

Measles

Factors Impacting Population Immunity

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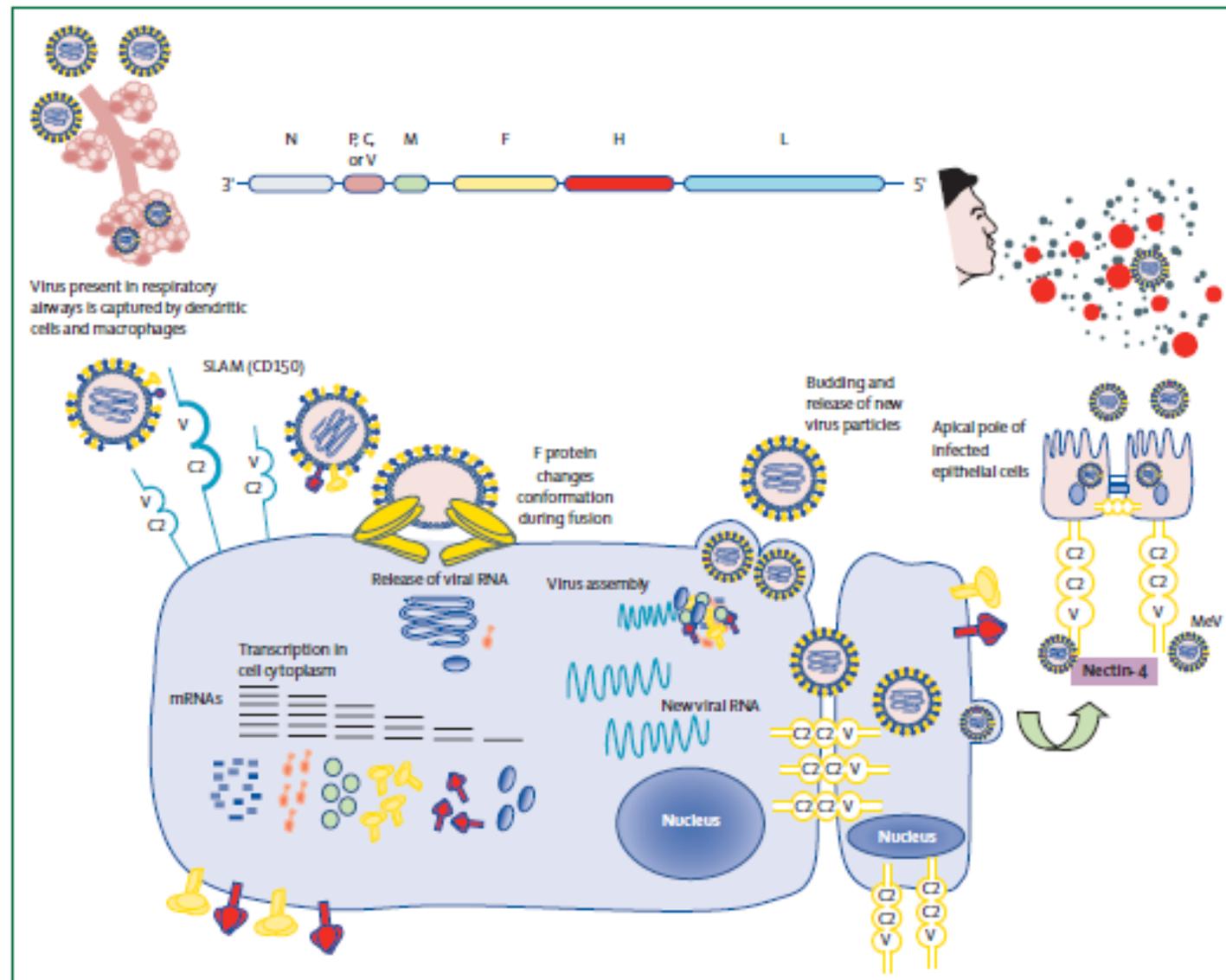
- I have no disclosures

Objectives

- Describe immune responses to measles infection
- Describe immune correlates of protection
- Describe waning of immune responses to measles

