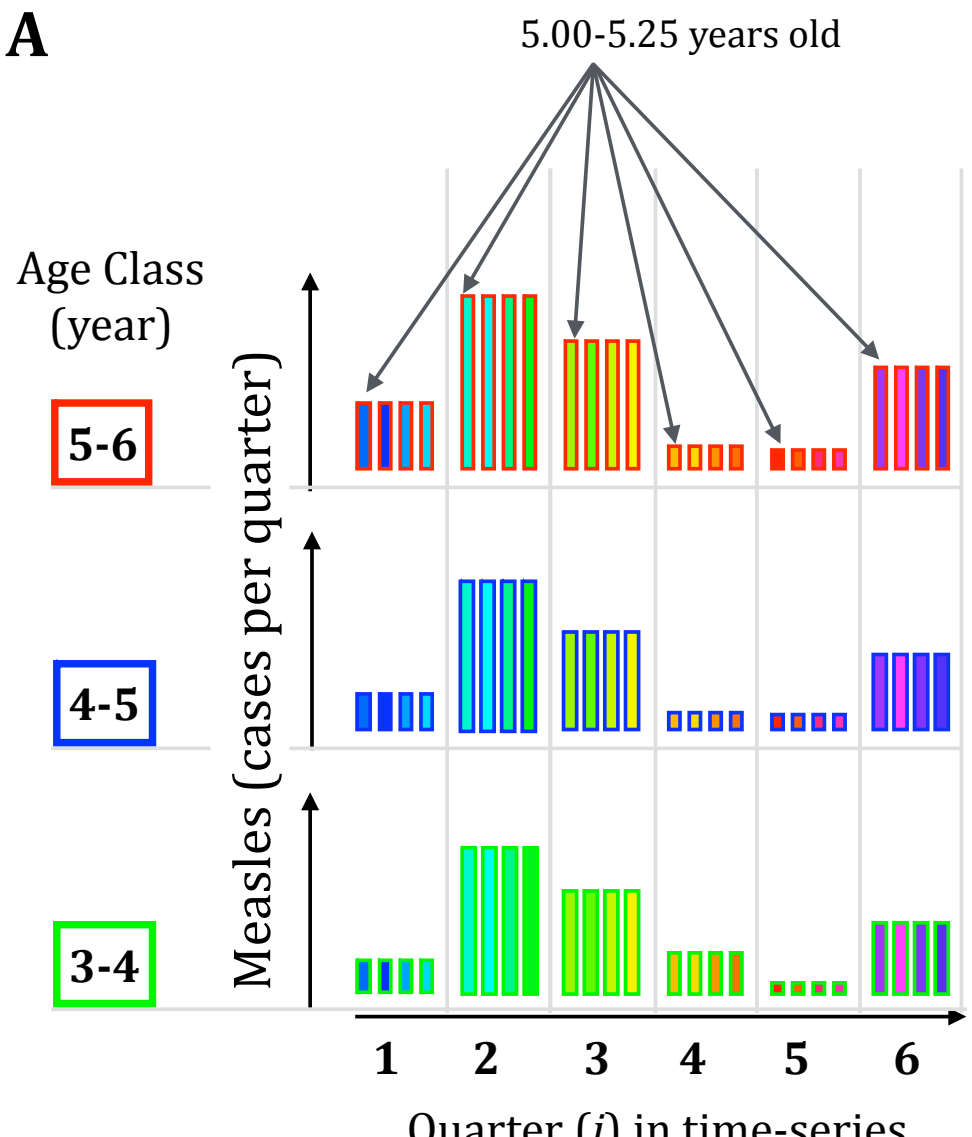


Measles Incidence (per 100,000)

Cause of death	20th Century Mortality Files - 1940-1949 - ICD5	20th Century Mortality Files - 1950-1957 - ICD6	20th Century Mortality Files 1958-1967 - ICD7	20th Century Mortality Files 1968-1978 - ICD8
Atypical Pneumonia		4920	4920	
Dysentery & diarrhea	27a	0450,0 451, 0452, 0453, 0454	0450,0 451, 0452, 0453, 0454	0040, 0041, 0042, 0043, 0044, 0048, 0049
Bacteria	24d, 25, 26	0540, 0640, 0641, 0642, 0643, 0644	0540, 0630,	0390, 0391, 0399
Bacterial Pneumonia				4820, 4821, 4822, 4823, 4829
Bronchitis	106a, 106c	5000, 5010	5000, 5010	4660, 4900, 5180
Bronchopneumonia	107(1), 107(2)	4910	4910	4850
Brucellosis	5	0440	0440	0230, 0231, 0232, 0239
Cholera	4	0430	0430	0000, 0001, 0009
Dysentery	27b, 27c, 27d	0470, 0480	0470, 0480	0090, 0091, 0092, 0099
Encephalitis		0820, 0830, 0831, 0832, 0833	820, 821, 822, 823, 830, 831, 832, 833	
Fungal		1320, 1330, 1340, 1341, 1342, 1343, 1344, 1345	1340, 1341, 1342, 1343, 1344, 1345	1130, 1140, 1160-69, 1170-79
Lobar Pneumonia	108(1), 108(2)	4900	4900	
Meningitis	81	3400, 3401, 3402, 3403, 9440	3400, 3401, 3402, 3403	3200, 3201, 3208, 3209
Meningococcal Infection		0571, 0572, 0573	0571, 0572, 0573	0361, 0368, 0369
Otitis	89a	3900, 3910, 3911, 3912, 3920, 3921, 3922	3900, 3910, 3911, 3912, 3920, 3921, 3922	3800, 3810, 3811, 3819, 3820, 3821, 3829
Paratyphoid	2	0410	0410	0020, 0021, 0022, 0029
Plague	3	0580, 0581, 0582	0580, 0581, 0582	0200, 0201, 0209
Pneumococcal Pneumonia				4810
Pneumonia	109(1), 109(2)	4930	4930	4860
Respiratory	114e(2)			
Scarlet Fever	8			
Septicaemia	24a	0530, 0531, 0532, 0533, 0534	0530, 0531, 0532, 0533, 0534	0380, 0381, 0382, 0388, 0389
Streptococcal	115b(2)	0510	0510	0340, 0341
Typhoid	1	0400	0400	10
Other URT		4700, 4710, 4720, 4721, 4740, 4750	4700, 4710, 4720, 4721, 4730, 4740, 4750	4600, 4610, 4620, 4630, 4640, 4650
Varicella	38e	0870	0870	520
Viral Pneumonia				4800
Viruses	38f			

Table S1: England and Wales mortality data: Datasets and their respective International Classification of Disease (ICD) codes for E&W non-measles mortality data.

