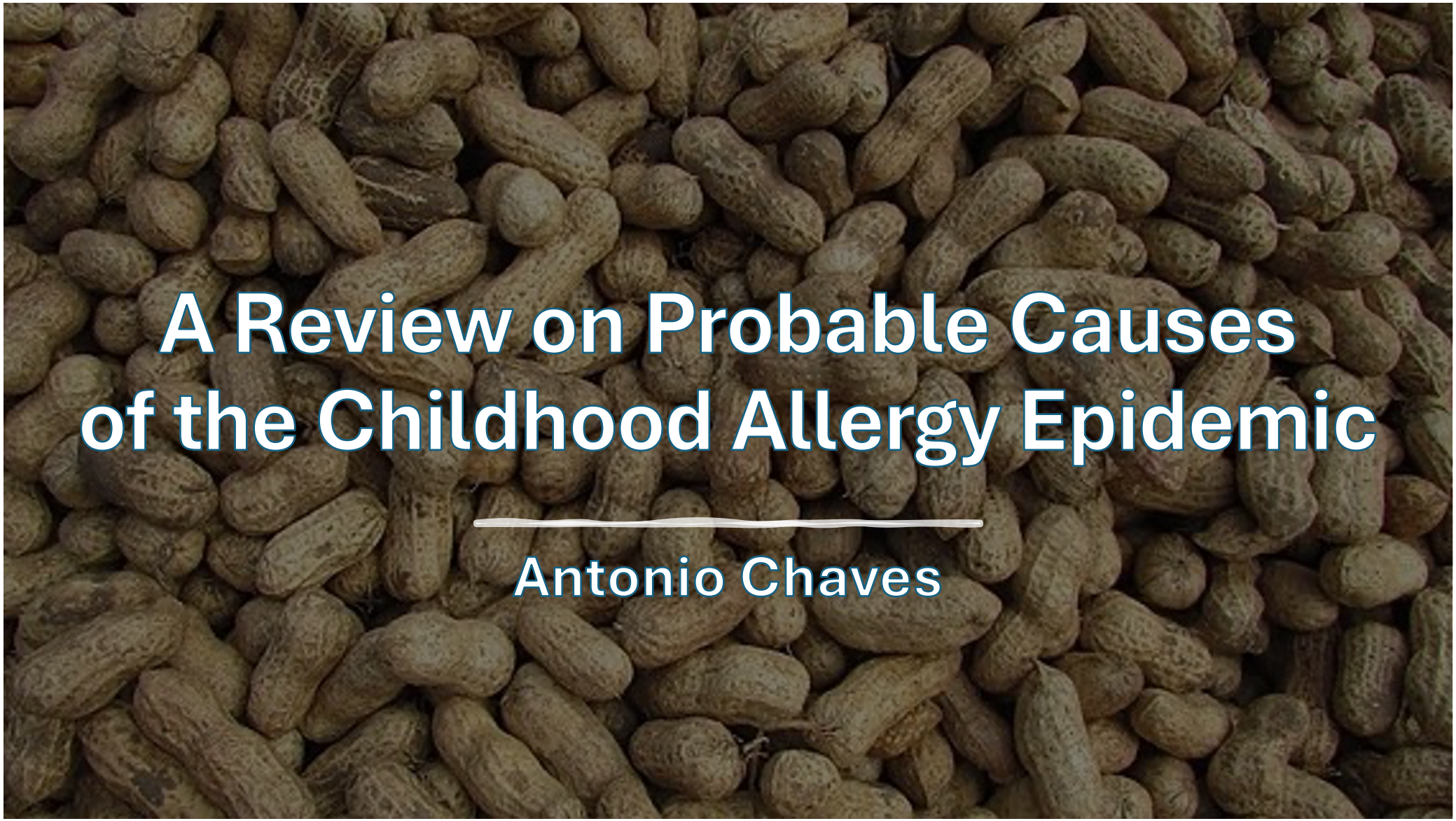
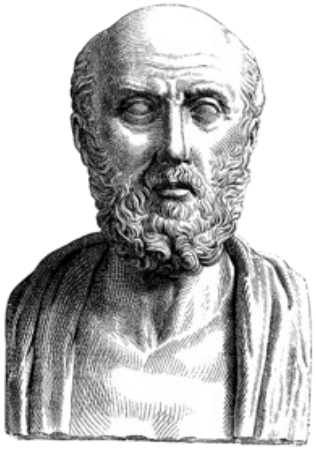


A Review on Probable Causes of the Childhood Allergy Epidemic

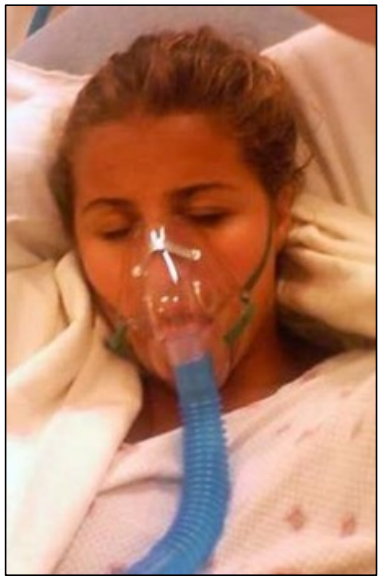
Antonio Chaves

Allergies have been recorded since ancient times.*

Hippocrates (460-375 BC) observed how some people were sickened by the consumption of cheese.



But in recent decades, life-threatening food allergies in children started to grow at an alarming rate. Here are some of the numbers:**



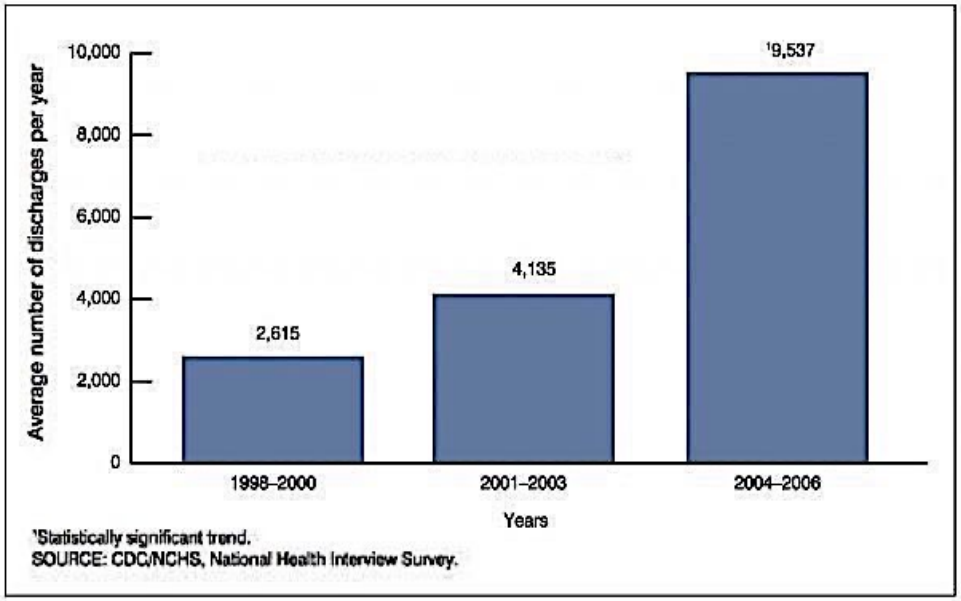
- **1 in 12 children** diagnosed in the U.S.
- **Every 2-3 minutes** there is an ER visit from food induced anaphylaxis.
- **40% of children** with food allergies experience a life-threatening reaction.
- **$4,184 cost per child** per year
- **$24.8 billion** cost to U.S. economy.