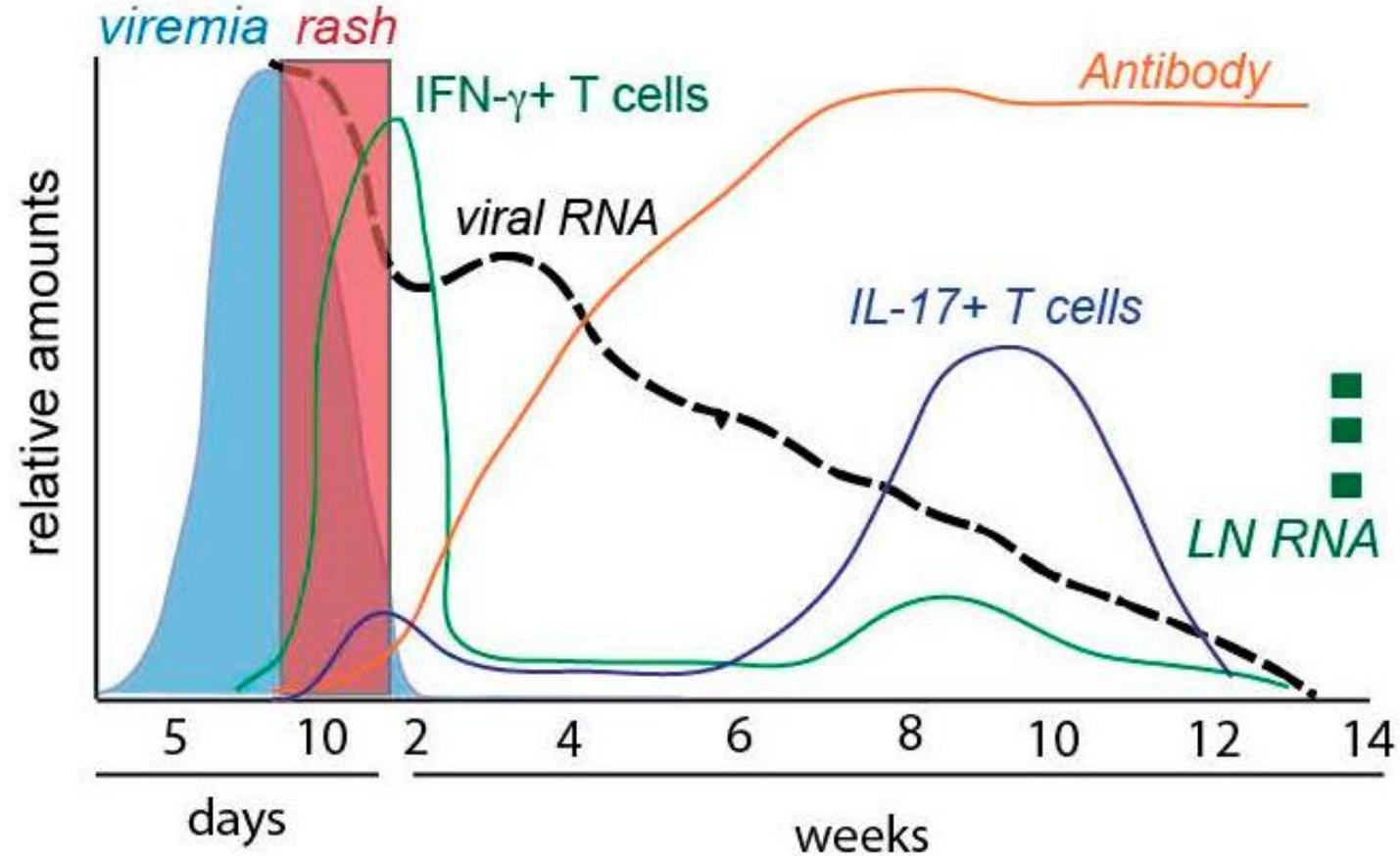
MEASLES PATHOGENESIS

- Measles virus (MeV) infects dendritic cells or alveolar macrophages of airways
- In regional lymph nodes, the immune response is initiated
- Infected lymphocytes spread the infection systemically
- In organs MeV infects additional cell types (endothelial, epithelial)

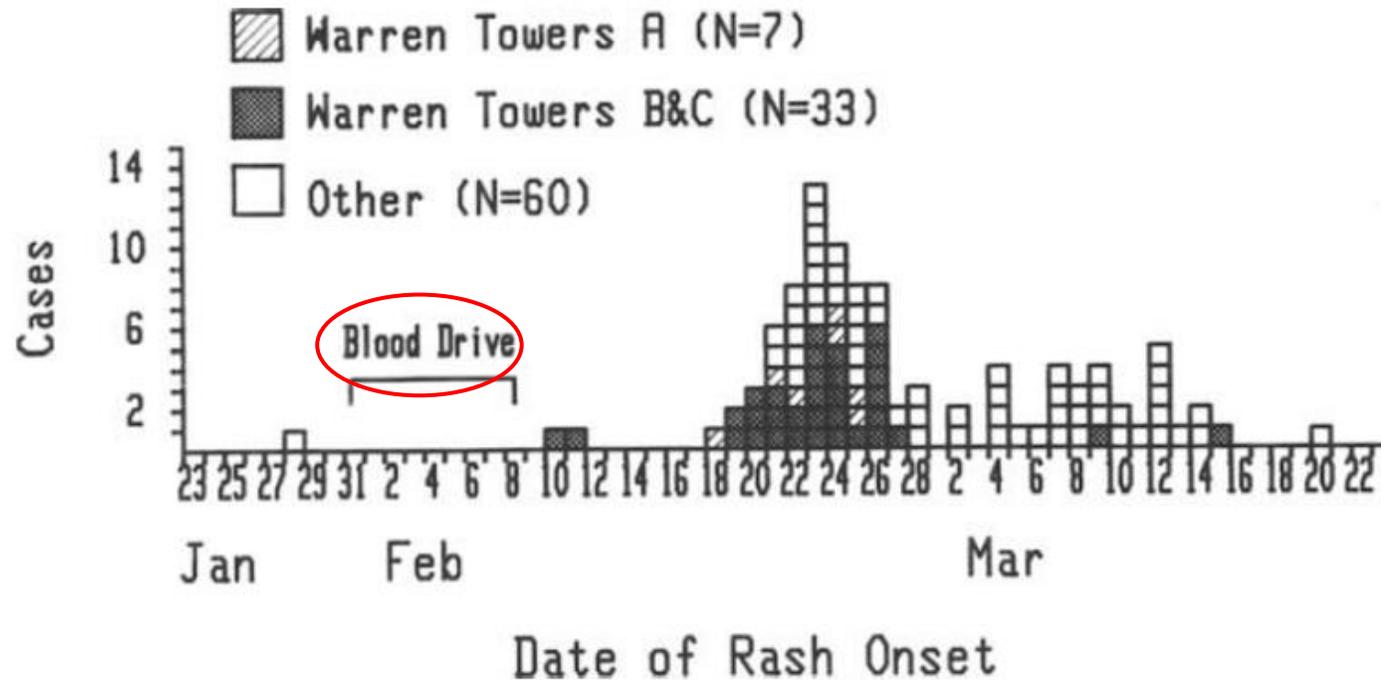


MEASLES PATHOGENESIS

- Incubation period: suppression of interferon responses (viral spread)
- Adaptive cellular responses coincide with the rash and clearance of viremia
- Antibody responses follow.
- Viral RNA detection can continue for weeks: immune activation.
- Post infection: lifelong immunity



Measles Correlate of Protection



- An outbreak of measles in Boston, 1985.
- The majority of cases at Boston Univ residential buildings
 - A blood drive occurred shortly before the outbreak

Measles Correlate of Protection

- Participants N=90, Pre-exposure blood N=80, Number of clinical cases=8
- Overall attack rate: 2.2%-4.4%
- Using plaque-reduction neutralization assay