Method of Transformation

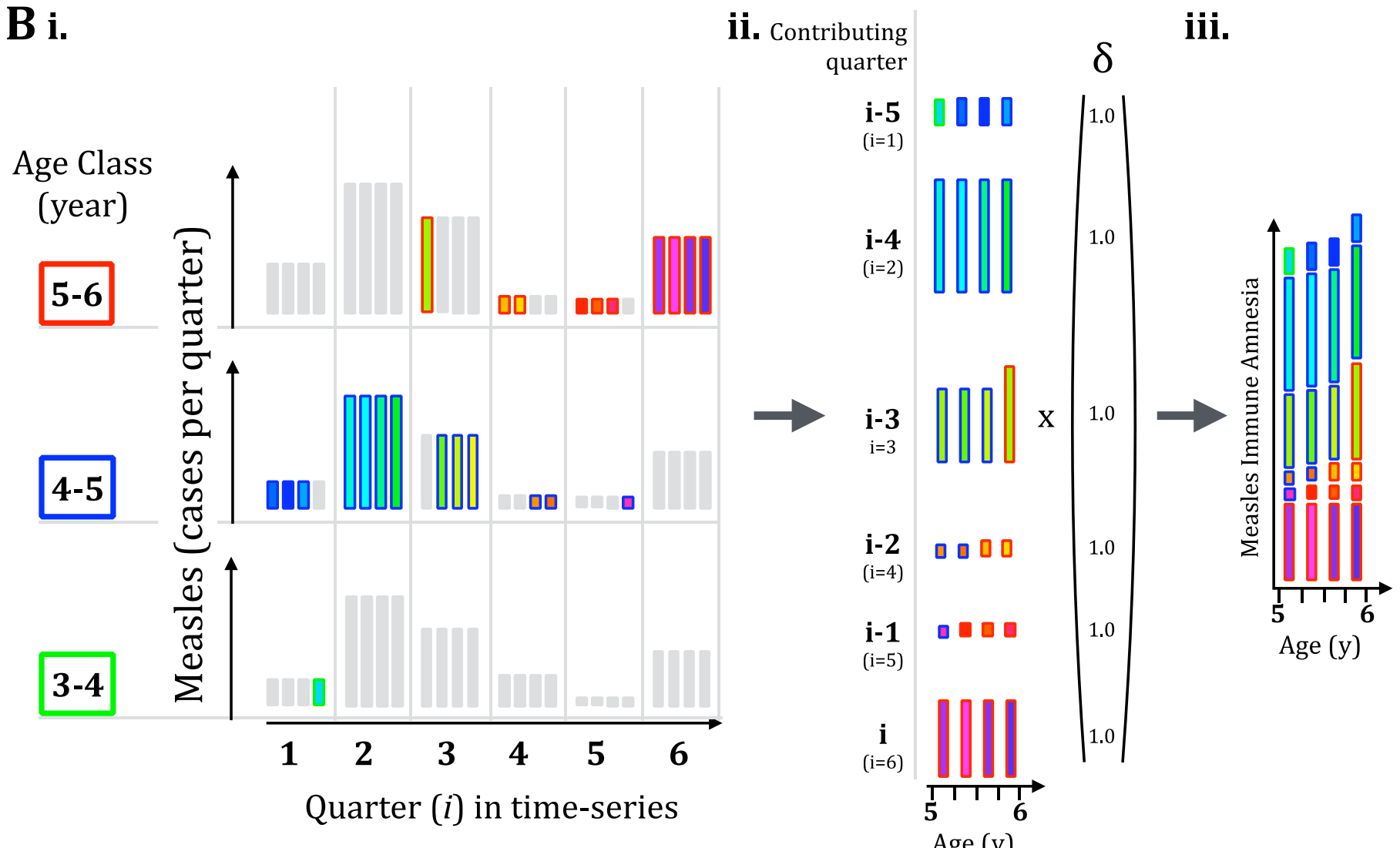


Two transformations

1) Additive (simple)
2) Gamma Response

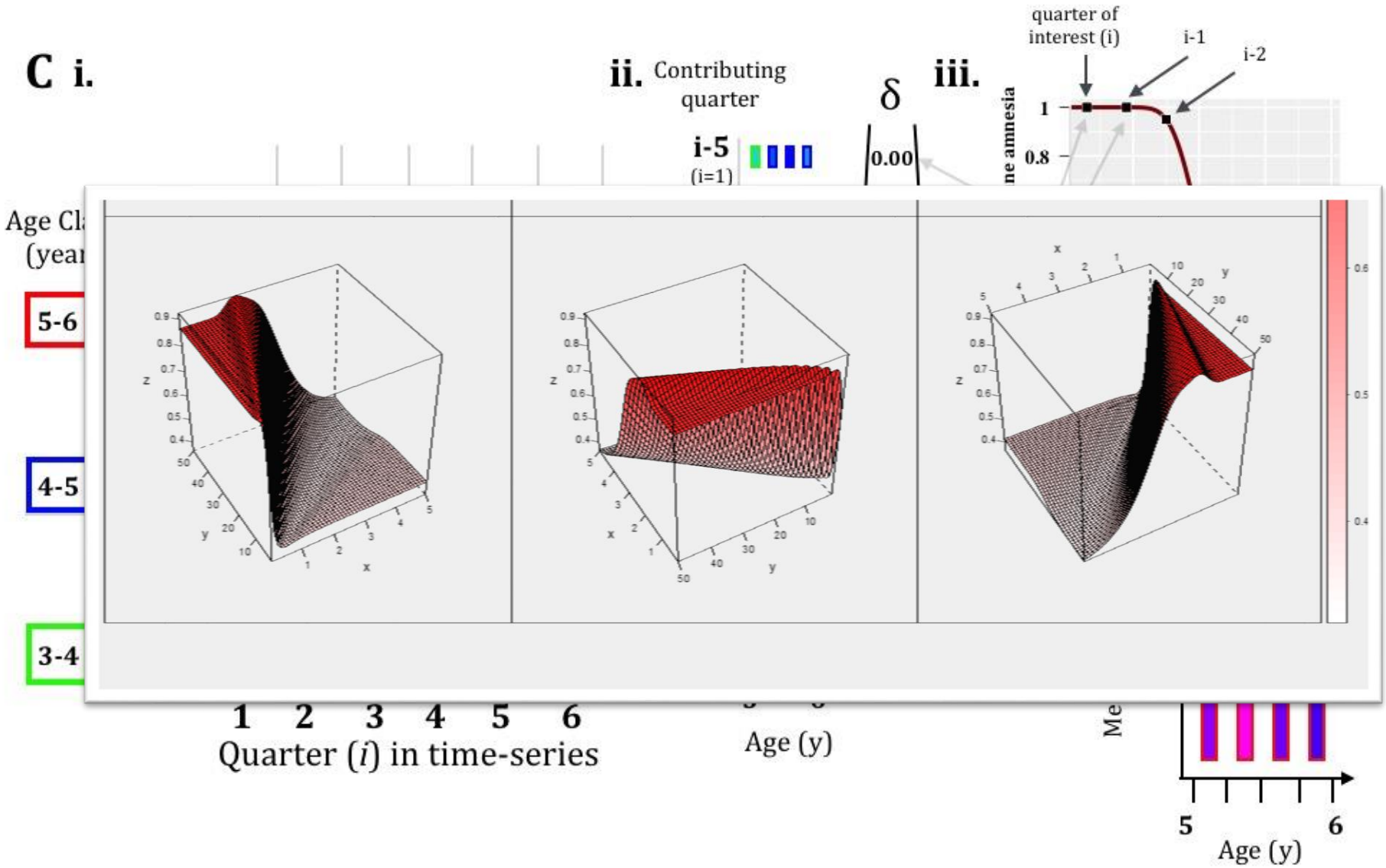
Transformation of the measles incidence data to immune-modulation data

