



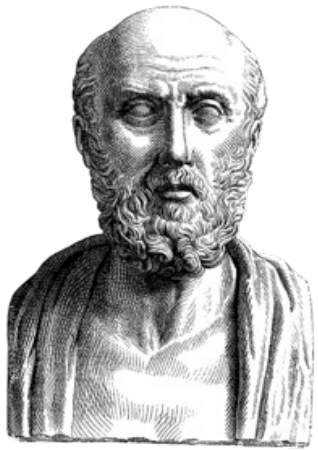
# A Review on Probable Causes of the Childhood Allergy Epidemic

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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:\*\***

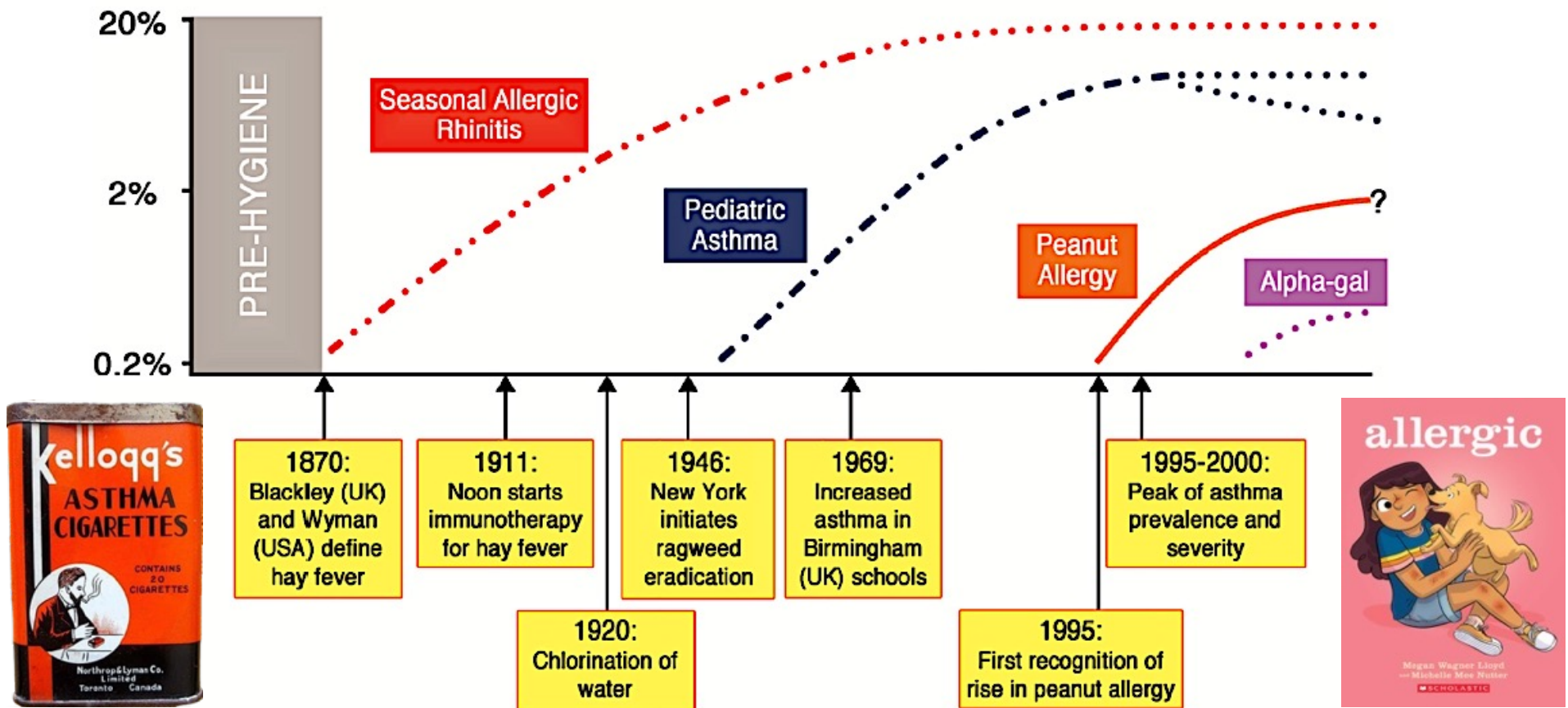


- **1 in 12 children** diagnosed in the U.S.
- **Every 2-3 minutes** there is an ER visit from food induced anaphylaxis.
- **40% of children** with food allergies experience a life-threatening reaction.
- **\$4,184 cost per child** per year
- **\$24.8 billion** cost to U.S. economy.

\* 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/>

## Sequential rises in three different allergic diseases



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<sup>th</sup> century hay-fever was regarded as an ailment of the “privileged” classes.