PRNT \leq 120
8/9 clinical measles

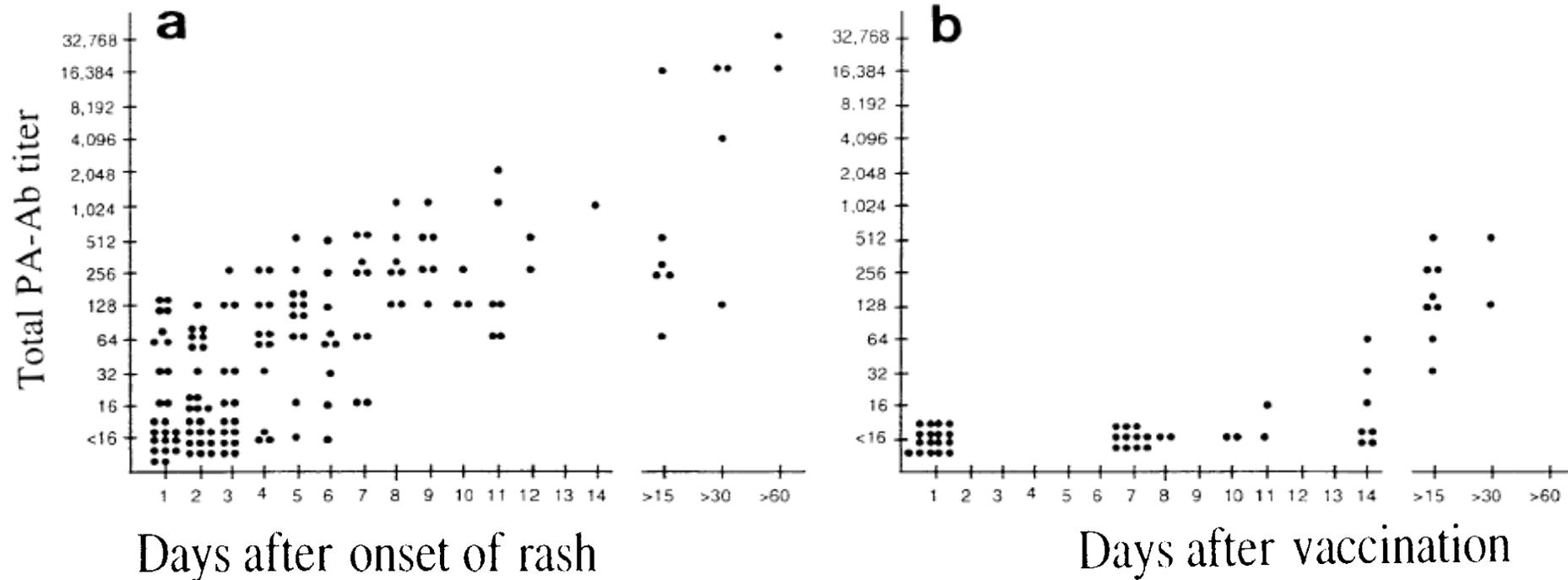
PRNT > 120
0/71 clinical measles

PRNT 216-874
7/11 serologic evidence of measles

Measles Correlate of Protection

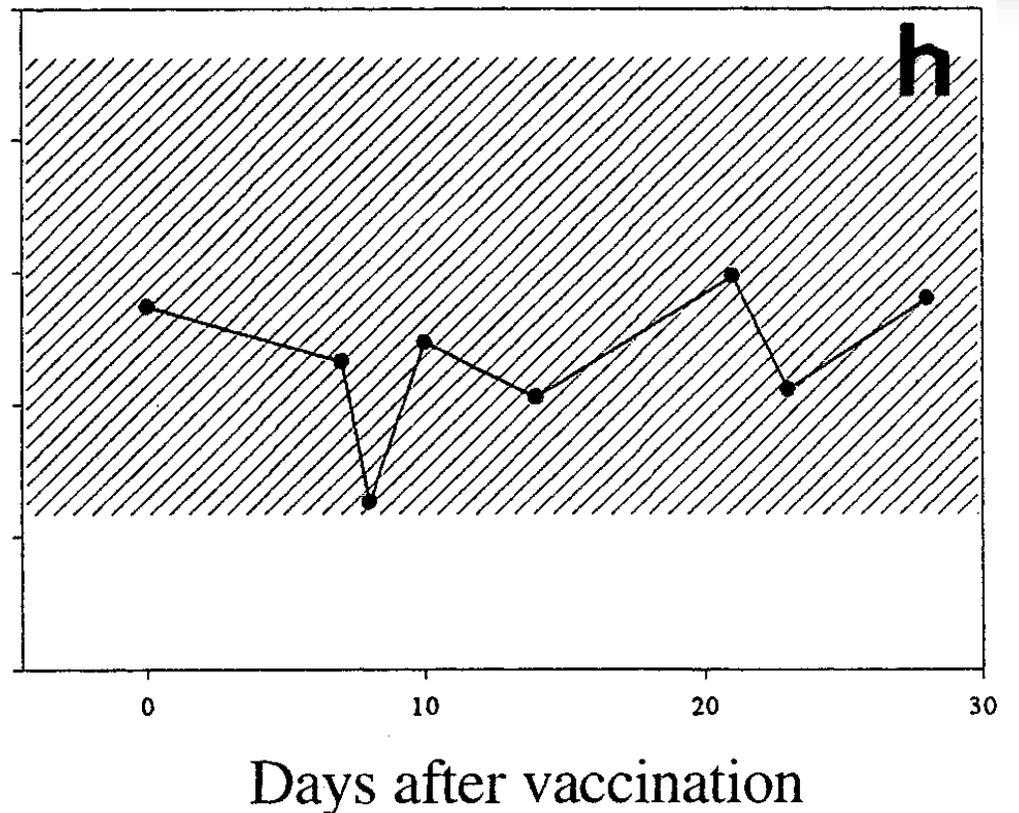
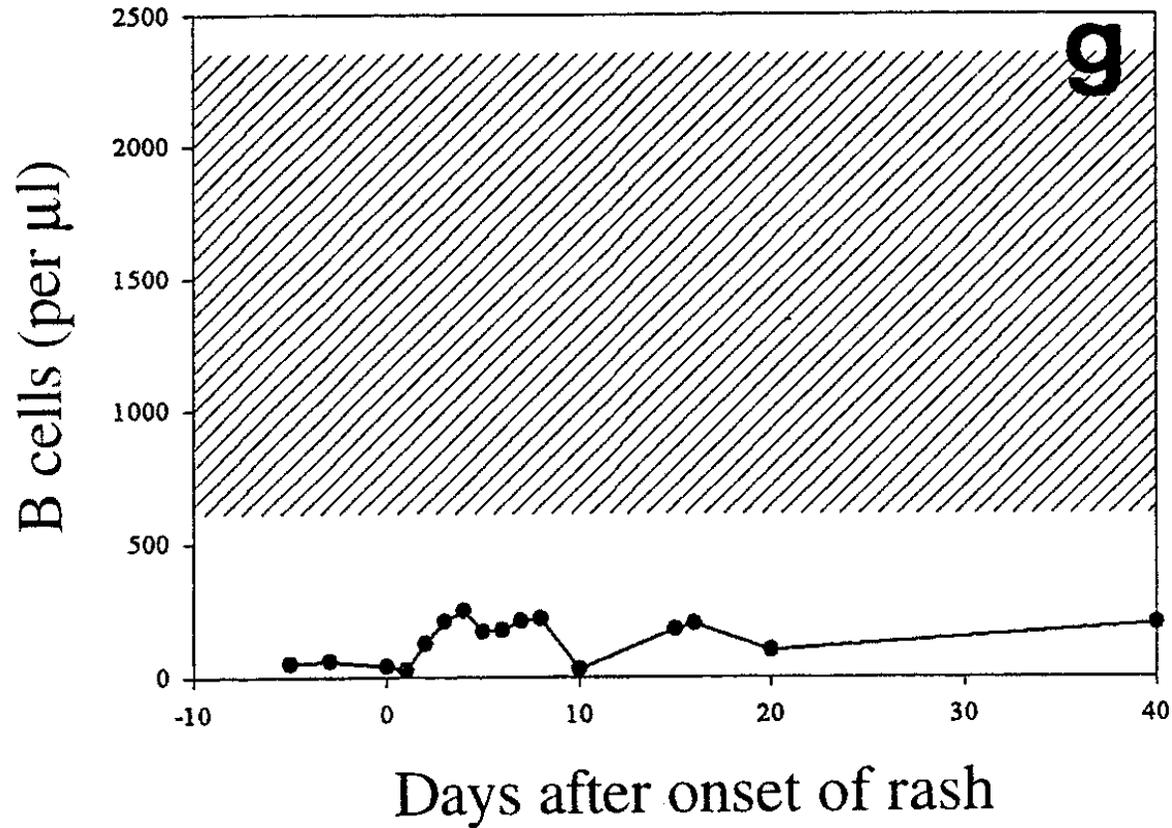
Subject(s)	PRN titer		IgM	Age of vaccination [‡]	
	Pre-exposure	Post-exposure			
Cases					
1	<16	35,363	287	12 mo	
2	38	17,723	<160	§	No vaccine, possible disease
3	80	39,268	102	(10 mo)	
4	86	NA	NA	28 mo	Unverified
5	86	101,339	<48	10 mo	
6	98	44,661	662	(11 mo, 11 y)	
7	118	14,157	509	6 y, 12 y	
8	120	13,638	90	8 mo, 10 y	

