Protective Immunity After Vaccination

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Overview

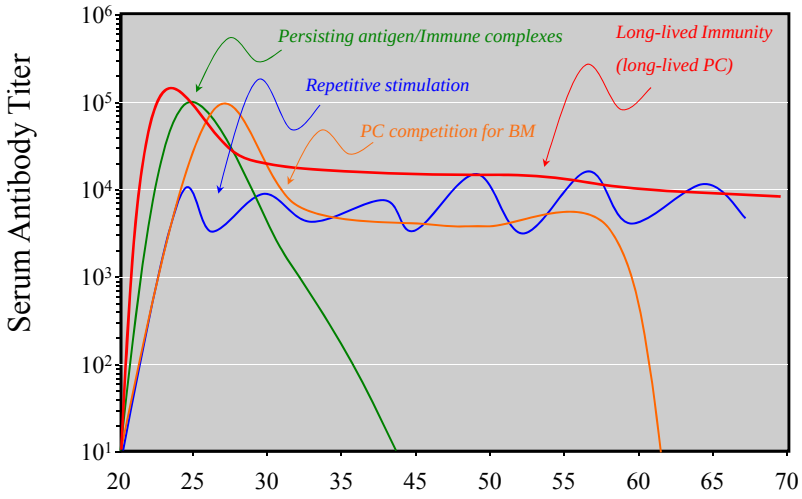
1) Models of long-term humoral immunity

2) (All) Vaccines require booster shots

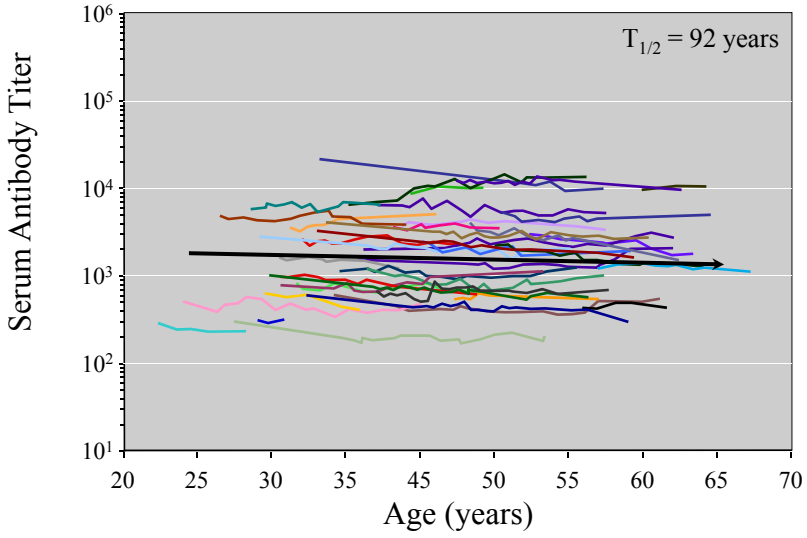
3) The Yellow Fever conundrum

4) Imprinted Model of long-term humoral immunity

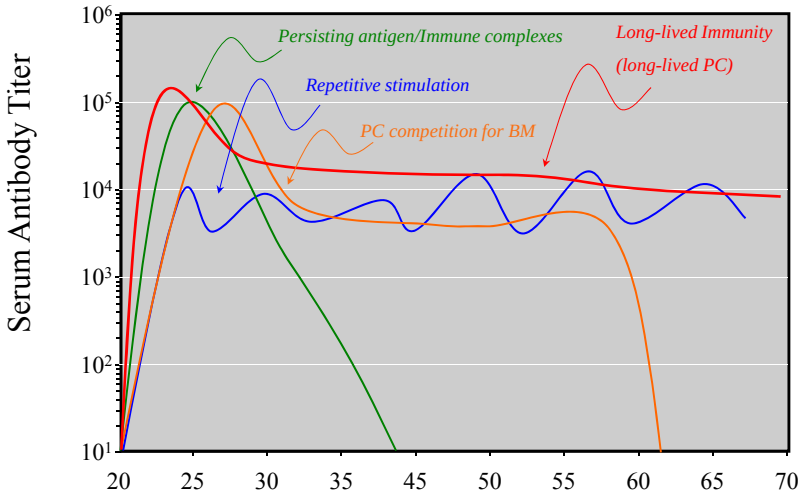
Predictions based on various models of humoral immunity