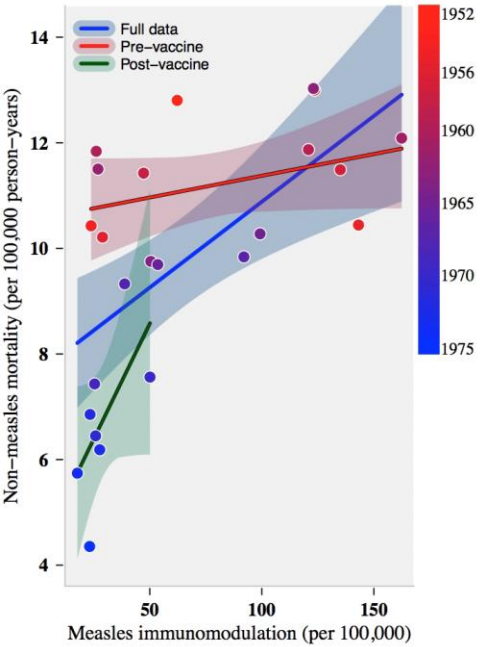
Calculate number of 5-6 year olds with immune-modulation in **quarter 6** of the time series from the **(A)** measles incidence using the Additive transformation assuming mean 18 months duration of immune-modulation

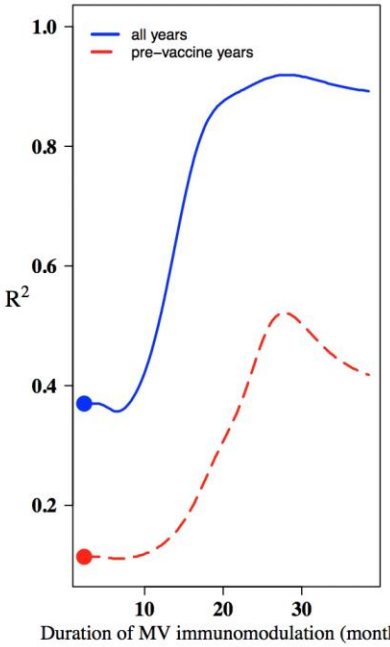


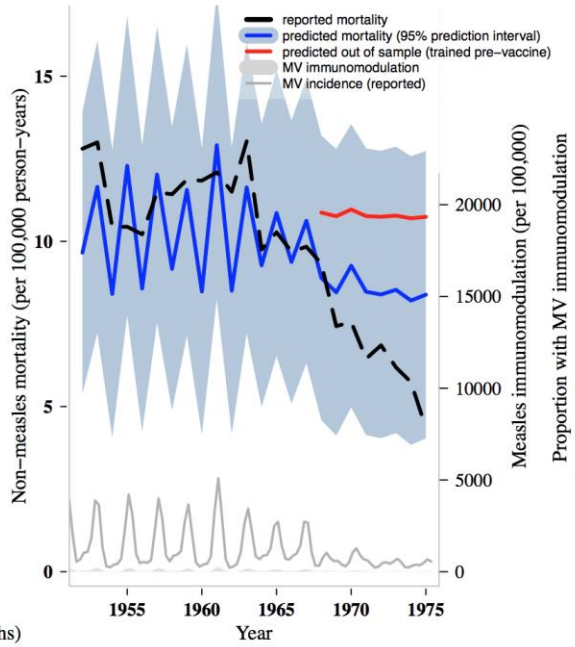
Transformation of the measles incidence data to immune-modulation data

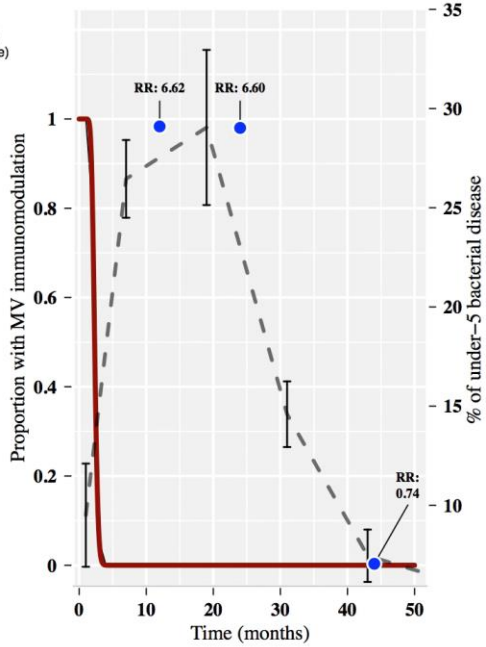
Calculate number of 5-6 year olds with immune-modulation in **quarter 6** of the time series from the **(A)** measles incidence using the **Gamma** transformation assuming mean **10** months duration of immune-modulation




Full data
Pre–vaccine
Post–vaccine
1952
1956
1960
1965
1970
1975
Non–measles mortality (per 100,000 person–years)
Measles immunomodulation (per 100,000)

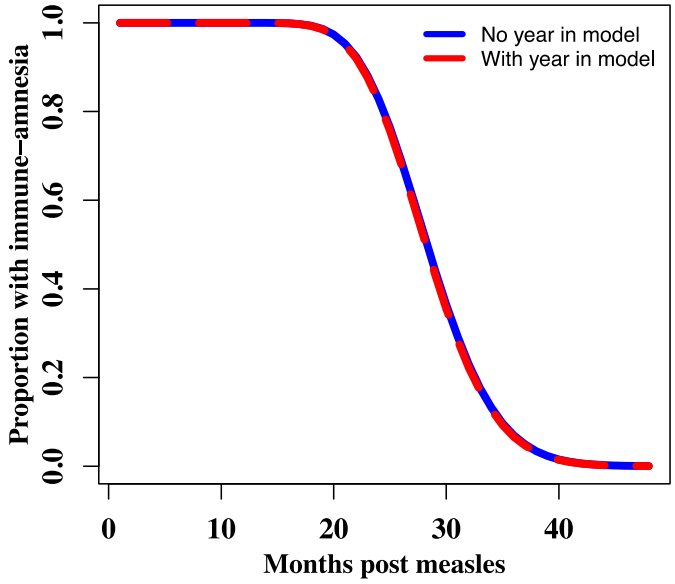

all years
pre–vaccine years
R^2
Duration of MV immunomodulation (months)


reported mortality
predicted mortality (95% prediction interval)
predicted out of sample (trained pre–vaccine)
MV immunomodulation
MV incidence (reported)
Non–measles mortality (per 100,000 person–years)
Measles immunomodulation (per 100,000)
Year

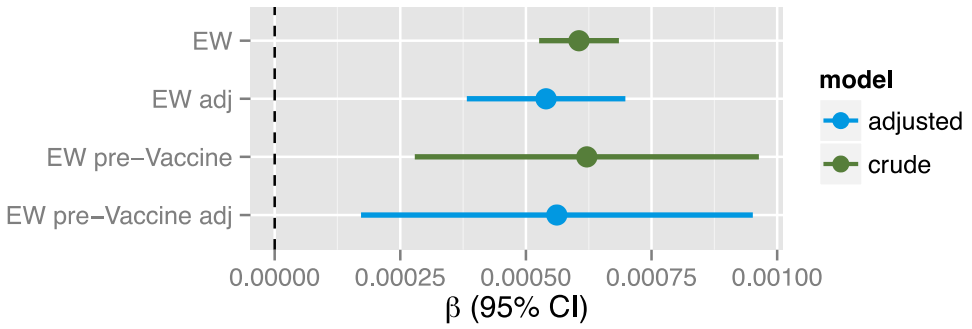

RR: 6.62
RR: 6.60
RR: 0.74
Proportion with MV immunomodulation
% of under–5 bacterial disease
Time (months)

Time effect?