Immune Response to Measles *Infection vs Vaccine*



- Population: 53 vaccine recipients and 147 acutely infected patients, 1-3 years of age
- The Particle Agglutination antibody titers post measles vaccination were 10-fold lower than post infection

Immune Response to Measles *Infection vs Vaccine*



- Apoptosis in uninfected lymphocytes in measles infected, but not in vaccinees

Immune Response to Measles Vaccines

Age-dependency

Age at time of vaccination, antibodies present	GMT (95% CI), mIU		
	Before vaccination	After first dose	After second dose
6 months			
Total	8 (4–16)	130 (58–292)	702 (344–1457)
PA	47 (31–71)	39 (16–95)	613 (174–1058)
NPA	NA	516 (209–1274)	1231 (511–3105)
9 months			
Total	2 (2–4)	835 (317–1882)	1546 (686–3484)
PA	27 (16–47)	70 (3–1890)	258 (27–2463)
NPA	NA	1496 (953–2350)	2356 (956–5811)
12 months, NPA	NA	1512 (1155–1984)	NA

The younger the age at vaccination the lower the humoral responses

Immune Response to Measles Vaccines

Age-dependency

Age at time of vaccination, antibodies present	Mean SI (SE)		
	Before vaccination	After first dose	After second dose
6 months			
Total	2.0 (0.2)	6.8 (1.7)	10.9 (1.7)
PA	2.2 (0.3)	4.5 (0.9)	10.9 (2.6)
NPA	1.7 (0.2)	8.5 (3.7)	11.4 (2.5)
9 months			
Total	1.6 (0.2)	8.4 (2.1)	7.5 (1.4)
PA	1.0 (0.1)	3.3 (1.6)	5.2 (1.5)
NPA	1.8 (0.3)	9.7 (2.5)	8.0 (1.8)
12 months, NPA	1.5 (0.1)	7.0 (0.9)	NA

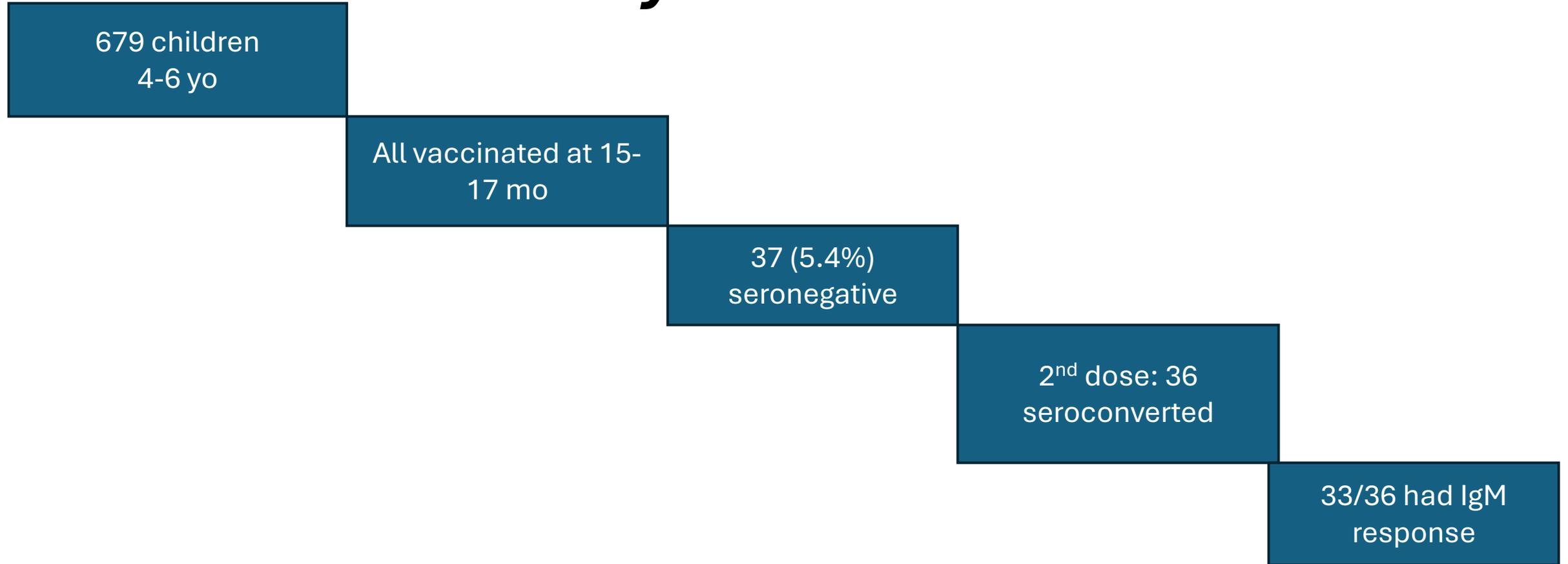
No appreciable effect of age on cellular responses to measles vaccine