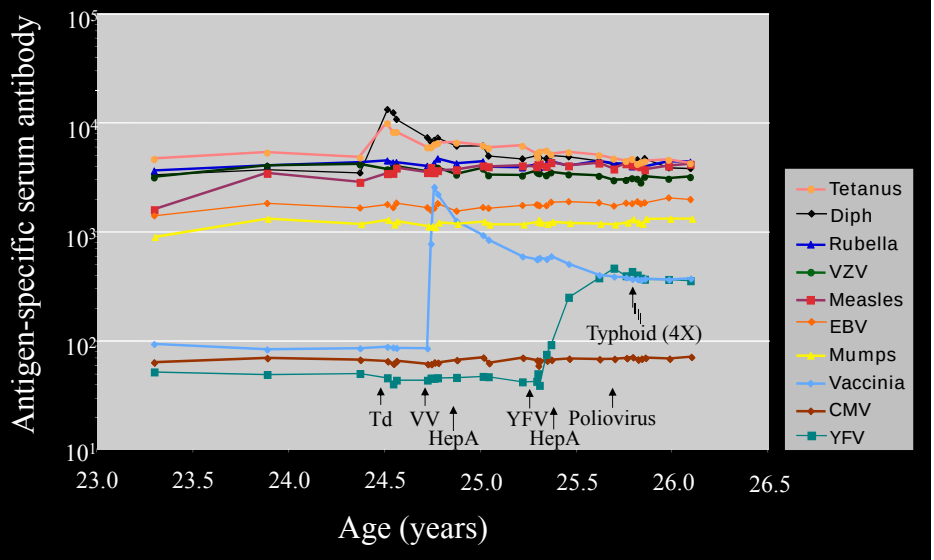
Smallpox vaccination induces antibody responses that are maintained essentially for life



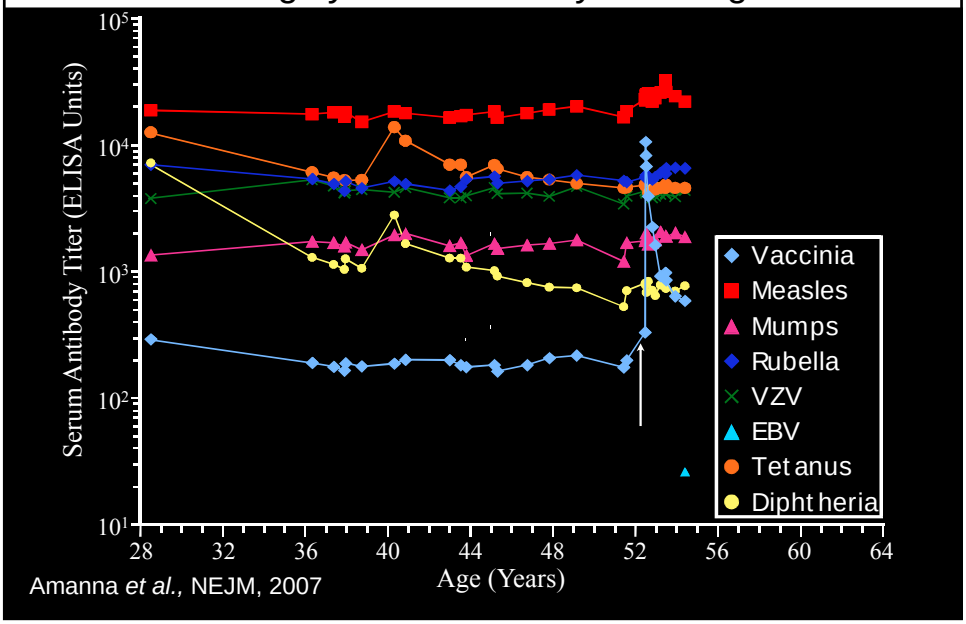
Predictions based on various models of humoral immunity



Virus-specific antibody responses are unaltered by heterologous infections



Maintenance of serum antibody levels appears to be largely determined by the antigen

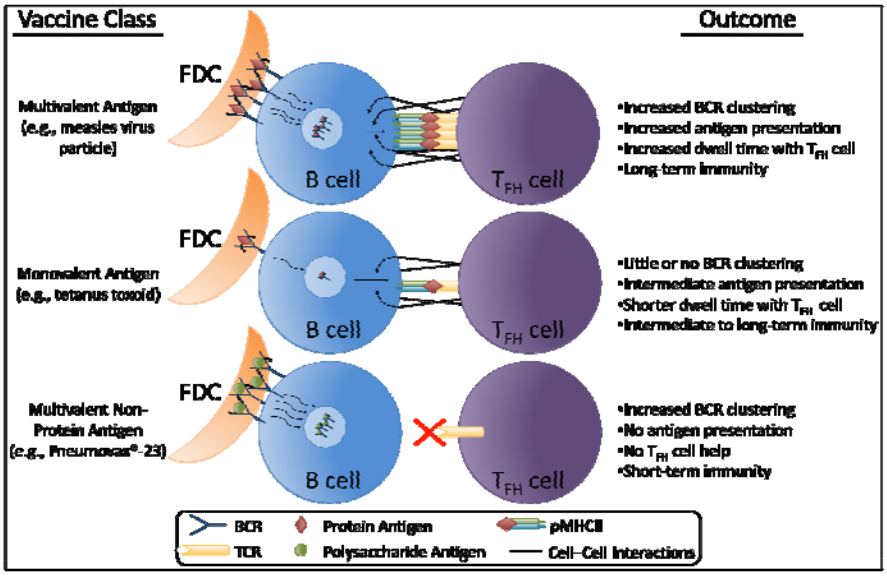


Amanna *et al.*, NEJM, 2007

Results of longitudinal analysis of serum antibody production indicate that antibody half-life differs between antigens