A

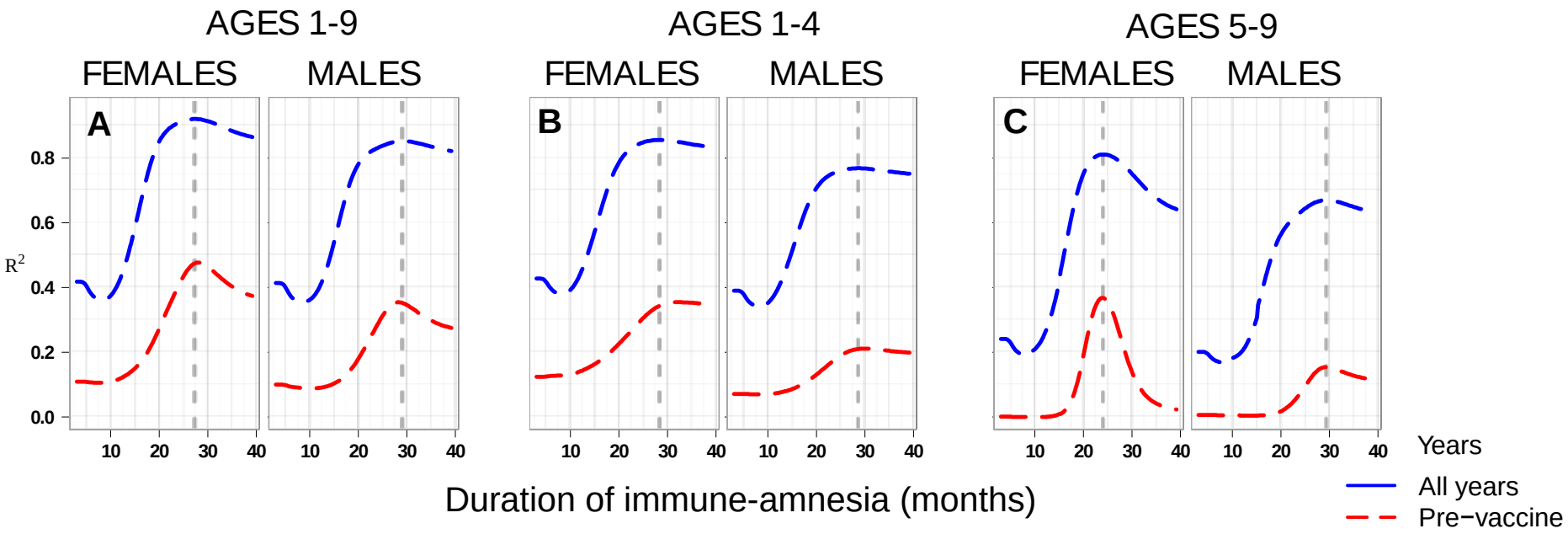


B

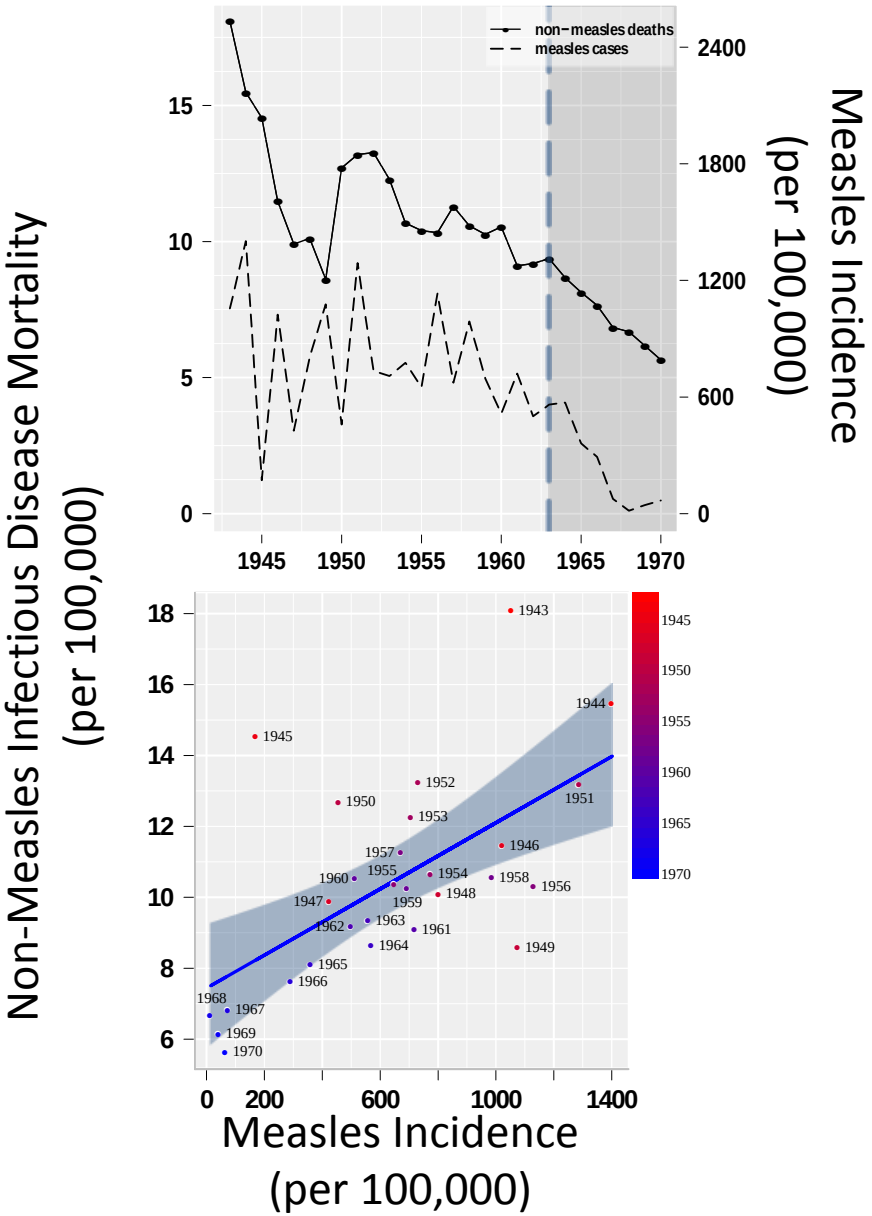


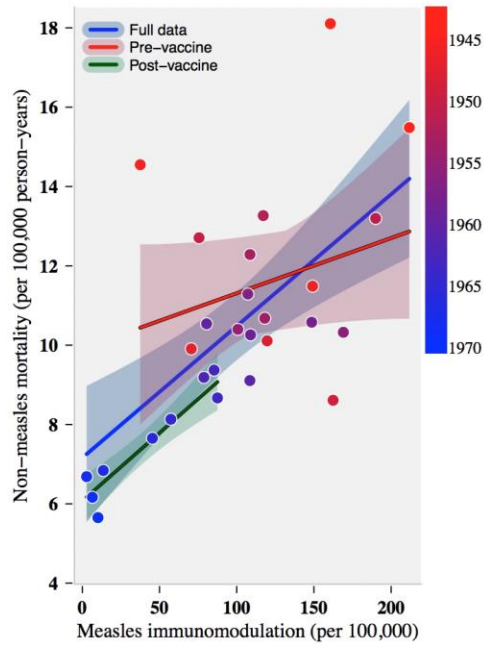
C

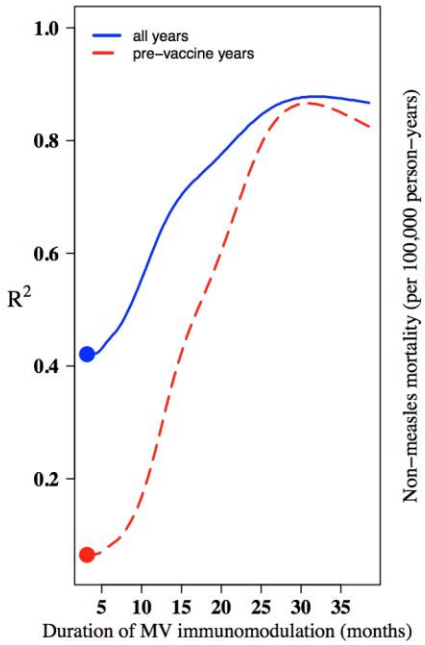
Years	Model	Predictor	β	P-value
All data	Crude	Immune amnesia	**6.07×10^{-4}**	**<.00001**
	Adjusted for year	Immune amnesia	**5.42×10^{-4}**	**<.00001**
		year	-4.19×10^{-2}	0.334
Pre-vaccine	Crude	immune amnesia	**6.21×10^{-4}**	**0.00163**
	Adjusted for year	immune amnesia	**5.616×10^{-4}**	**0.00825**
		year	3.85×10^{-2}	0.465

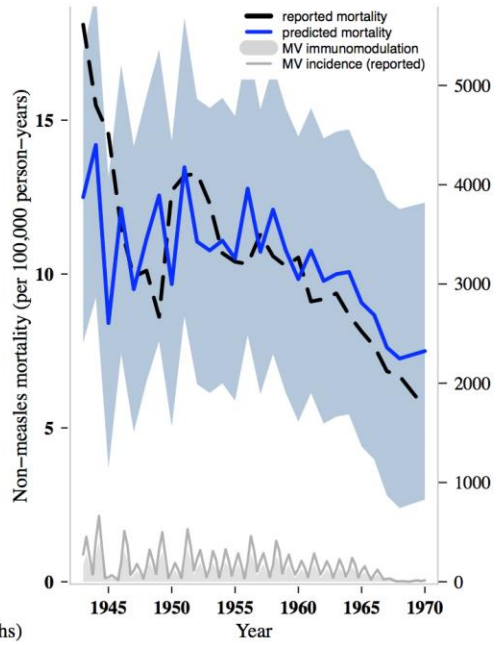

AGES 1-9
AGES 1-4
AGES 5-9
FEMALES
MALES
A
B
C
R^2
0.0
0.2
0.4
0.6
0.8
10
20
30
40
Duration of immune-amnesia (months)
Years
All years
Pre−vaccine

USA


non−measles deaths
measles cases
Non-Measles Infectious Disease Mortality (per 100,000)
Measles Incidence (per 100,000)
Measles Incidence (per 100,000)


Full data
Pre−vaccine
Post−vaccine
Non−measles mortality (per 100,000 person−years)
Measles immunomodulation (per 100,000)
1945
1950
1955
1960
1965
1970