* Mark Jackson in "Allergy: History of a Modern Malady." *Reakton Books*, 2006, p. 28

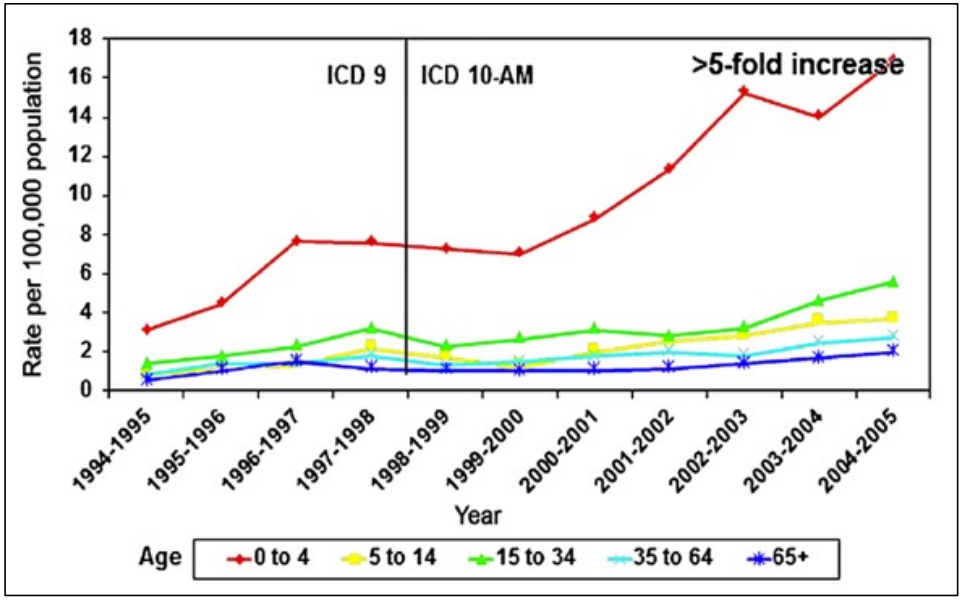
** EAT (2025) Food Allergy Statistics: https://endallergiestogether.com/research/food-allergy-statistics/

Life-threatening food allergies are not only increasing in the US…
Similar trends are also occurring other Western nations, especially in Australia and the UK.

Figure 4. Average number of hospital discharges per year among children under age 18 years with any diagnosis related to food allergy: United States, 1998–2006 *

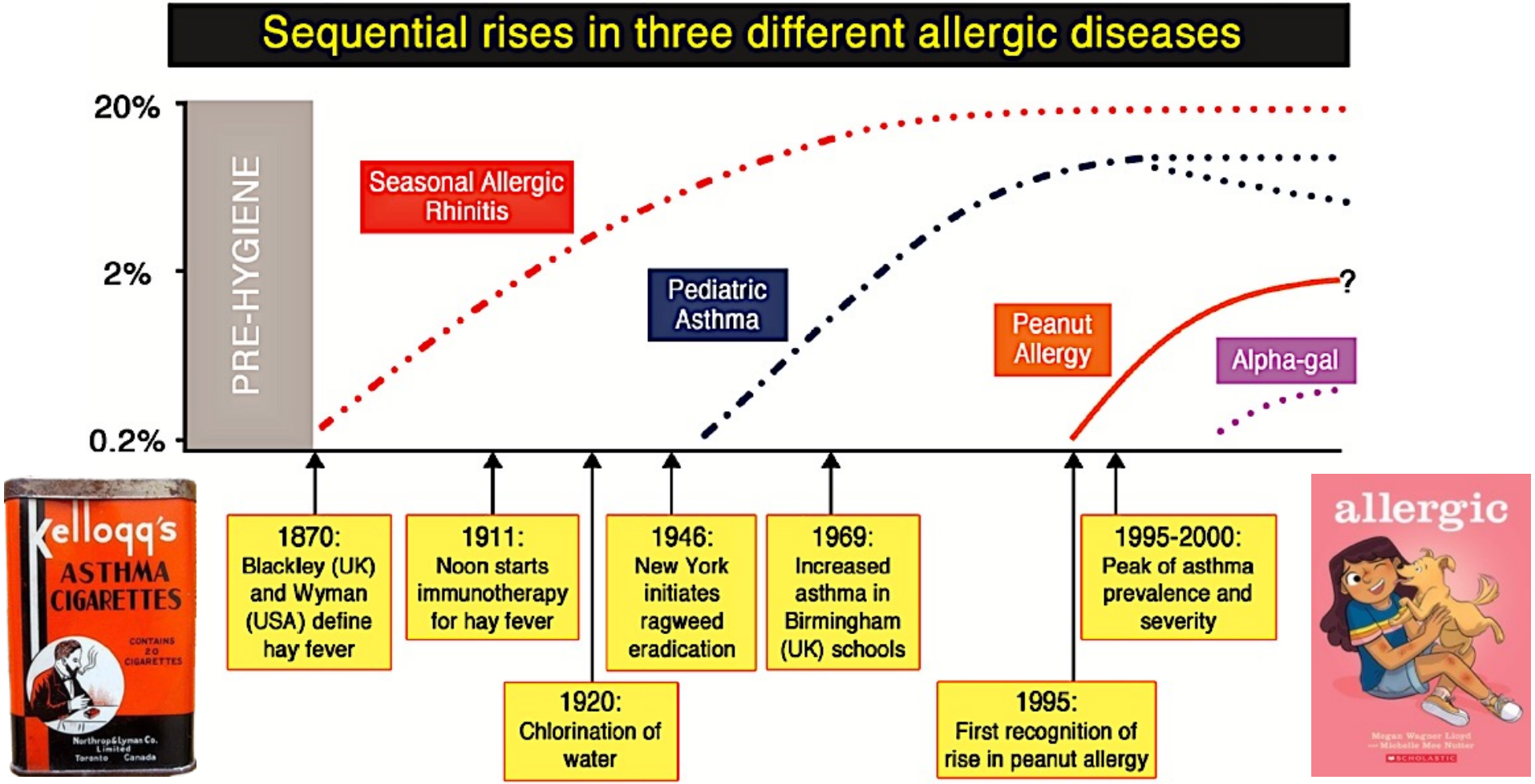


Food-induced hospital anaphylaxis admissions in Australia.**



* CDC (2008) "Food Allergy Among U.S. Children: Trends in Prevalence and Hospitalizations." NCHS Data Brief No. 10, October 2008 https://www.cdc.gov/nchs/products/databriefs/db10.htm

** From Liew *et al.* J Allergy Clin Immunol 2009; 123:434e42. As cited in Sampson (2016) "Food Allergy: Past, Present, and Future." Allergology International 65: 363-369 https://www.sciencedirect.com/science/article/pii/S1323893016301137



Thomas Platt-Mills in "The Allergy Epidemics: 1870–2010." *J Allergy Clin Immunol*. July 2015, 136(1): 3–13
https://pmc.ncbi.nlm.nih.gov/articles/PMC4617537/