Vaccination to Eliminate Measles Transmission

- The high transmissibility of measles poses a significant challenge to elimination.
- $R_0=14-18$
- Goal of immunization program: decrease the population susceptibility to the lowest possible $\longrightarrow R<1$
- If target $R=0.8$, and average $R_0=16$, no more than 5% of the public can be susceptible.
- Measles elimination: >95% vaccine coverage.

Immune Response to Measles Vaccines

Why two doses?



Immune Response to Measles Vaccines

Why two doses?

- Seroprotection to a first dose of vaccine: 92-95% (given @12 mo)
- What is the effectiveness in the field?

	No. of MCV1 VE point estimates	Median	Interquartile range	
			25th percentile	75th percentile
Lab confirmed/vx hx ascertained by record estimates				
Age of 1st dose				
9–11 months	9	84.0%	72.0%	95.0%
≥12 months	34	92.5%	84.8%	97.0%
Any age, (≥9months)	44	92.0%	84.0%	96.8%

A meta-analysis of vaccine effectiveness of a single dose by age of receipt

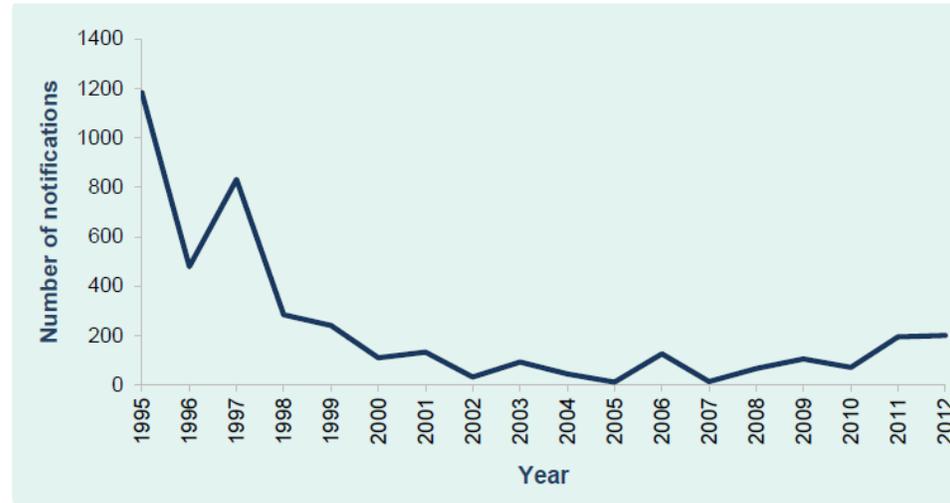
Measles Vaccine Effectiveness 1 or 2 doses?

- An outbreak in the Alaska, 1998
- 33 cases in schools
- School A (50.4% received 2 doses) and School B (45.5% received 2 doses)
- Relative Risk of measles in 2dose recipients vs 1dose recipients=0.06
- Incremental VE of 2 doses vs 1 dose= 94.1%

School	Enrollment	No. of doses of MCV received ^a		
		0	1	≥2
A	2192	0/1	16/1070	0/1105
B	1487	0/7	1/802	1/676
Total	3679	0/8	17/1872	1/1781

N with measles/N without measles.

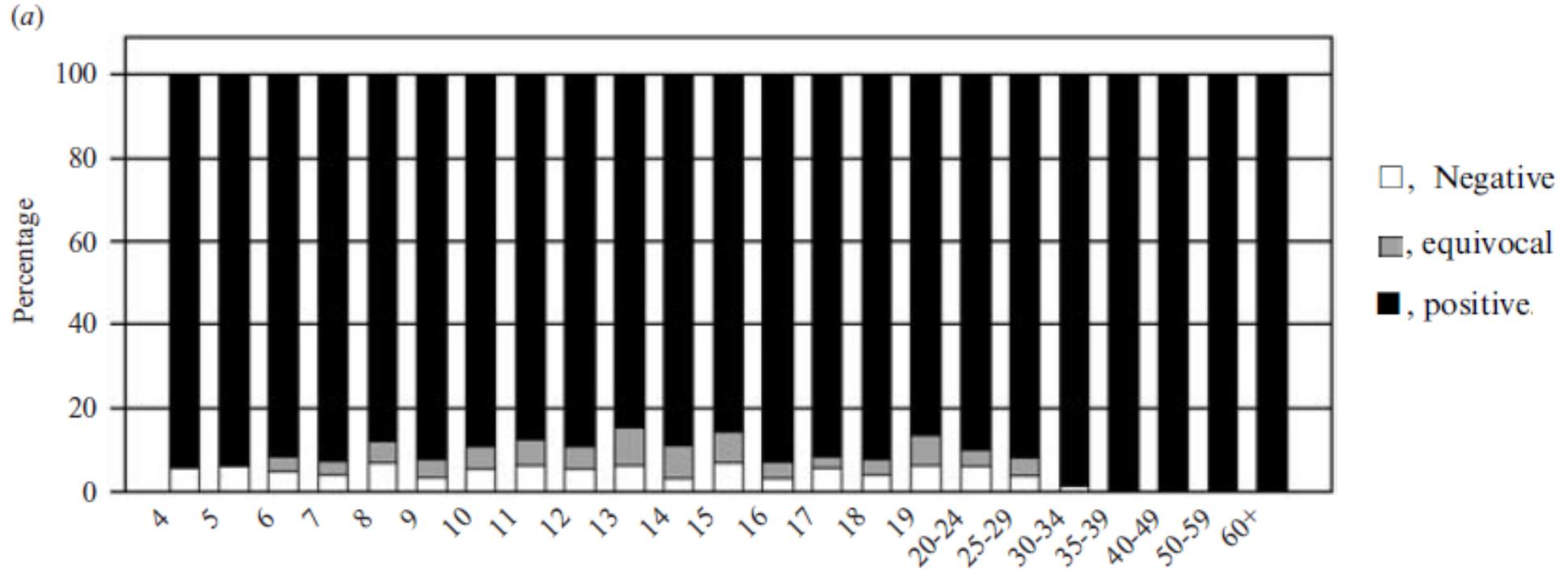
Measles Vaccine Effectiveness 1 or 2 doses?