all years
pre−vaccine years
R^2
Duration of MV immunomodulation (months)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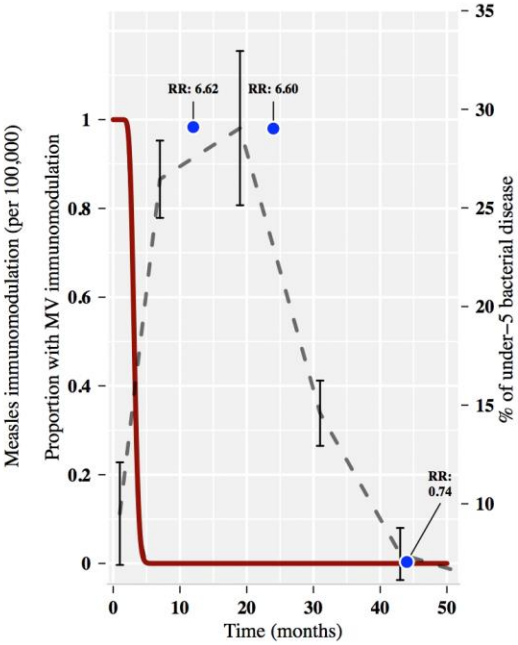
predicted mortality
MV immunomodulation
MV incidence (reported)
Non−measles mortality (per 100,000 person−years)