Antigen	$T_{1/2}$ (years)	95% CI (years)
Tetanus	11	10-14
Diphtheria	19	14-33
VZV	50	30-153
Vaccinia	92	46-∞
Rubella	114	48-∞
EBV	11,552	63-∞
Mumps	542	90-∞
Measles	3,014	104-∞

Imprinted Lifespan model of humoral immunity



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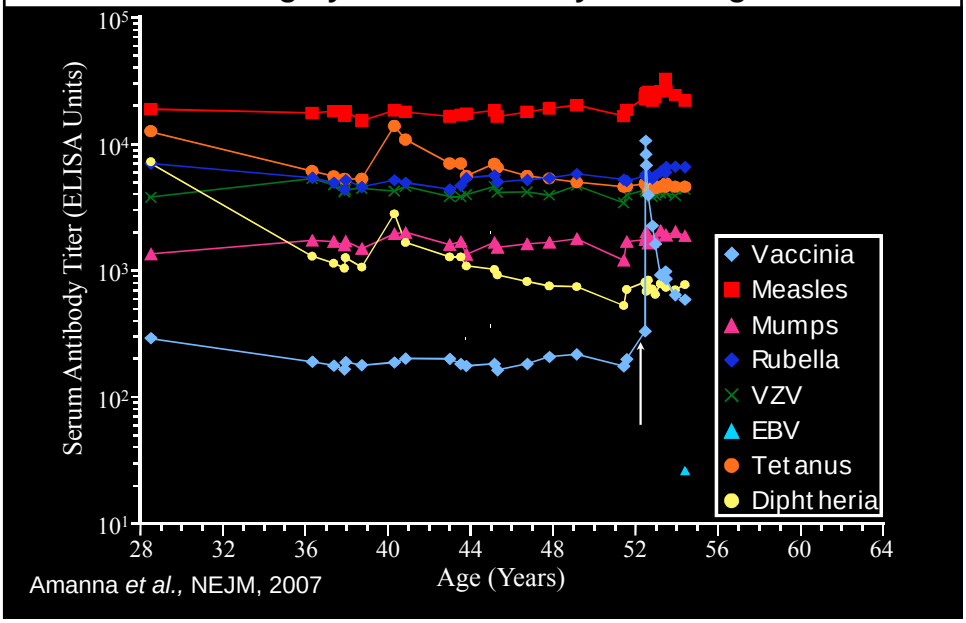
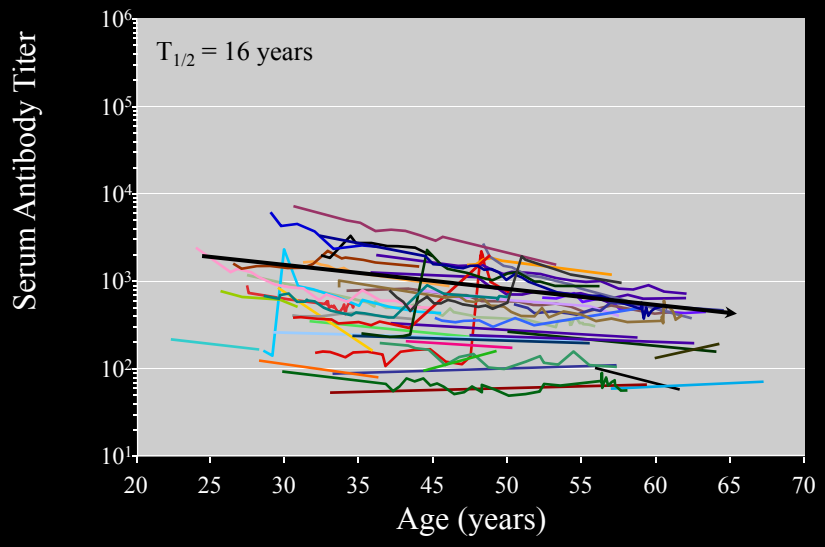
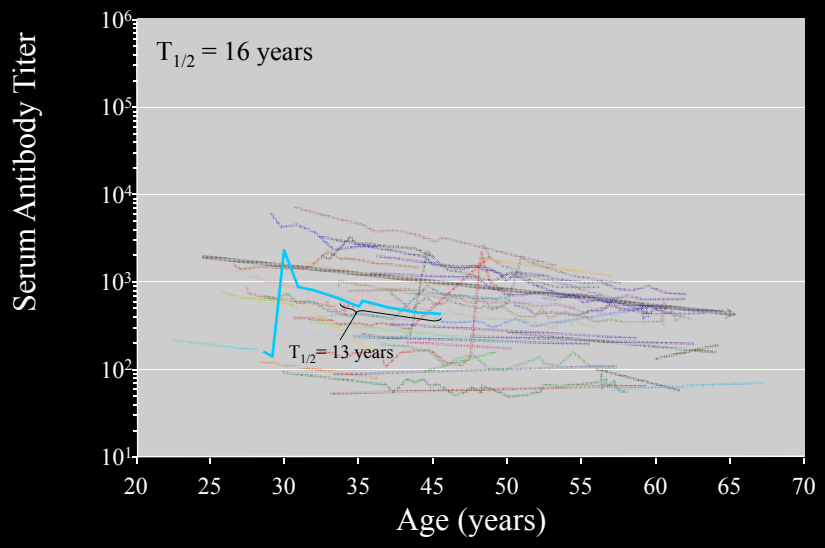