N of measles notifications, Australia, 1995–2012

Doses	Number of cases (%) <i>n</i> = 189	Number of controls (%) <i>n</i> = 3780	VE % (95% CI)
0	160 (84.7)	437 (11.6)	—
1	22 (11.6)	1403 (37.1)	96.7 (94.5–98.0)
At least 1	29 (15.3)	3343 (88.4)	98.7 (97.9–99.2)
2	7 (3.7)	1940 (51.3)	99.7 (99.2–99.9)

Measles Immunity Waning Infection vs Vaccine

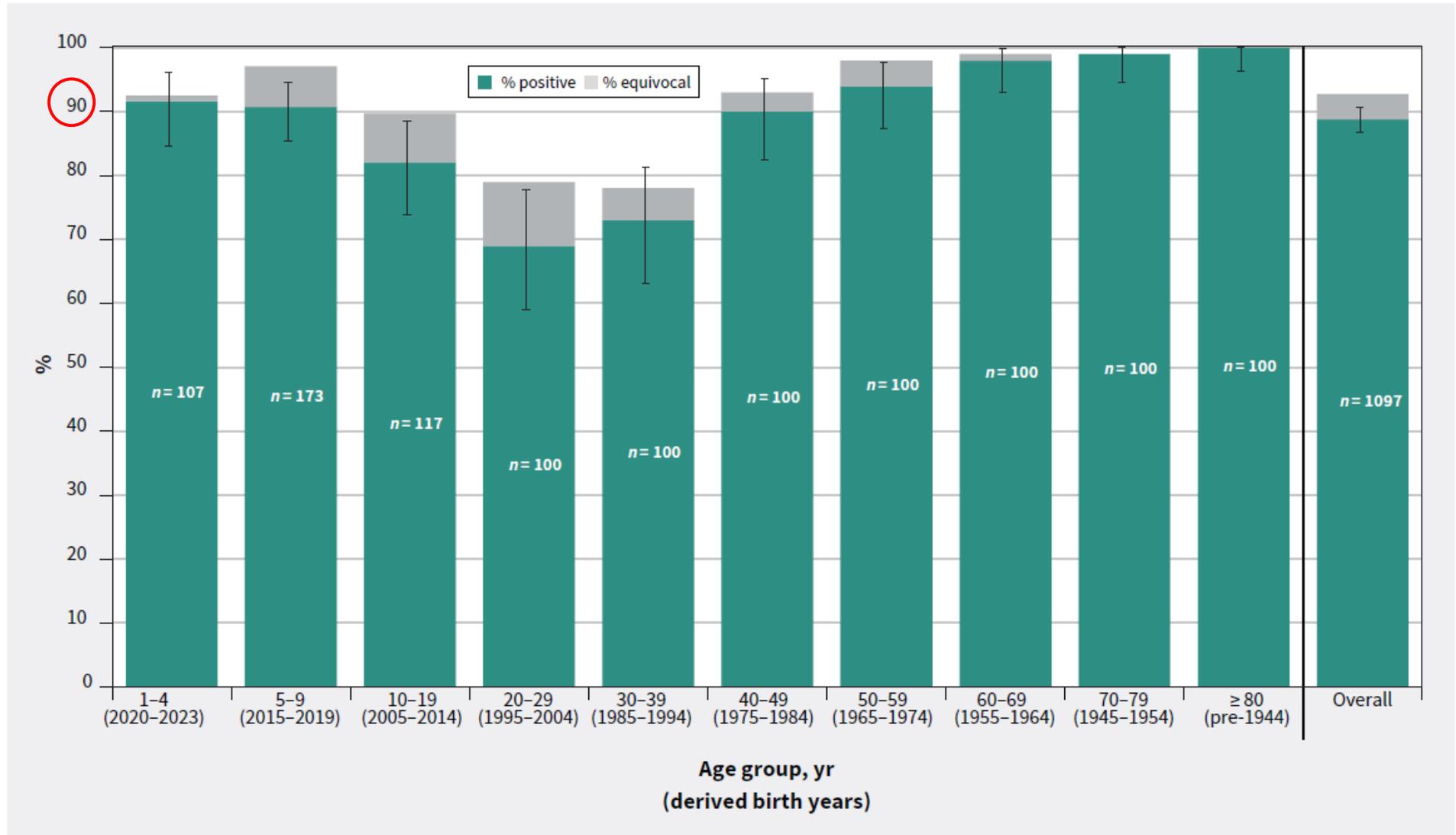


Seroprevalence by age of antibodies against measles, Luxembourg 2000-2001

- Measles vaccine first dose coverage=91.1%
- 99.5% of all adults born prior to 1970 are antibody-positive; 91.3% for adults born between 1970 and 1979, and to 89.9% for individuals born after 1980.