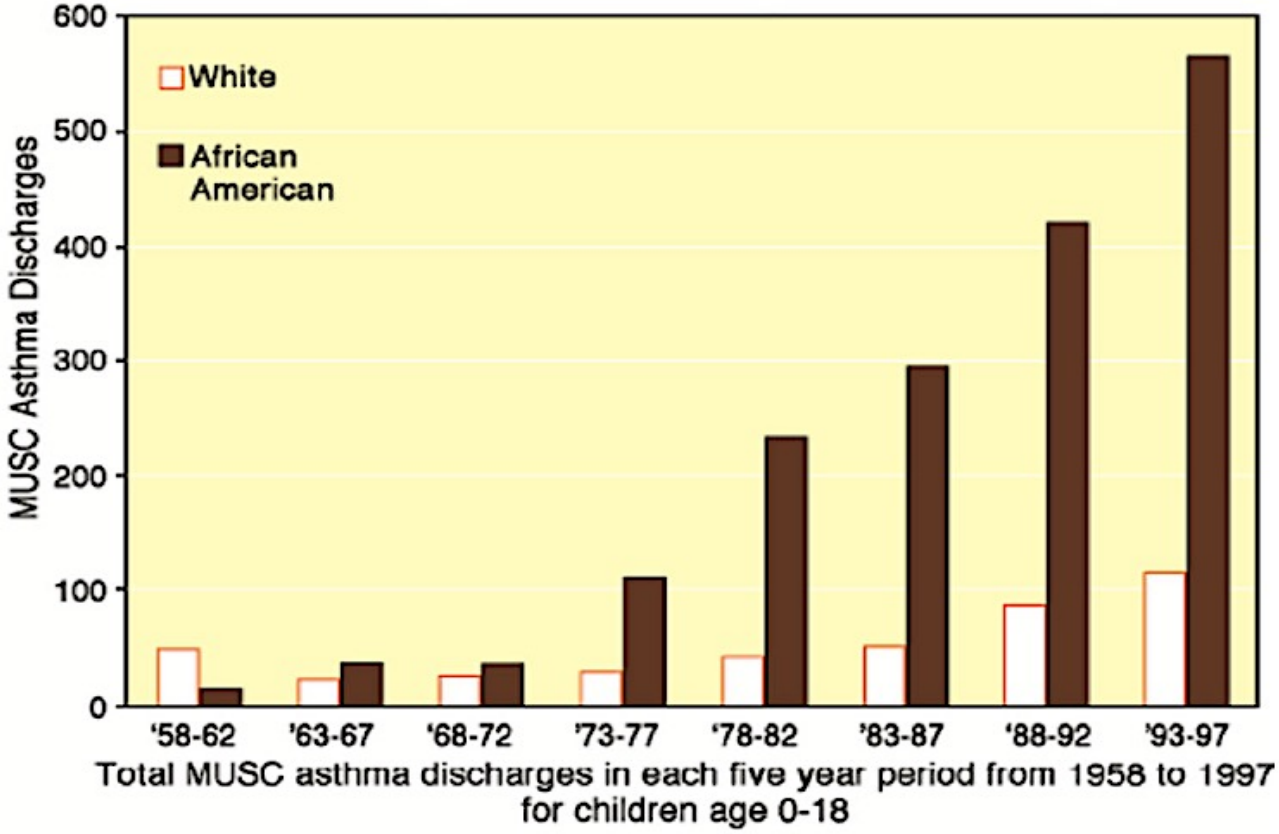
During the 19 century, hay-fever was regarded as an ailment of the “privileged” classes.

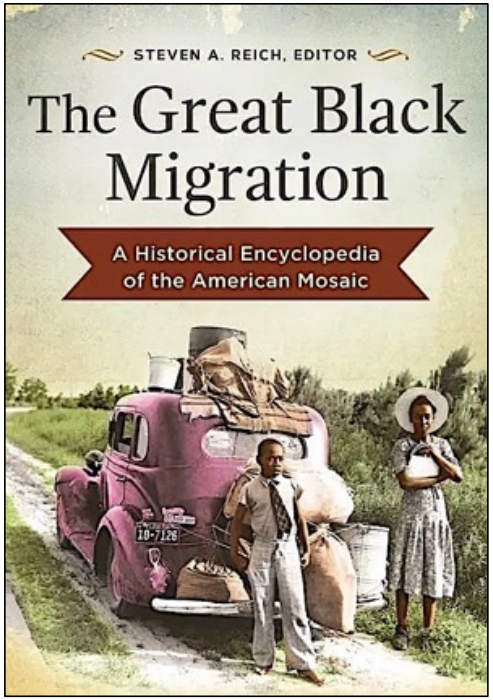
And when hay-fever appears …it chooses the man before the woman, the educated before the ignorant, the gentle before the rude, the courtier before the clown …It prefers the temperate to the torrid zone, it seeks the city before the country, and out of every climate it chooses the Anglo-Saxon, or at least the English-speaking race.

Lecture given at the West London Medico-Chirurgical Society by Sir Andrew Clark in 1887.*

* Mark Jackson in “Allergy: History of a Modern Malady.” *Reakton Books*, 2006, p. 62

But respiratory allergies became increasingly “inclusive” as black Americans relocated to cities.





Thomas Platt-Mills in “The Allergy Epidemics: 1870–2010.” *J. Allergy Clin. Immunol*. July 2015 , 136(1): 3–13
https://pmc.ncbi.nlm.nih.gov/articles/PMC4617537/

Epidemiologist David Strachan was the first to clearly articulate the "hygiene hypothesis."

...allergic diseases (could have been) *prevented by infection in early childhood, transmitted by unhygienic contact with older siblings, or acquired prenatally from a mother infected by contact with her older children.*

David Strachan, 1989

# of older siblings *	Prevalence of hay fever at age 23**	Prevalence of hay fever at age 11**	Prevalence of infantile eczema **
0	20.4	10.0	6.1
1	15.0	7.9	5.2
2	12.5	5.0	4.6
3	10.6	4.0	3.7
4+	8.6	2.6	2.8

* The original table presented a significant (but lesser) effect of younger siblings on hay fever (data not shown).
** Adjusted for father's social class, housing tenure and shared household amenities in childhood, breast feeding, region of birth, and cigarette-smoking at 23 (n = 17,414).

David Strachan "Hay fever, hygiene, and household size." *British Medical Journal,* November 1989, 299(6710): 1229-1260
https://pmc.ncbi.nlm.nih.gov/articles/PMC1838109/

This study of military recruits in Italy showed that recruits with prior exposure to ingested pathogens (*Toxoplasma gondii*, *Helicobacter pylori*, and hepatitis A) had less allergies.

Prior infection with measles, mumps, rubella, chicken pox, cytomegalovirus, or herpes had no noticeable effect on allergy outcomes (data not shown).

Our data ...support(s) the hypothesis that daily ingestion of traditionally processed food, not treated with antimicrobial preservatives and not subjected to hygienic procedures, may help to prevent atopy.

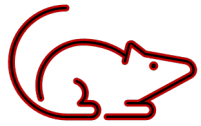
	Index of exposure to orofecal and foodborne infections			
	0 (n=796)	1 (n=618)	2 or 3 (n=245)	P value*
Prevalence of sensitisation to allergens (weal ⩾3 mm)				
Dermatophagoides pteronyssinus	160 (20.1)	99 (16.0)	27 (11.0)	0.001
Cat	68 (8.5)	38 (6.1)	6 (2.4)	0.001
Mixed grass	118 (14.8)	75 (12.1)	21 (8.6)	0.008
Mixed grass	118 (14.8)	75 (12.1)	21 (8.6)	0.008
Respiratory allergic disease				
Allergic rhinitis (with or without asthma)	123 (15.5)	82 (13.3)	16 (6.5)	0.001
Allergic asthma (with or without rhinitis)	38 (4.8)	21 (3.4)	1 (0.4)	0.002
Total (allergic rhinitis or asthma)	134 (16.8)	89 (14.4)	17 (6.9)	0.000

*Test for linear trend.