Amanna *et al.*, NEJM, 2007

Longitudinal analysis of antibody responses to *B. pertussis* toxin



Longitudinal analysis of antibody responses following pertussis vaccination or infection



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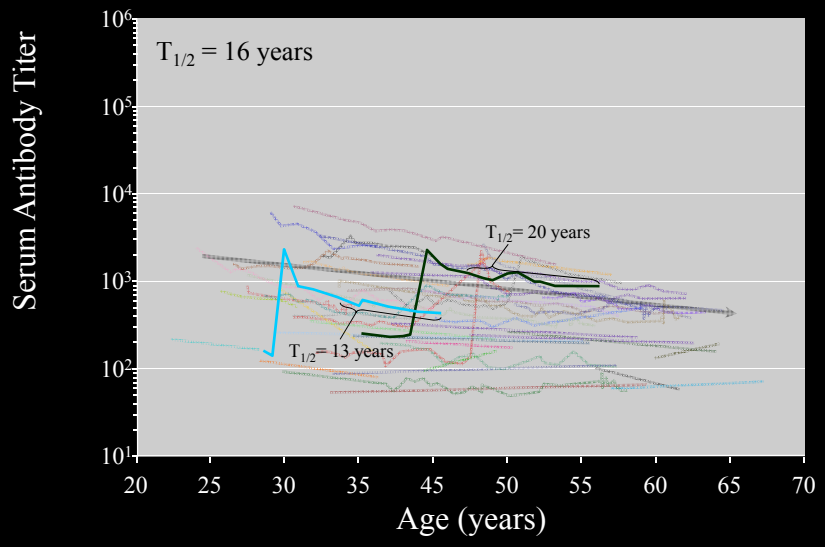

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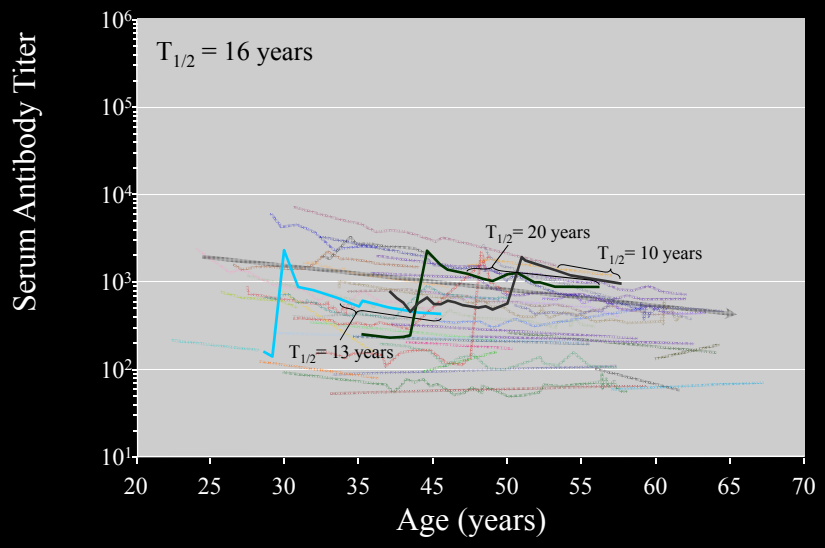

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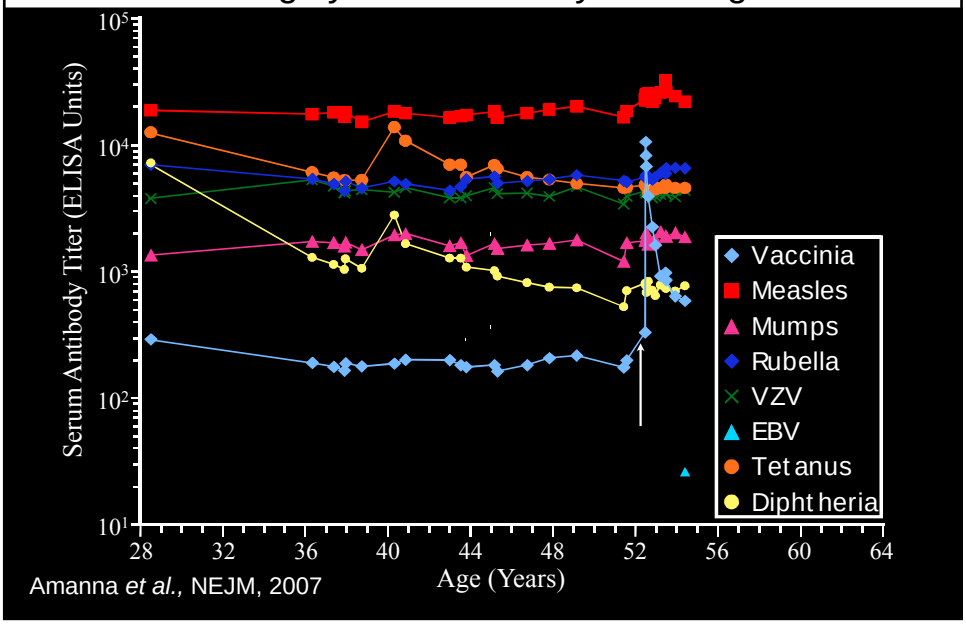