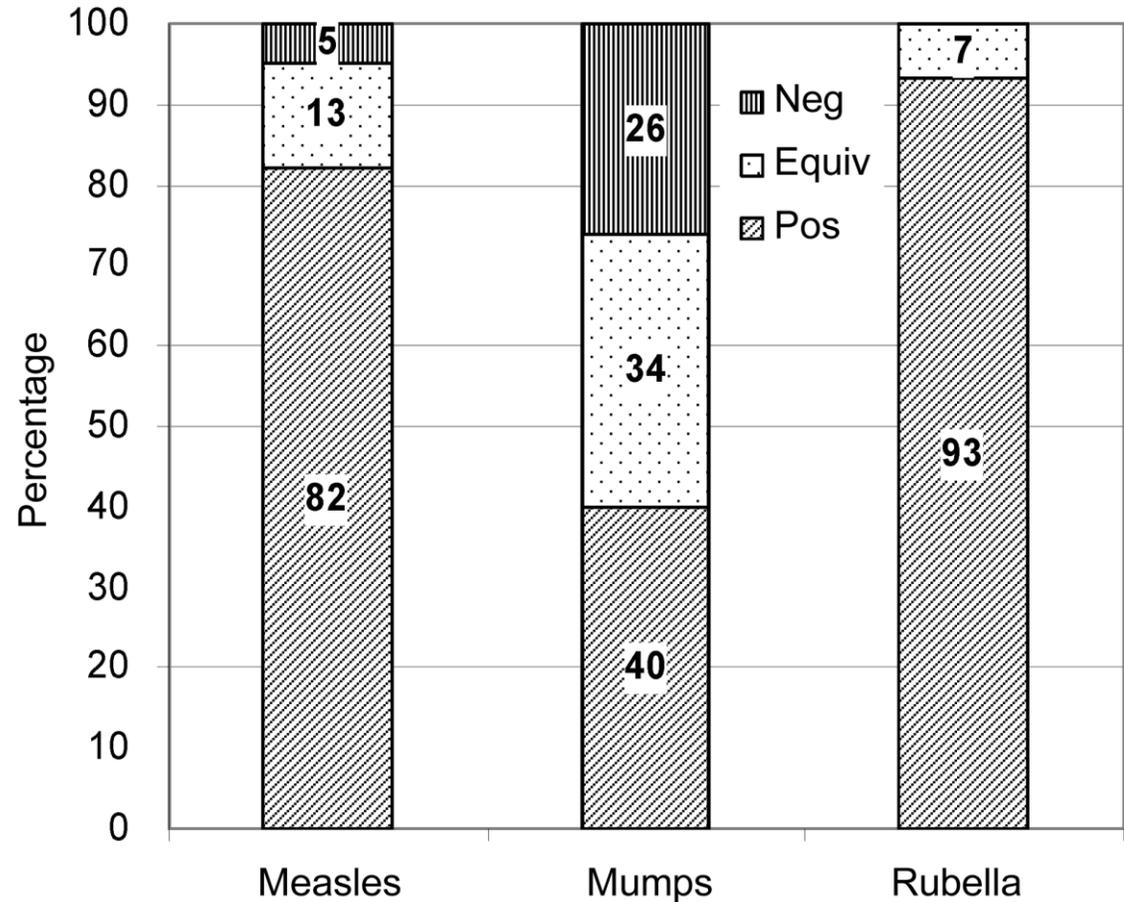
Measles Immunity Waning Canada

- Residual clinical lab samples
- Assay is EIA
- Year 2025
- Unknown Vaccine status

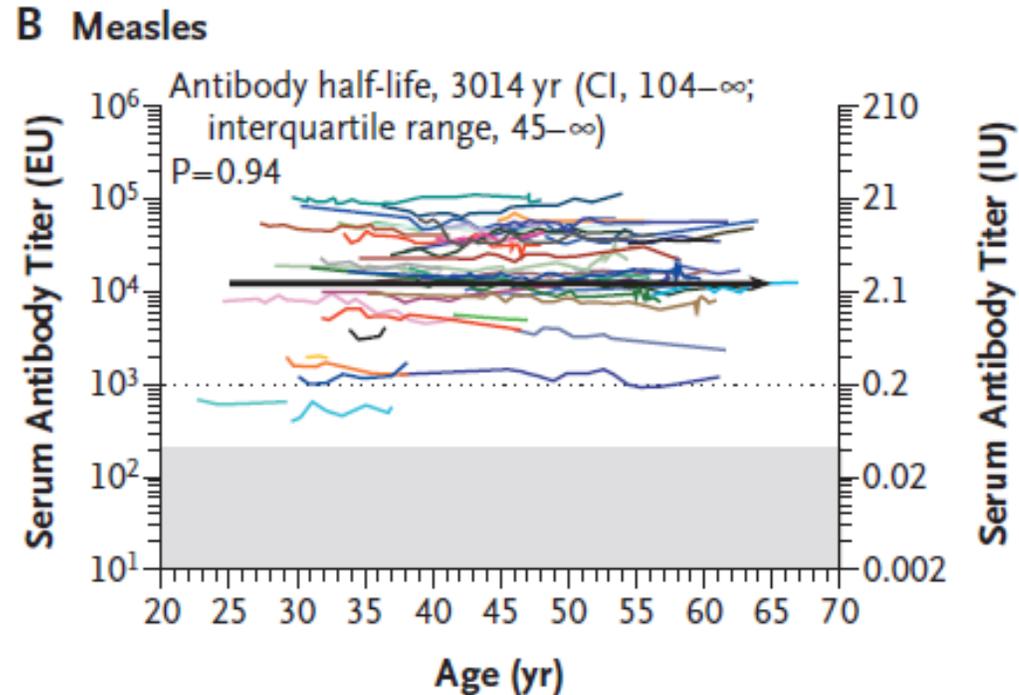


Measles Immunity Waning Finland

- 183 children vaccinated with 2 doses MMR
- EIA Ab 20 yrs later (2002)
- 95%, 74%, and 100% of vaccinees were seropositive for measles, mumps, and rubella
- 85% of 177 vaccinees had measurable measles Ab in oral fluids