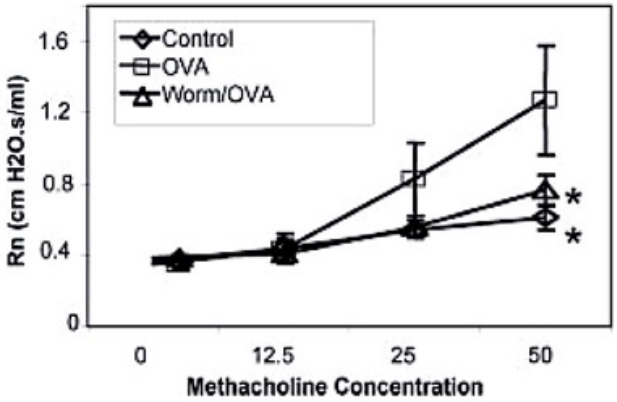
Matricardi *et al.* "Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study." *British Medical Journal* February 2000, 320: 412-417
https://pubmed.ncbi.nlm.nih.gov/10669445/

These two experiments show how prior infection with parasitic roundworms may also play a role in preventing respiratory allergies in sensitized mice.

Mice were sensitized via injection of the antigen with alum as the adjuvant.

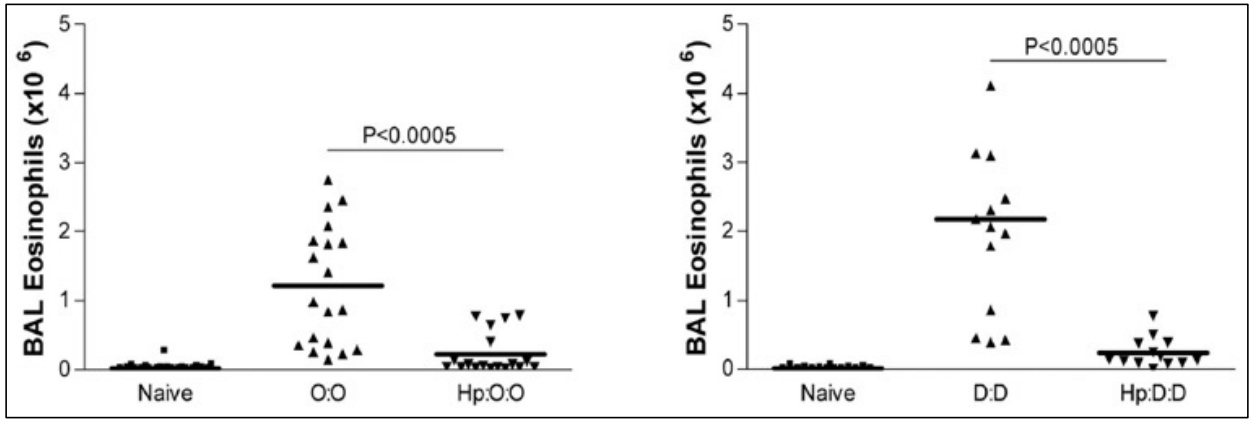


Bronchial Constriction in Response to Methacholine in Mice Challenged with Aerosolized Ovalbumin*



Control = non-sensitized mice
OVA = mice sensitized to ovalbumin.
Worm/OVA = sensitized mice infected with worms prior to sensitization.

Eosinophil Levels in Lungs of Mice Challenged with Ovalbumin or Dust Mite**



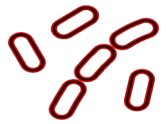
Naïve = non-sensitized mice (control)
O:O or D:D = mice sensitized to ovalbumin or the dust mite allergen Der p 1
Hp = mice infected with worms prior to sensitization

*Kitagaki *et al.* "Intestinal Helminths Protect in a Murine Model of Asthma." *J. of Immunology* (2006) 117(3): 1628-1635. https://pubmed.ncbi.nlm.nih.gov/16849471/

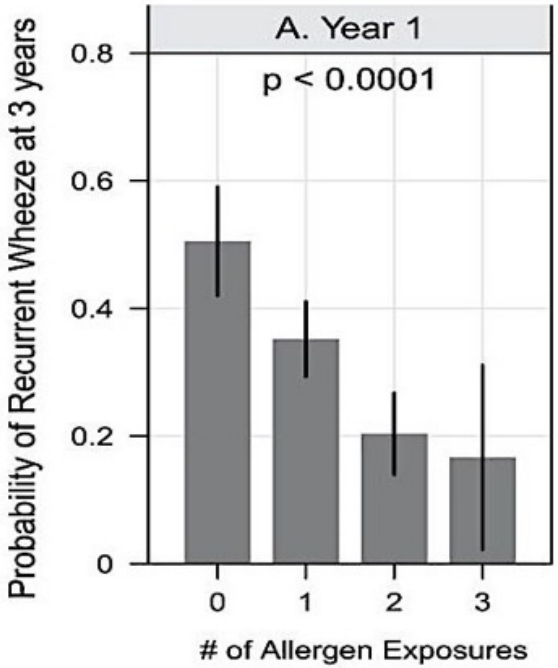
**Wilson *et al.* "Suppression of Allergic Airway Inflammation by Helminth-induced Regulatory T-Cells." *J. of Exper. Medicine* (2005) 202(9): 1199-1212. https://pubmed.ncbi.nlm.nih.gov/16275759/

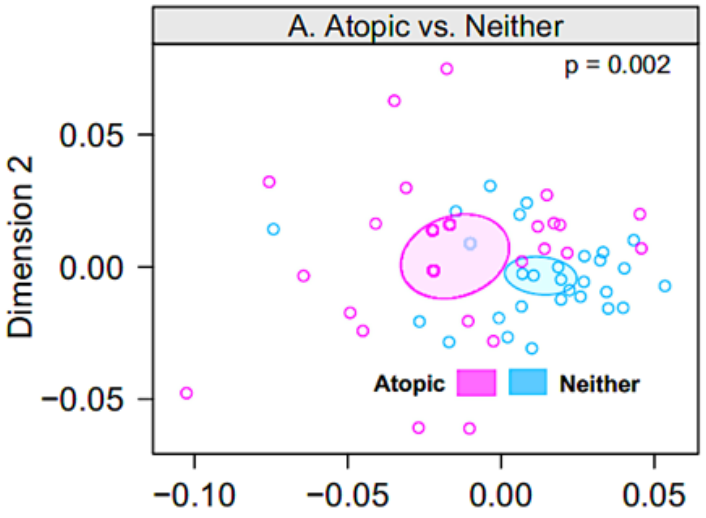
This study from John Hopkins found that infants exposed to cockroach droppings, mouse and cat dander during the first year of life had lower rates of wheezing by age 3.

The same study also recorded significant difference in the gut bacteria of children with allergies versus children with no detectable allergy symptoms.