Amanna *et al.*, NEJM, 2007

Clinical Infectious Diseases

MAJOR ARTICLE

Durability of Vaccine-Induced Immunity Against Tetanus and Diphtheria Toxins: A Cross-sectional Analysis

Erika Hammarlund,[1] Archana Thomas,[1] Elizabeth A. Poore,[2] Ian J. Amanna,[2] Abby E. Rynko,[1] Motomi Mori,[3,4] Zunqiu Chen,[4] and Mark K. Slifka[1]

[1]Division of Neuroscience, Oregon National Primate Research Center, Department of Molecular Microbiology and Immunology, Oregon Health & Science University, [2]Najit Technologies, Beaverton, [3]Biostatistics Shared Resource, Knight Cancer Institute, and [4]Division of Biostatistics, Department of Public Health & Preventive Medicine, Oregon Health & Science University, Portland

Background. Many adult immunization schedules recommend that tetanus and diphtheria vaccination be performed every 10 years. In light of current epidemiological trends of disease incidence and rates of vaccine-associated adverse events, the 10-year re-vaccination schedule has come into question.

Methods. We performed cross-sectional analysis of serum antibody titers in 546 adult subjects stratified by age or sex. All serological results were converted to international units after calibration with international serum standards.

Results. Approximately 97% of the population was seropositive to tetanus and diphtheria as defined by a protective serum antibody titer of ≥0.01 IU/mL. Mean antibody titers were 3.6 and 0.35 IU/mL against tetanus and diphtheria, respectively. Antibody responses to tetanus declined with an estimated half-life of 14 years (95% confidence interval, 11–17 years), whereas antibody responses to diphtheria were more long-lived and declined with an estimated half-life of 27 years (18–51 years). Mathematical models combining antibody magnitude and duration predict that 95% of the population will remain protected against tetanus and diphtheria for ≥30 years without requiring further booster vaccination.

Conclusions. These studies demonstrate that durable levels of protective antitoxin immunity exist in the majority of vaccinated individuals. Together, this suggests that it may no longer be necessary to administer booster vaccinations every 10 years and that the current adult vaccination schedule for tetanus and diphtheria should be revisited.

INQUISITR
NEWS WORTH SHARING

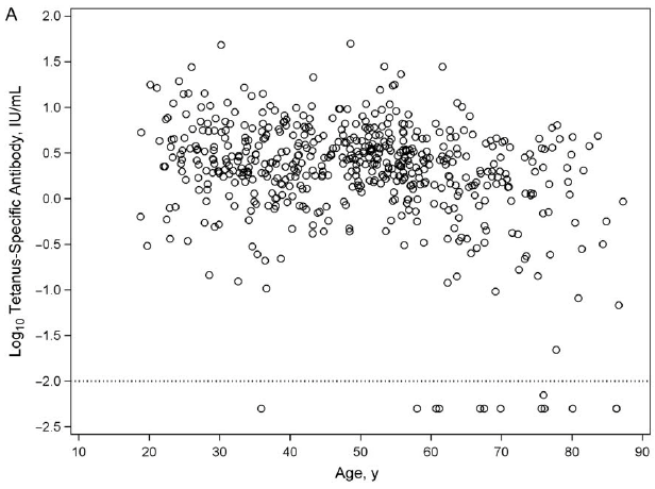
MARCH 26, 2016

BOOSTER SHOT STUDY DROPS TETANUS VACCINE BOMBSHELL

JEREMY LAUKKONEN

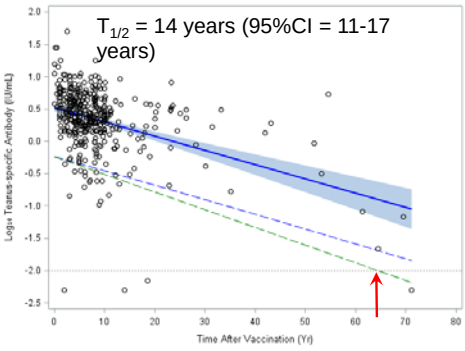
A new booster shot study suggests that the current tetanus vaccine booster schedule may be severe overkill. Booster shots were previously thought to last just 10 years, but data from this new study indicates that immunity granted by the tetanus vaccine could last more than 30 years.