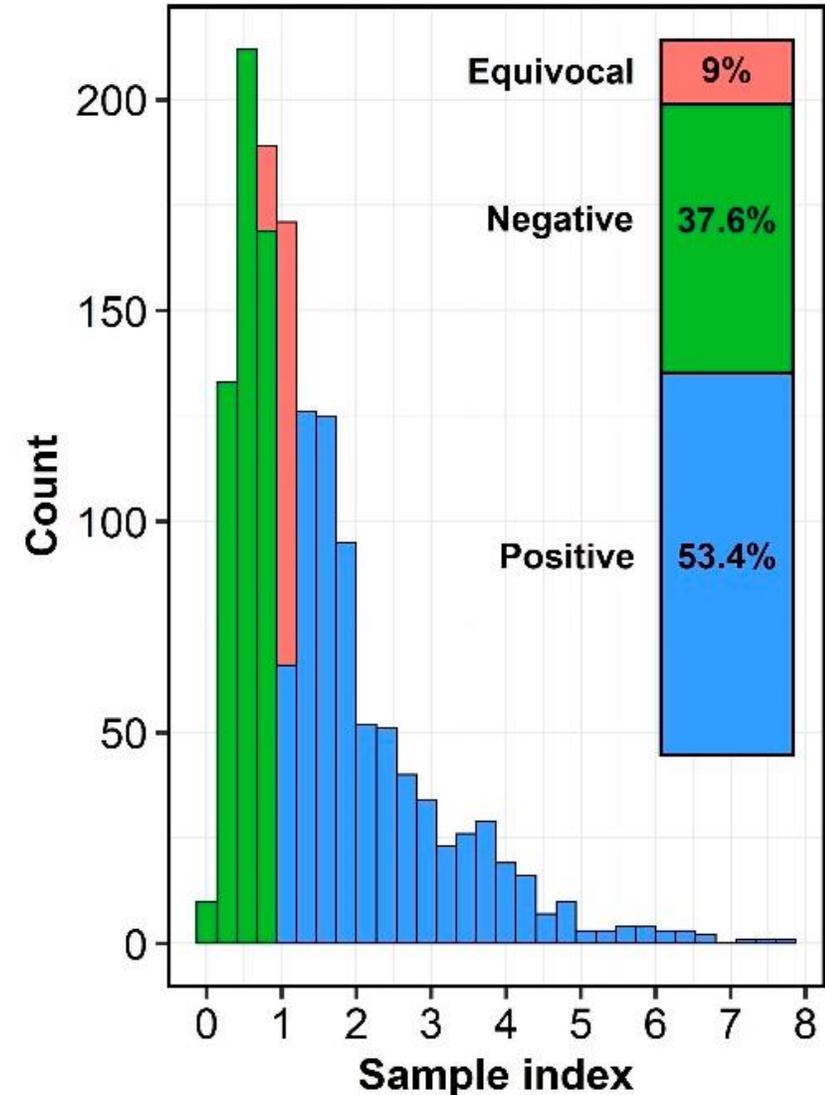
Measles Immunity Waning USA



- Individuals in the US were followed for 26 years
- Mean age at study exit 52 yo/Almost all exposed to measles infection.
- No antibody waning
- No correlation between memory B cells and Ab levels

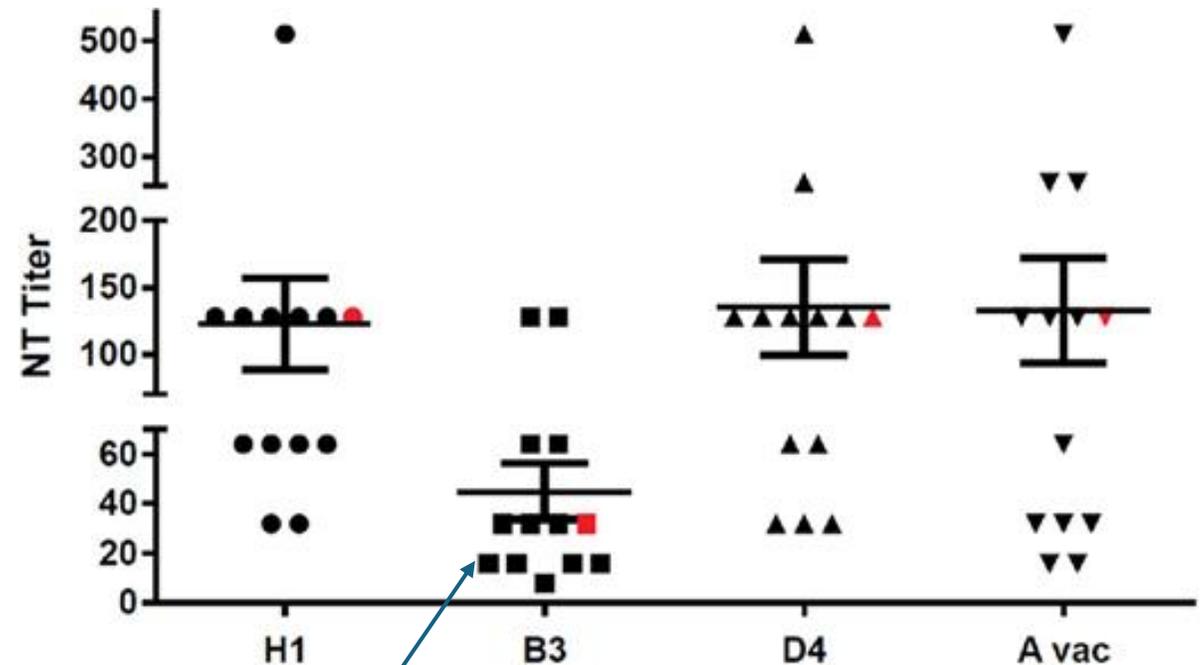
Measles Immunity Waning USA

- Biobanked sera, 1393 Adults, 20-44 years
- Olmstead County, Minnesota
- Vaccine coverage is ~90%
- Vaccine history not available on 1147 ppts
- Assay utilized ELISA
- Abs decreased with age



Measles Neutralization by Genotype

- Sera from recipients of 2 MMR doses (age=5yrs)
- Assay=FRNT
- With variable Neut titers, vaccine sera neutralized a wide array of circulating genotypes
- Genotype A is extinct from human circulation



B3 strains were neutralized at higher titers in other studies

CONCLUSIONS

- Measles vaccine elicits an immune response that is qualitatively similar to infection
- High transmissibility of measles necessitates high vaccine coverage to limit transmission: 2 doses needed for >95% serologic response
- Neutralizing Ab titers are a correlate of protection from infection and disease. Cellular immunity is key, though less well understood.
- Two doses are more effective than 1 dose at measles prevention.
- Antibody waning occurs faster with vaccine than infection
- Vaccine elicited antibodies neutralize currently circulating strains



- **Questions: Hana.ElSahly@bcm.edu**