Measles immunomodulation (per 100,000)
Year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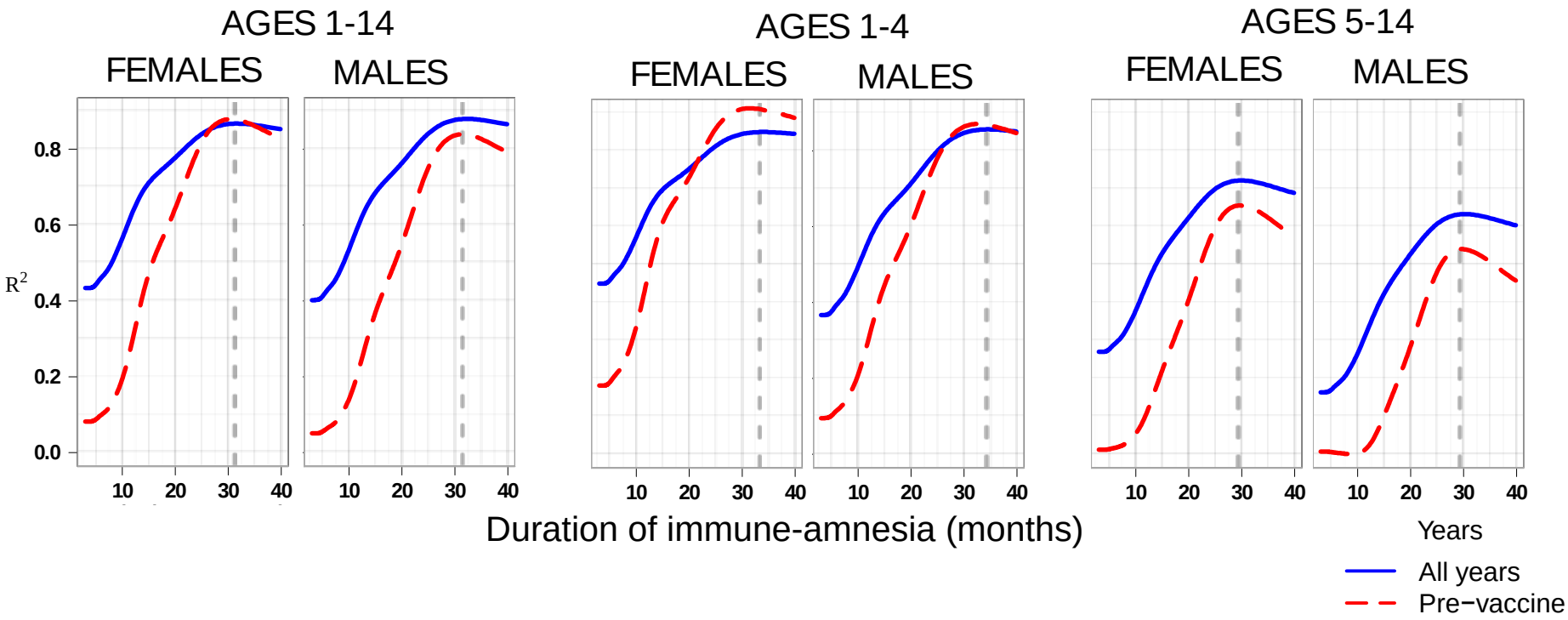
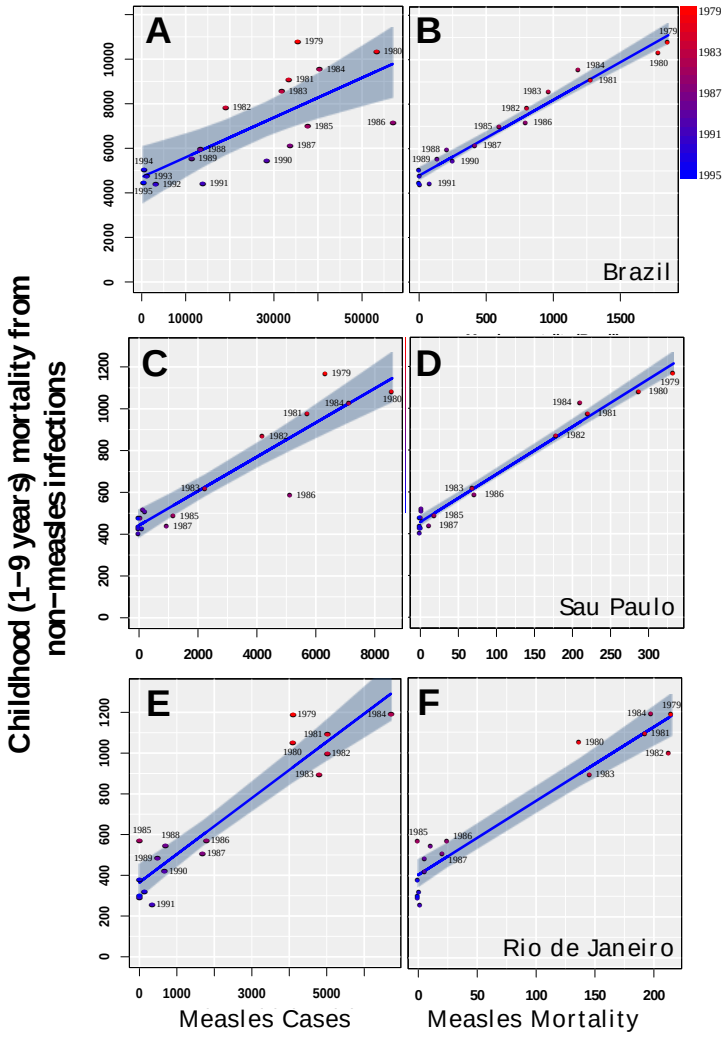
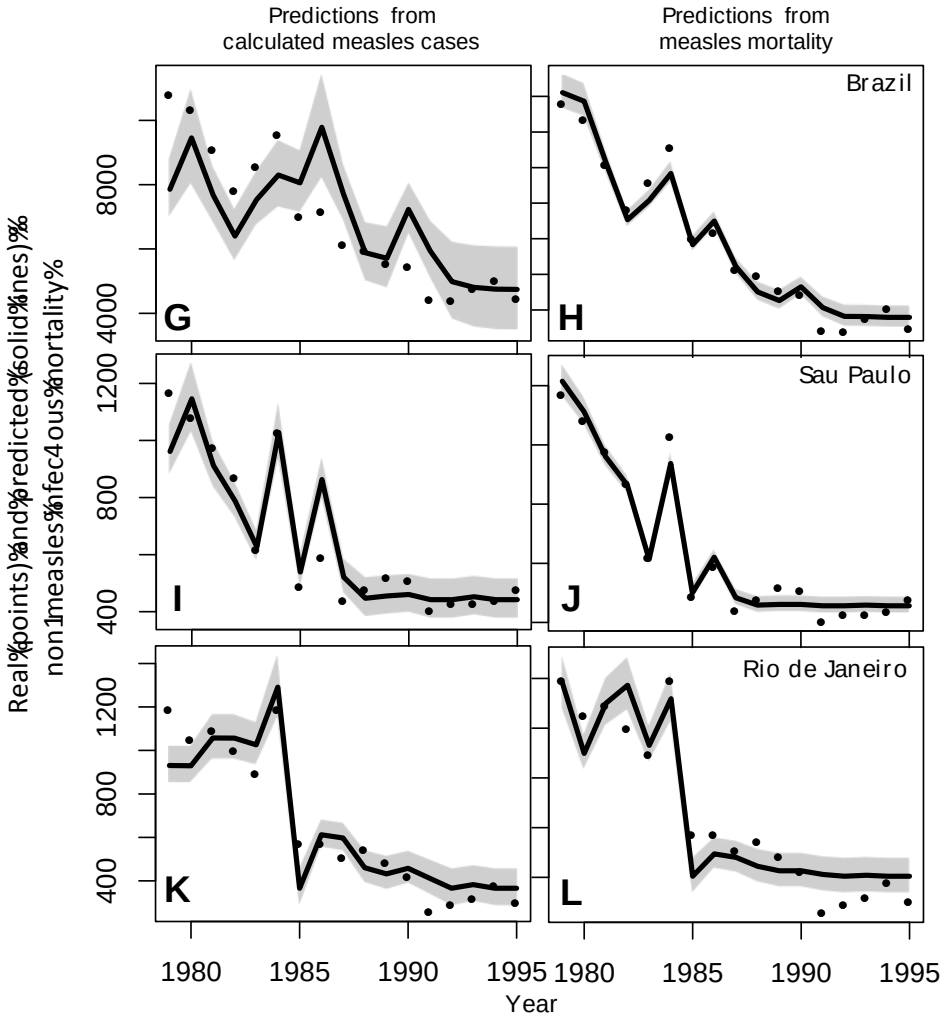
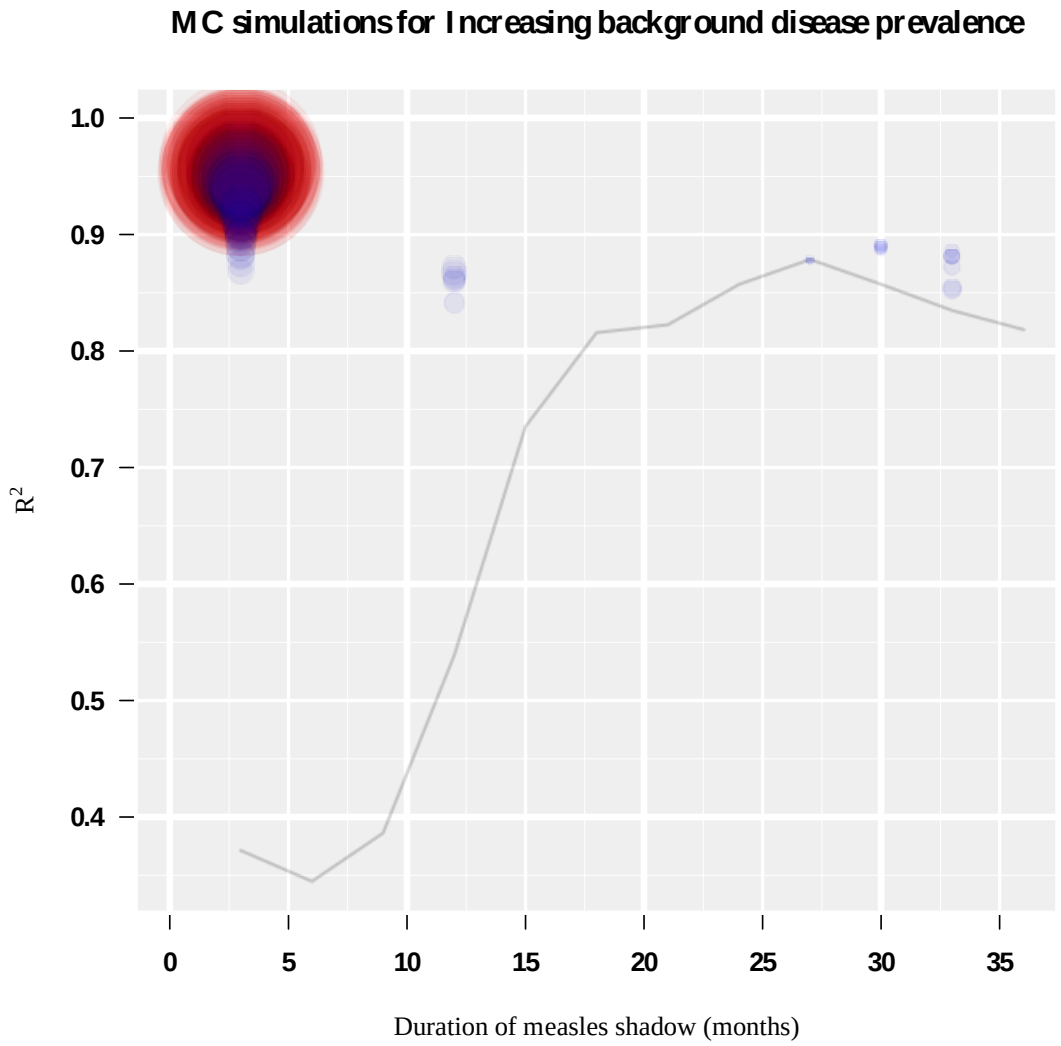