Approximately 97% of the total adult population has protective immunity against tetanus (99% of people <60 years of age)

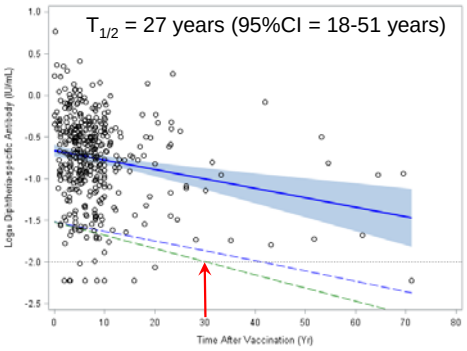


Monovalent antigens, tetanus and diphtheria, induce long-term immunity that decays slowly over time

Tetanus



Diphtheria



Which vaccines offer
"One Shot and Lifelong Immunity"?

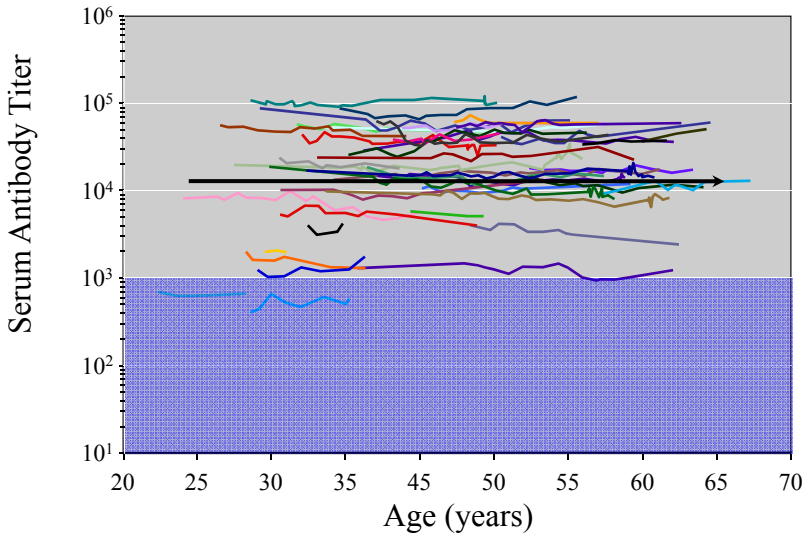
Wild-type viruses induce long-term immunity but artificially attenuated viruses require booster vaccination

Wild-type Virus	Artificially attenuated vaccine virus requiring booster shots
Measles	MMR
Mumps	MMR
Polio	OPV
Smallpox, Cowpox,Vaccinia*	MVA
Yellow fever	YFV-17D**
Varicella Zoster Virus	VZV-Oka

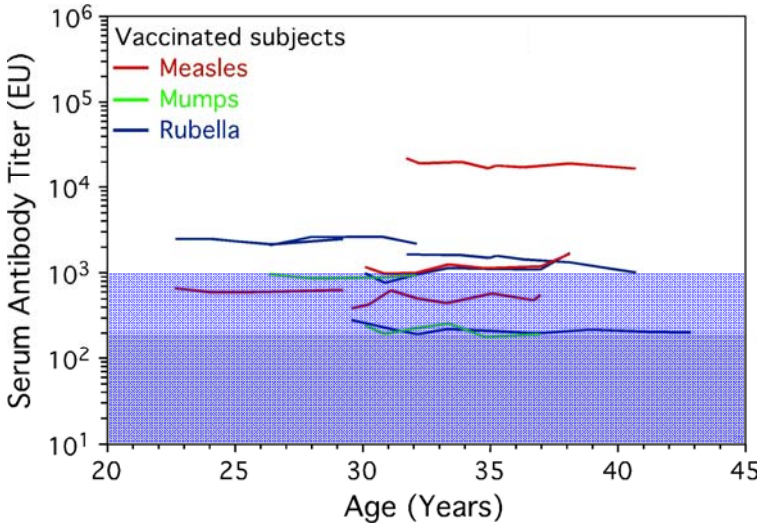
*Vaccinia represents a naturally attenuated virus (likely horsepox)

**YFV vaccination induces long-term immunity in only about *60-70% of subjects*

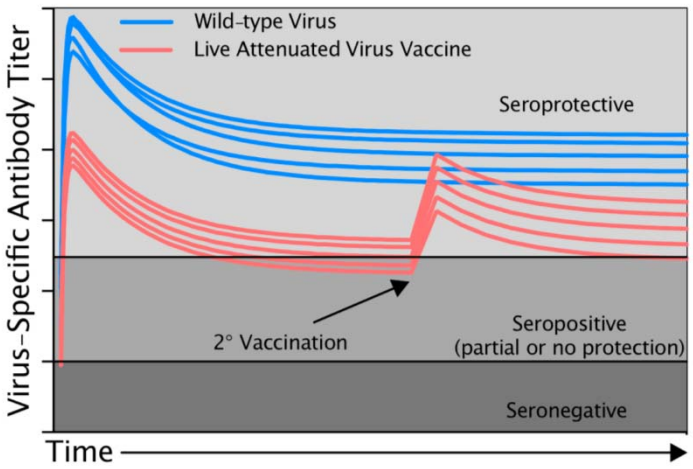
Longitudinal analysis of antiviral antibody responses following measles infection