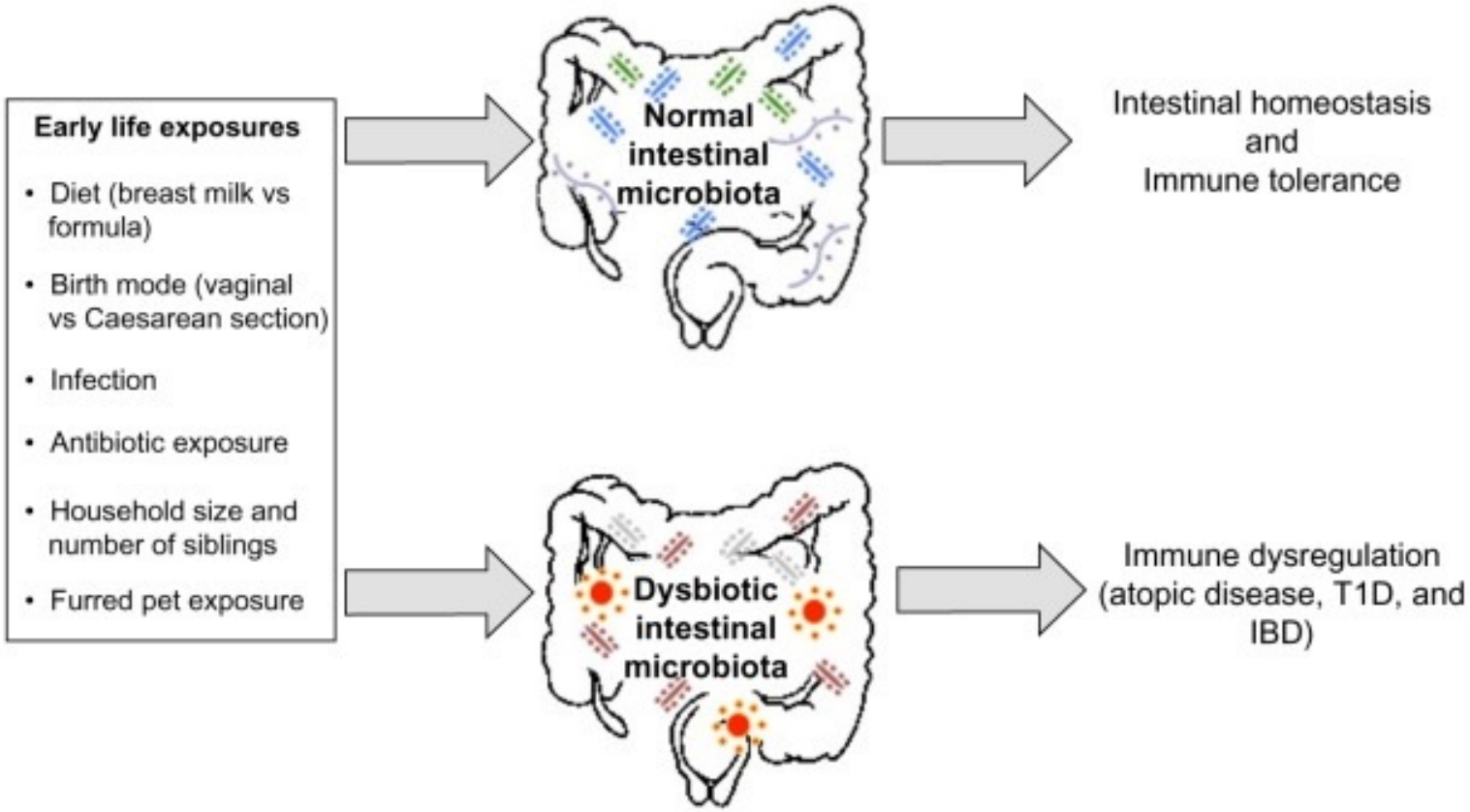
Our observations raise the possibility that the optimal conditions to promote tolerance might be early-life antigenic exposure to allergen in conjunction with exposure to particular bacteria, such as those identified in this study.





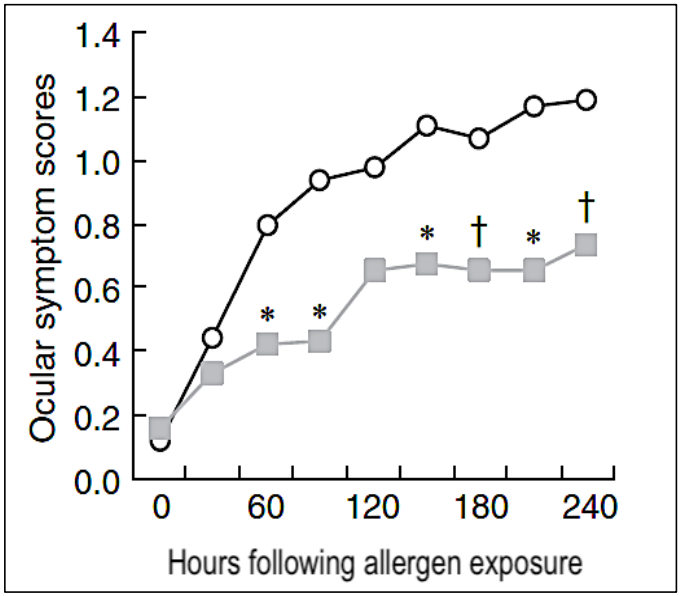
Lynch *et al.* "Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children." *Journal of Allergy and Clinical Immunology* (2014) 134(3): 593-601.
https://www.jacionline.org/article/S0091-6749(14)00593-4/fulltext

Immune dysregulation is now increasingly attributed to breakdown of the gut biome.



Stiemsma *et al.* "The hygiene hypothesis: current perspectives and future therapies." *Immuno Targets and Therapy* July 27, 2015. https://pmc.ncbi.nlm.nih.gov/articles/PMC4918254/pdf/itt-4-143.pdf

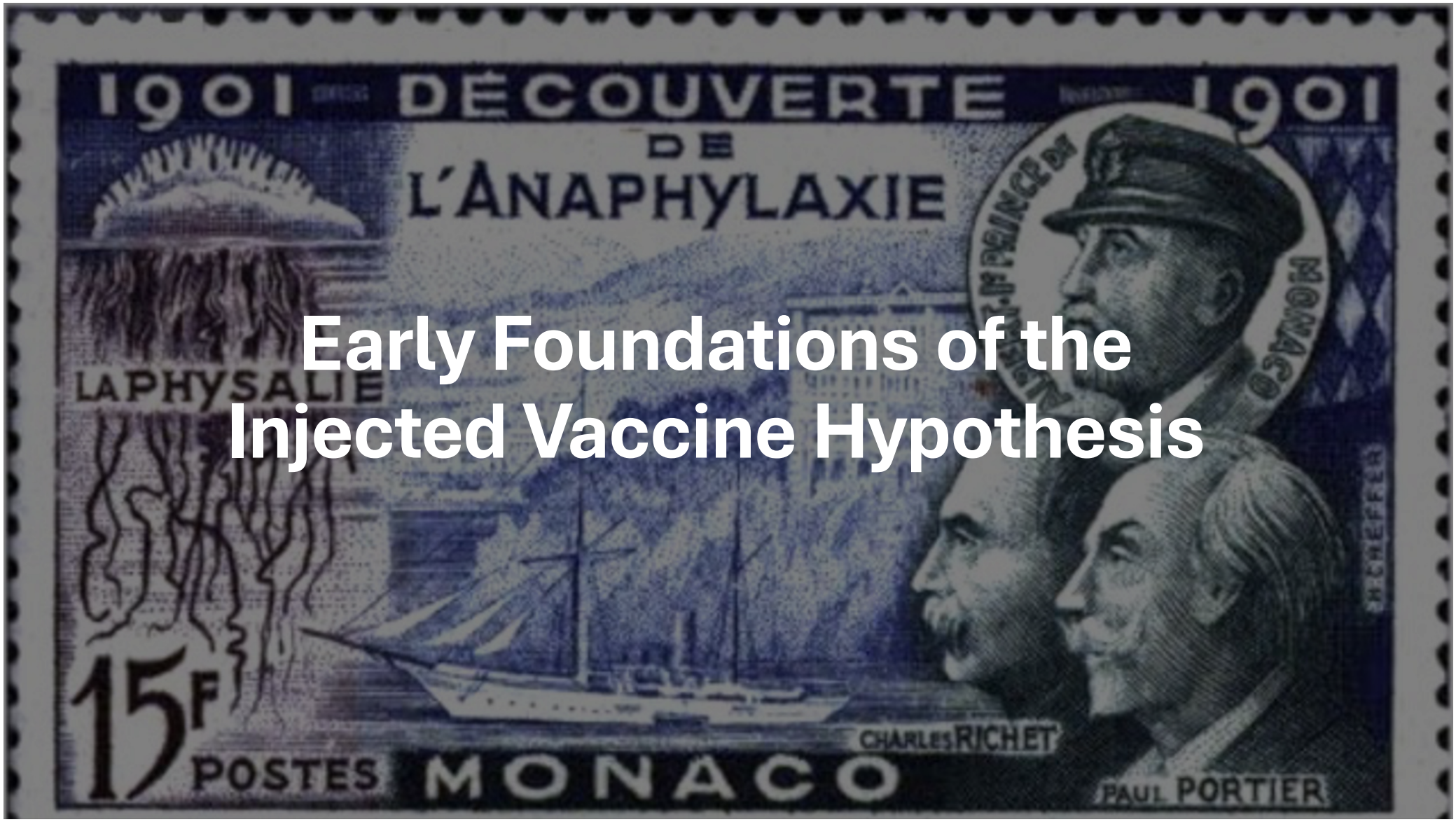
In this experiment, a probiotic powder consumed twice a day for four weeks significantly improved hay fever symptoms of patients allergic to Japanese cedar.