AGES 1-14
FEMALES
MALES
AGES 1-4
FEMALES
MALES
AGES 5-14
FEMALES
MALES
R^2
0.0
0.2
0.4
0.6
0.8
10
20
30
40
Duration of immune-amnesia (months)
Years
All years
Pre−vaccine

High vs. Low Income (Disease Prevalence)?





High vs. Low Income (Disease Prevalence)?

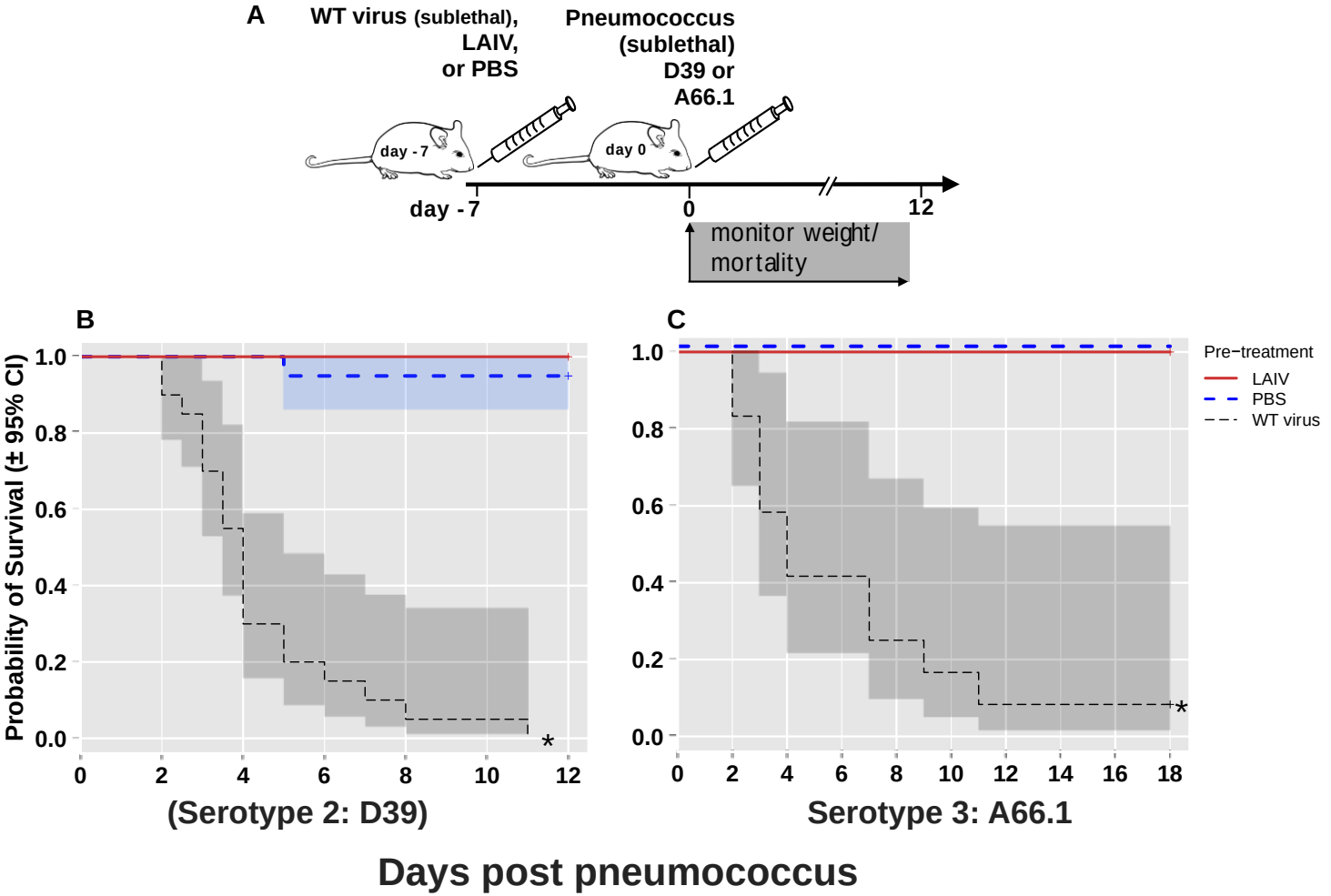


Live Influenza Vaccines and bacterial infections
(If time permits…)