Vaccine-induced measles-specific antibody is long-lived, but often resides at or below the protective threshold



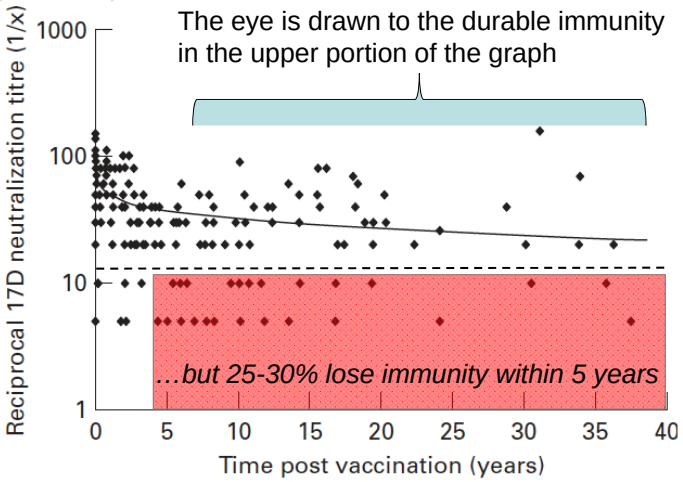
Relationship between long-lived immunity and long-term protection



The Yellow Fever *Conundrum*

Assessment of IgG antibodies against yellow fever virus after vaccination with 17D by different assays: neutralization test, haemagglutination inhibition test, immunofluorescence assay and ELISA

M. Niedrig[1], M. Lademann[2], P. Emmerich[3] and M. Lafrenz[2]



Bulletin of the World Health Organization, **59** (6): 895-900 (1981)

Persistence of neutralizing antibody 30 – 35 years after immunization with 17D yellow fever vaccine

J. D. POLAND,[1] C. H. CALISHER,[2] T. P. MONATH,[3] W. G. DOWNS,[4] & K. MURPHY[5]

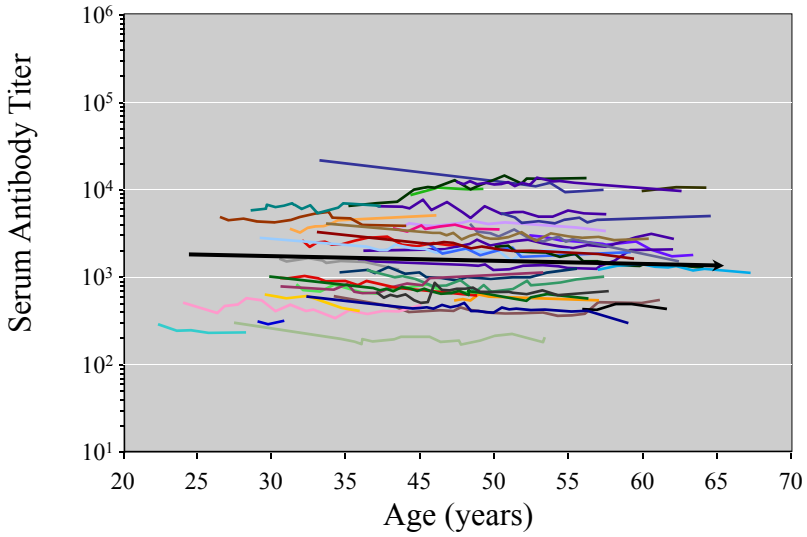
Table 4. Distribution of PRNT antibody titres among servicemen meeting one or more criteria for YF immunization

Branch	No. of criteria	Study group		Prevalence of PRNT antibody (%)						
		No.	% of branch	< 2	⩾ 2	⩾ 4	⩾ 8	⩾ 16	⩾ 32	⩾ 64
Army	1	30	67	50	50	50	47	43	33	23
	⩾ 2	15	33	20	80	80	67	53	53	33
Navy & air corps	1	36	62	6	94	89	86	75	67	50
	⩾ 2	22	38	0	100	100	91	82	68	55
Total	1	66	64	26	74	72	69	61	52	38
	⩾ 2	37	36	8	92	92	81	70	62	46