Total study group, $n = 21$		Numbers of subjects						
		day 0	day 1	day 2	day 3	day 4	day 5	Sum
Oral medicines	Placebo	9	4	2	1	1	1	18
	BB536	5	2	0	0	0	0	7*
Nasal sprays	Placebo	5	5	2	2	2	2	18
	BB536	2	5	1	1	2	2	13
Eye drops	Placebo	3	5	2	3	2	2	17
	BB536	1	2	0	1	1	1	6*

* $p < 0.05$, difference in total counts *vs* placebo groups, Fisher's exact test.

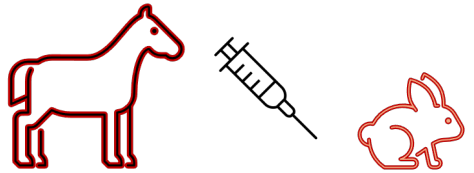
Xiao *et al.* "Clinical Efficacy of Probiotic *Bifidobacterium longum* for the Treatment of Symptoms of Japanese Cedar Pollen Allergy in Subjects Evaluated in an Environmental Exposure Unit." *Allergology International* (2007) 56 (1) 67-75
https://pubmed.ncbi.nlm.nih.gov/17259812/



Early Foundations of the Injected Vaccine Hypothesis

In 1902 Charles Richet and Paul Portier attempted to generate immunity by injecting sublethal doses of sea anemone toxin into dogs and saw that nearly all died after the second dose. Richet coined the term "**anaphylaxis**" to describe this unexpected "**absence of protection**" from the second injection.

In 1903 Maurice Arthus showed that sensitization could also be accomplished with non-toxic substances after he injected horse plasma into rabbits. The term "**Arthus phenomenon**" would later be used to describe adverse reactions to serum therapy.



In 1906 Clemens Von Pirquet concluded that **immunity and sensitization are two sides of the immune response** and coined the term "**allergy**" to describe this "**altered reactivity**" to antigens. He based this on clinical observation of adverse reactions to serum therapy and vaccine boosters. This model was not well-received, probably because it raised new concerns on the safety of these practices.

Mark Jackson in "Allergy: History of a Modern Malady." *Reakton Books*, 2006, pp. 10, 21, 32

In most of these examples of experiments spanning over 100 years, the animals were sensitized via injection; often with the help of an adjuvant (the same as modern-day vaccines).

Ref.	Year	Antigen(s)	Animal	Sensitization method(s)	Evaluation method(s)
1	2023	Ovalbumin	Mouse	Injection with alum as the adjuvant.	Responses to ingestion challenge: • Scratching, sneezing, and nasal rubbing. • IgE levels in plasma. • Eosinophil levels in lungs.
2	2022	Ragweed pollen	Mouse	Intranasal application under anesthesia of 6 doses over 21 days.	Responses to inhalation challenge: • Eosinophil and neutrophil levels in lungs. • Inflammation of lungs. • Airway resistance of lungs.
3	2018	Whey protein	Mouse	Intragastric application with cholera toxin as adjuvant.	Responses to ingestion challenge: • Digging frequency. • IgE levels in plasma. • Mast cell activity in brain and intestine. • 5-hydroxymethylcytosine immunoreactivity in amygdala.
4	2003	Dust mites	Mouse	Injection with alum as the adjuvant.	Responses to inhalation challenge: • IgE levels in plasma. • Eosinophil levels in blood. • Cytokine levels in lungs. • Airway resistance of lungs.
5	1960	Ovalbumin	Guinea pig	• Injection with 0.5 % phenol as solvent. • Passive sensitization via injection with rabbit antisera.	Histamine release by lung tissue cultured *in vitro* after the addition of antigen to the culture media.
6	1937	Picryl chloride & 2,4-Dinitro-chloro-benzene	Guinea pig	Injection with saline as the solvent.	• Anaphylaxis and death in response to reinjection. • Skin redness and swelling in response to topical application.
7	1903	Horse plasma	Rabbit	Injection of plasma.	Edema, necrosis, and death in response to reinjection.

A sudden spike in gelatin allergies Japanese infants in the 1990's was traced to a change in the schedule whereby a gelatin-containing DTaP was given at a much earlier age.

To address this problem DTaP vaccines ingredients in Japan were changed after 1998.

In the 1989-1993 schedule (top), the DTaP was introduced at 18 months. In the 1994 schedule (middle), the gelatin-containing DTaP was introduced at 6 months.*

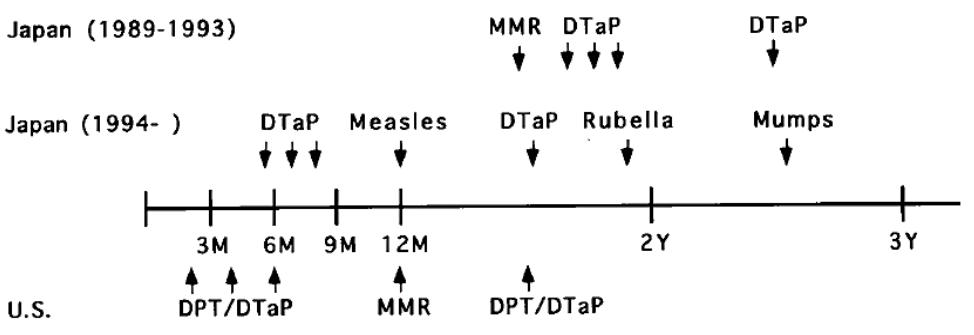


FIG 1. Immunization schedules in Japan and the US.

Nearly half the children who had received the gelatin-containing DTAP had the allergy. No children in the control group had the allergy.**

Table 6. DTaP vaccination histories of children with anti-gelatin IgE and systemic immediate-type allergic reactions to vaccines

History of DTaP vaccine	Allergic reactions	
	+	–
with gelatin	54	72
without gelatin	0	29