Live Attenuated Influenza Vaccine Enhances Colonization of *Streptococcus pneumoniae* and *Staphylococcus aureus* in Mice

Michael J. Mina, Jonathan A. McCullers and Keith P. Klugman

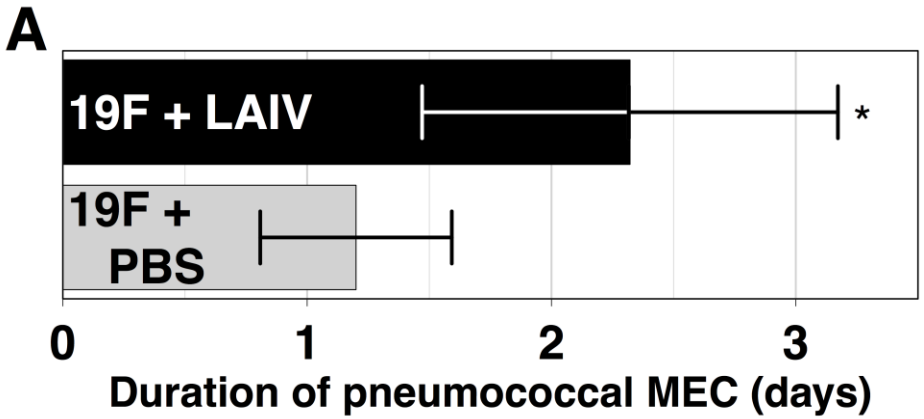
2014. Live Attenuated Influenza Vaccine Enhances Colonization of *Streptococcus pneumoniae* and *Staphylococcus aureus* in Mice. mBio 5(1): . doi:10.1128/mBio.01040-13.

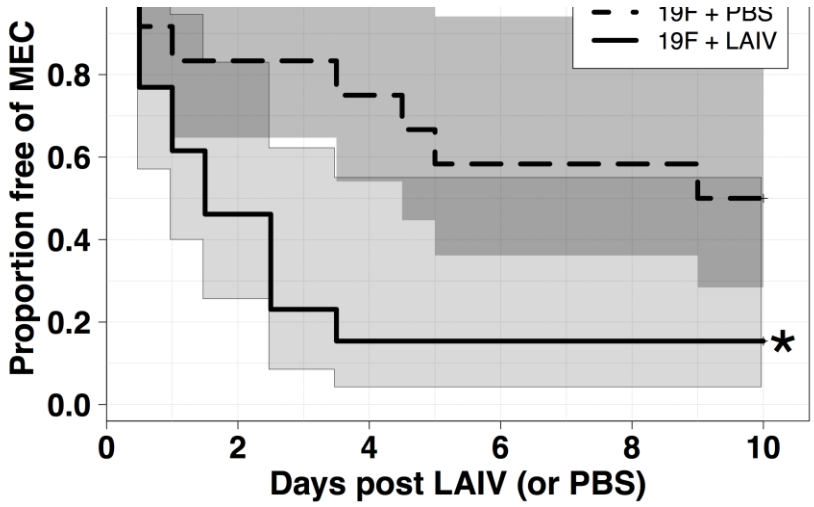


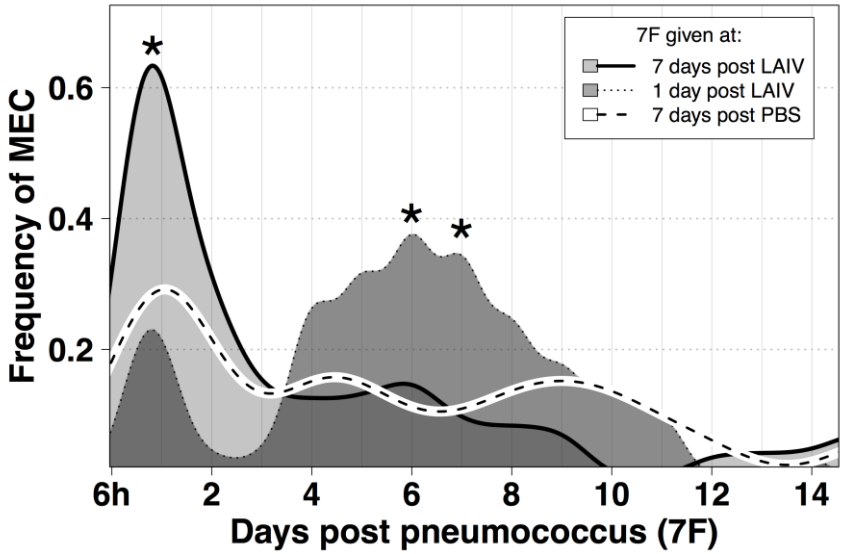
Live Attenuated Influenza Virus Increases Pneumococcal Translocation and Persistence Within the Middle Ear

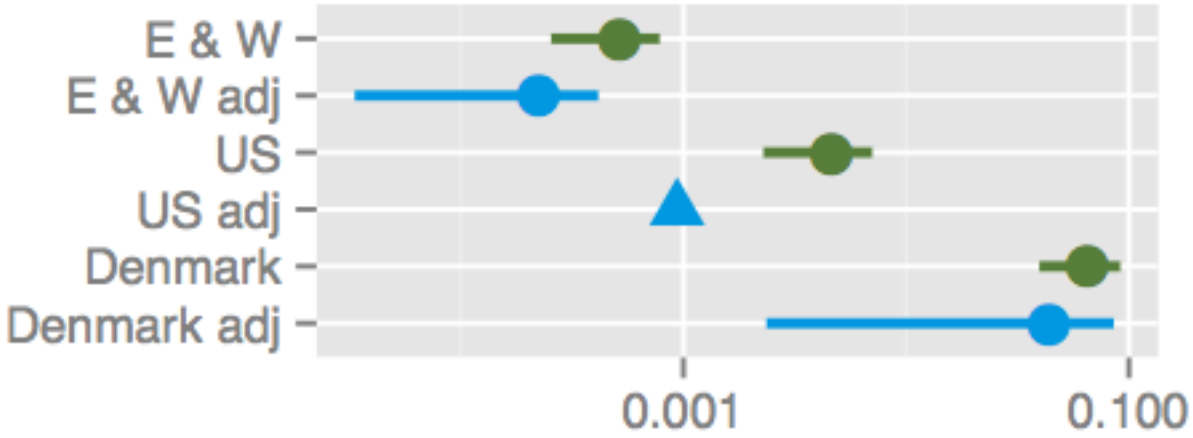
Michael J. Mina,[1,2,3] Keith P. Klugman,[2] Jason W. Rosch,[3] and Jonathan A. McCullers[3]

[1]Medical Scientist Training Program, Emory University School of Medicine, and [2]Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, Georgia; and [3]Department of Infectious Diseases, St Jude Children's Research Hospital, Memphis, Tennessee








E & W
E & W adj
US
US adj
Denmark
Denmark adj
0.001
0.100

Example: Calculate the number of **5-6 year olds** with MV immunomodulation in the **6th quarter** of the time-series using the **Additive Transformation** and a **duration of MV immunomodulation = 18 months**.