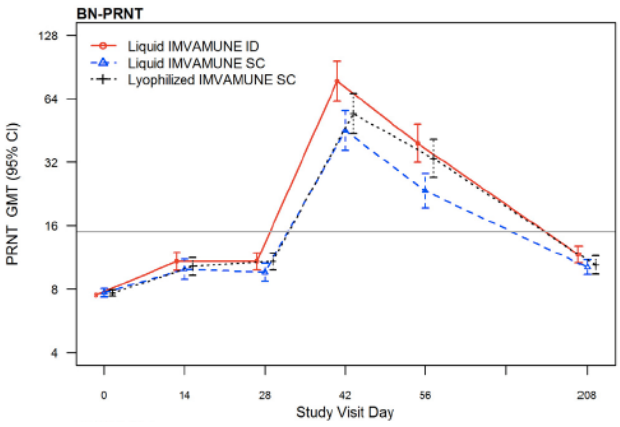
Conclusion: Protective immunity *can* be maintained for 30-35 years after vaccination – *but 30-40% of individuals may be left unprotected without administering a booster vaccination*

Why are some individuals endowed with lifelong immunity against yellow fever and others are not?

Smallpox vaccination induces antibody responses that are maintained essentially for life



Antibody responses to MVA decline rapidly even after two doses

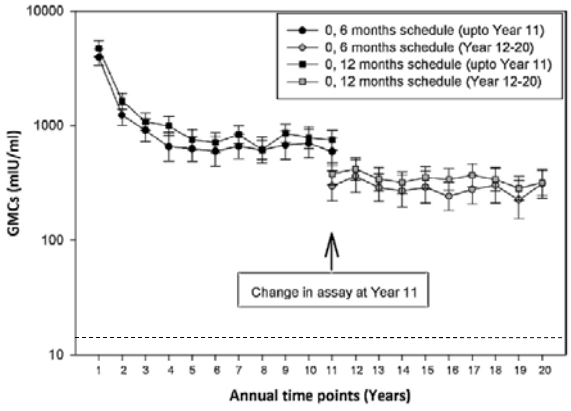


S.E. Frey *et al.* Comparison of lyophilized versus liquid modified vaccinia Ankara(MVA) formulations and subcutaneous versus intradermal routes of administration in healthy vaccinia-naïve subjects. Vaccine, 2015

Does this mean that *All* vaccines elicit only short-lived immunity?

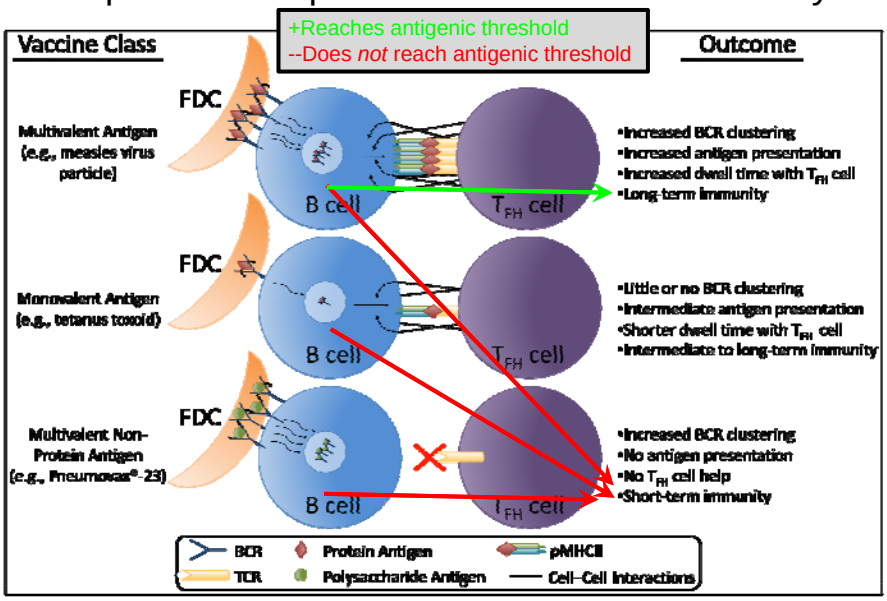
(The answer: No.)

Antibody responses to inactivated Hep A virus are maintained for *decades* after two doses



H. Theeten *et al.* Long-term antibody persistence after vaccination with a 2-dose Havrix™ (inactivated hepatitis A vaccine): 20 years of observed data and long-term model-based predictions. Vaccine, 2015

Imprinted Lifespan model of humoral immunity



Conclusions

- Monovalent protein antigens are less likely to induce life-long immunity but if high titers are reached (e.g., tetanus/diphtheria) then protective immunity may be maintained for decades as long as antibodies remain above the protective threshold
- Active infection or addition of adjuvants that induce inflammation (e.g., CpG/LPS from *B. Pertussis*) are unlikely to increase the durability of the immune response to specific antigens
- Multivalent antigens (e.g., viruses or VLPs) typically induce long-term immunity, especially if antigen persists due to modestly prolonged infection or by addition of alum to maintain an antigen depot
- Based on these points, vaccination against influenza could be improved by switching from “split virus” to whole-virus formulations, preferably with an alum-containing adjuvant.
  - *note that safety/reactogenicity issues would need to be resolved

Acknowledgements

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