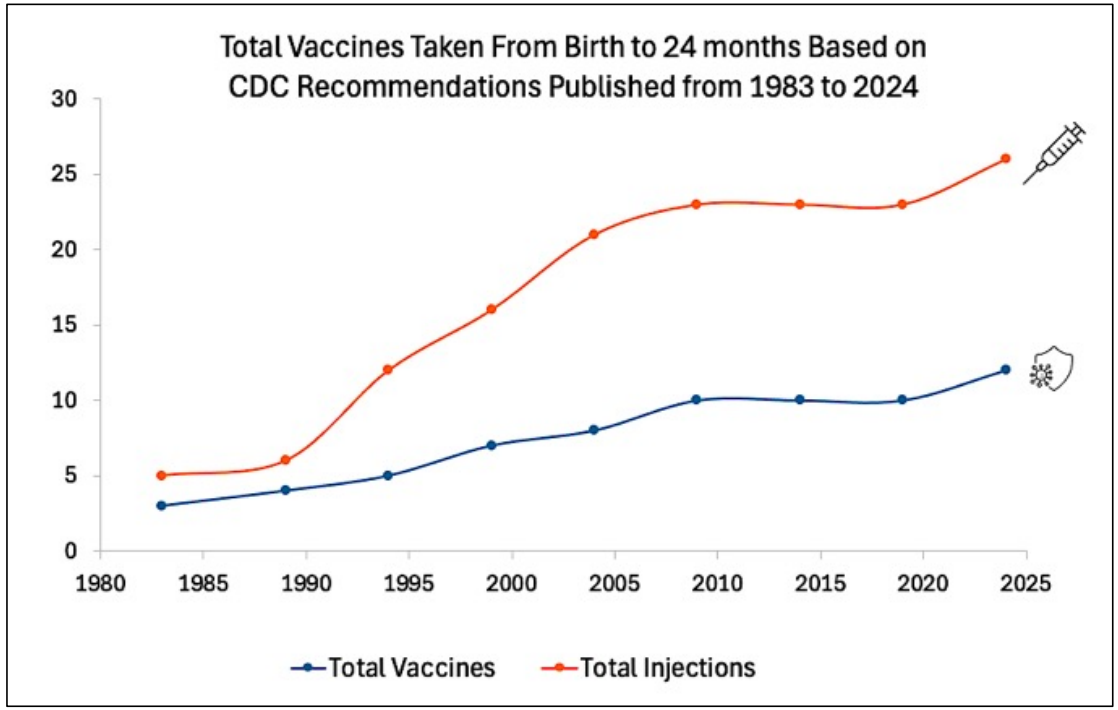
Significant relationship between histories of vaccination with gelatin-containing DTaP vaccine and anti-gelatin IgE production ($P < 0.001$).

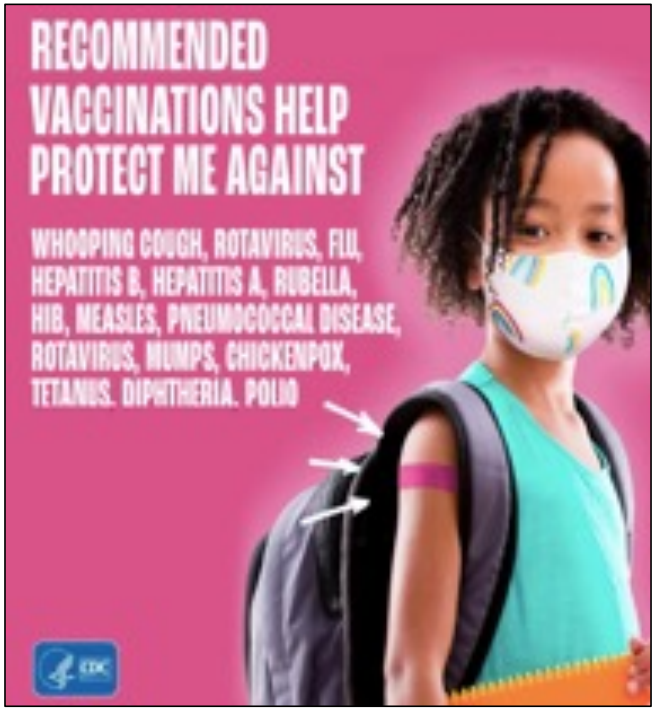
* Nakayama *et al.* "A clinical analysis of gelatin allergy and determination of its causal relationship to the previous administration of gelatin-containing acellular pertussis vaccine combined with diphtheria and tetanus toxoids." J. Allergy Clin. Immunol. Feb. 1999, 103 (2.1) 321-325 https://pubmed.ncbi.nlm.nih.gov/9949325/

** Sakaguchi and Sakae "Systemic Allergic Reactions to Gelatin Included in Vaccines as a Stabilizer." *Japanese J. Infect. Dis.* (2000) 53: 189-195 https://www.jstage.jst.go.jp/article/yoken/53/5/53_JJID.2000.189/_pdf/-char/en

The "National Childhood Vaccine Injury Act of 1986" provided liability protection to manufacturers of all products listed on the US childhood immunization schedule.

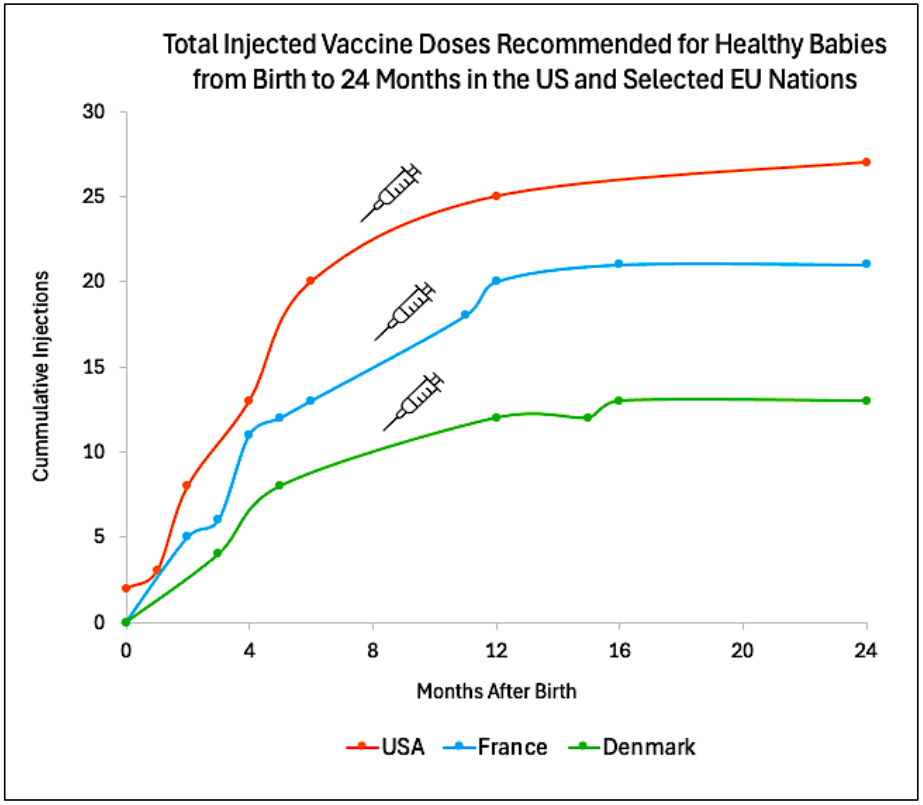
This was followed by a quadrupling of the immunization schedule from 1990 to 2010.





CDC: Immunization Schedule-Related Resources for Healthcare Providers. https://www.cdc.gov/vaccines/hcp/imz-schedules/resources.html?CDC_AAref_Val=https://www.cdc.gov/vaccines/schedules/hcp/schedule-related-resources.html

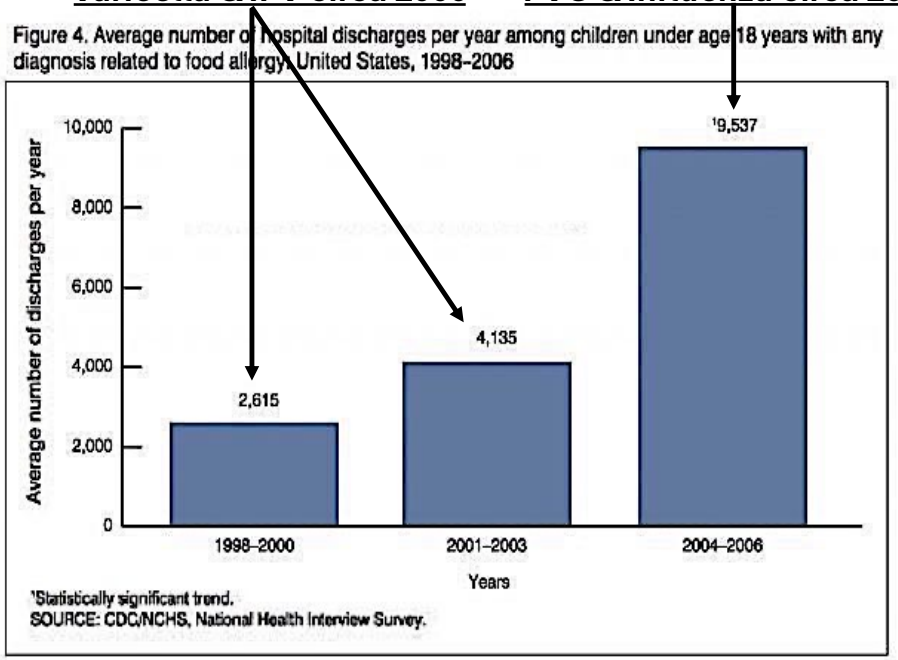
Currently, the US vaccine recommendations far exceed amount recommended in the EU.



Data sources: The CDC Immunization Schedule-Related Resources for Healthcare Providers. https://www.cdc.gov/vaccines/hcp/imz-schedules/resources.html?CDC_AAref_Val=https://www.cdc.gov/vaccines/schedules/hcp/schedule-related-resources.html
and the ECDC: Vaccine Scheduler. https://vaccine-schedule.ecdc.europa.eu/

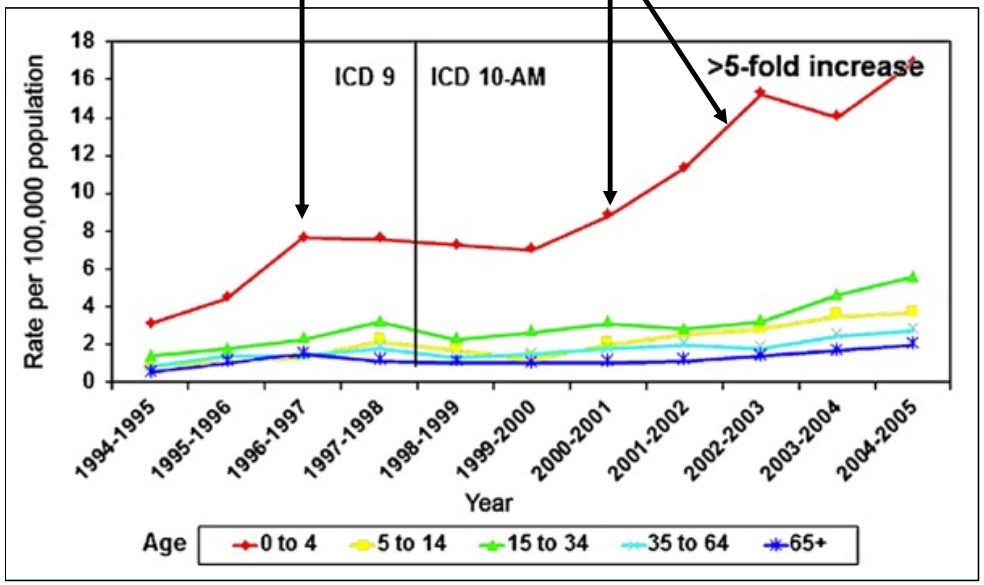
Did these additional vaccines play a role in these additional food allergy hospitalizations?

***Varicella* & *IPV* circa 2000** **PVC & *Influenza* circa 2004**



***Hib 3* circa 1997** ***Hep B* circa 2001**

Food-induced hospital anaphylaxis admissions in Australia



Food allergy data sources: CDC (2008) "Food Allergy Among U.S. Children: Trends in Prevalence and Hospitalizations." NCHS Data Brief No. 10, October 2008 https://www.cdc.gov/nchs/products/databriefs/db10.htm
and Liew *et al.* J Allergy Clin Immunol 2009; 123:434e42. As cited in Sampson (2016) "Food Allergy: Past, Present, and Future." Allergology International 65: 363-369 https://www.sciencedirect.com/science/article/pii/S1323893016301137

Vaccination data sources: The CDC Immunization Schedule-Related Resources for Healthcare Providers. https://www.cdc.gov/vaccines/hcp/imz-schedules/resources.html?CDC_AAref_Val=https://www.cdc.gov/vaccines/schedules/hcp/schedule-related-resources.html
and Vanderslott *et al.* (2024) "Our World in Data: Vaccination." https://ourworldindata.org/vaccination

The graph showing how the US childhood vaccine schedule expanded from 1983 to 2024 is based on this table.

Total vaccines recommended by the CDC from birth to 24 months

Vaccine name	1983	1989	1994	1999	2004	2009	2014	2019	2024
DTP	4	4	4						
DTaP				4	4	4	4	4	4
OPV	3*	3*	3*						
IPV				3	3	3	3	3	3
MMR	1	1	1	1	1	1	1	1	1
HbCV		1							
Hib			4	4	4	4	4	4	4
Hep B			3	3	3	3	3	3	3
Varicella				1	1	1	1	1	1
PVC					4	4	4	4	4
Influenza					1	1	1	1	1
Hep A						2	2	2	2
Rotavirus				3*		3*	2*	2*	2*
COVID-19									1
RSV									2
Total Vaccines	3	4	5	7	8	10	10	10	12
Total Doses	8	9	15	19	21	26	25	25	28
Total Injections	5	6	12	16	21	23	23	23	26

* These vaccines are not injected.

Data sources: https://www.cdc.gov/vaccines/hcp/imz-schedules/resources.html?CDC_AAref_Val=https://www.cdc.gov/vaccines/schedules/hcp/schedule-related-resources.html

The graph comparing the US childhood vaccine schedule to the schedules of France and Denmark is based on this table.

Vaccine recommendations for healthy children from birth to 24 months

Vaccine	Birth	1 mo.	2 mo.	3 mo.	4 mo.	5 mo.	6 mo.	7 mo.	8 mo.	9 mo.	10 mo.	11 mo.	12 mo.	14 mo.	15 mo.	16 mo.	18 mo.	24 mo.
USA																		
RSV	1																	
Hep B	1	1					1											
Rotavirus*			1*		1*													
DTaP			1		1		1								1			
Hib			1		1		1						1					
PCV			1		1		1						1					
IPV			1		1		1											
COVID-19							1											
Influenza							1											
MMR												1	1					
Varicella												1	1					
Hep A													1					1
Total Injections	2	1	5		5		7						5	1				1
Cummulative Injections	**2**	**3**	**8**		**13**		**20**						**25**	**26**				**27**
Denmark																		
DTaP				1		1							1					
Hib				1		1							1					
PCV				1		1							1					
IPV				1		1							1					
MMR																1		
Total Injections				4		4							4			1		
Cummulative Injections				**4**		**8**							**12**			**13**		
France																		
Rotavirus*			1*		1*	1*												
DTaP			1		1							1						
Hib			1		1							1						
PCV			1		1							1						
IPV			1		1							1						
Hep B			1		1							1						
Meningococcal				1		1	1						1			1		
MMR													1					
Total Injections			5	1	5	1	1					5	2			1		
Cummulative Injections			**5**	**6**	**11**	**12**	**13**					**18**	**20**			**21**		

* These vaccines are not injected.

Data sources: https://www.cdc.gov/vaccines/hcp/imz-schedules/resources.html?CDC_AAref_Val=https://www.cdc.gov/vaccines/schedules/hcp/schedule-related-resources.html
and https://vaccine-schedule.ecdc.europa.eu/

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