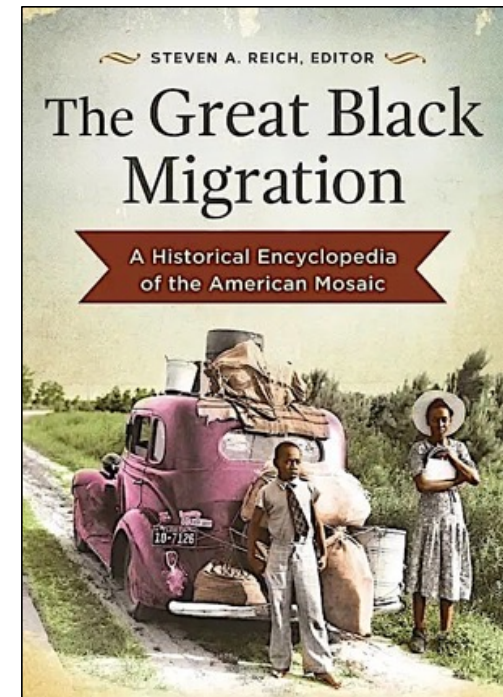
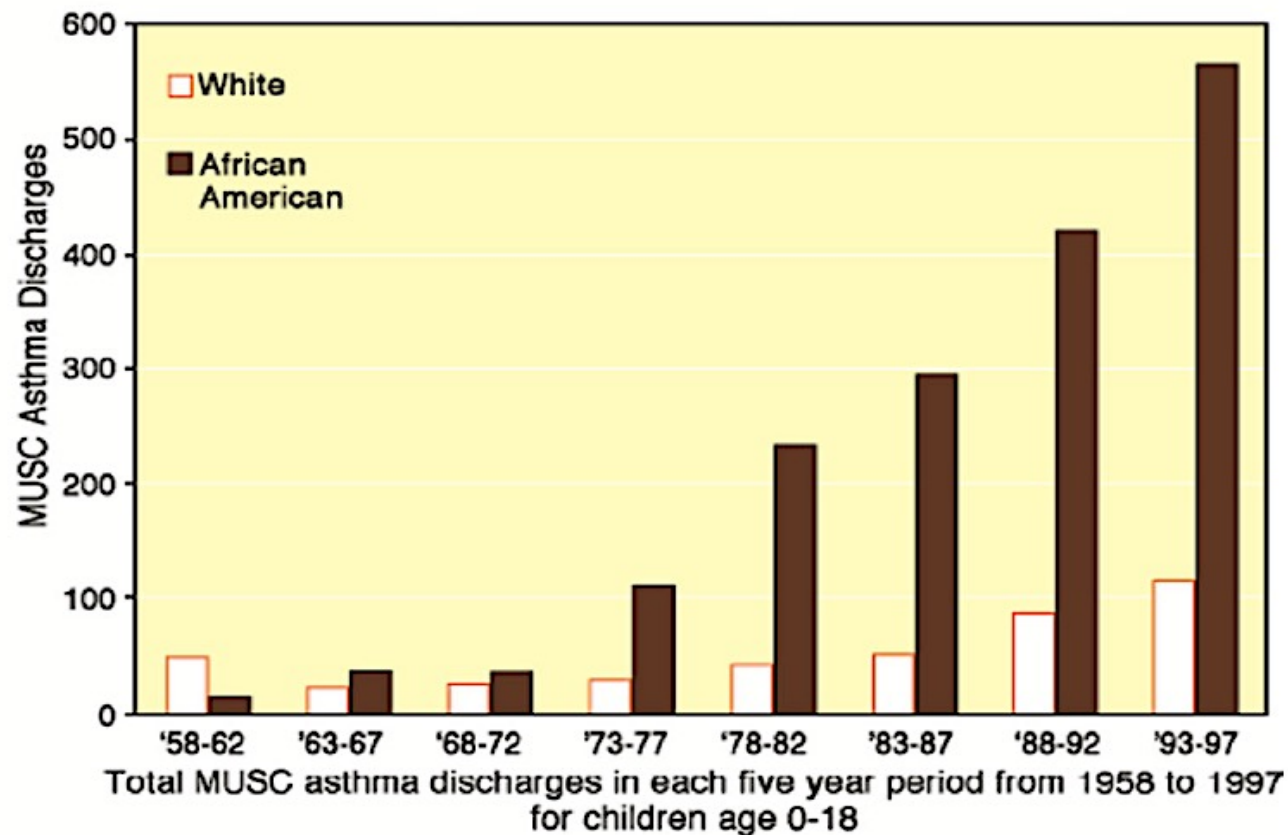
*And when hay-fever appears ...it chooses the man before the woman, the educated before the ignorant, the gentle before the rude, the courtier before the clown ...It prefers the temperate to the torrid zone, it seeks the city before the country, and out of every climate it chooses the Anglo-Saxon, or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

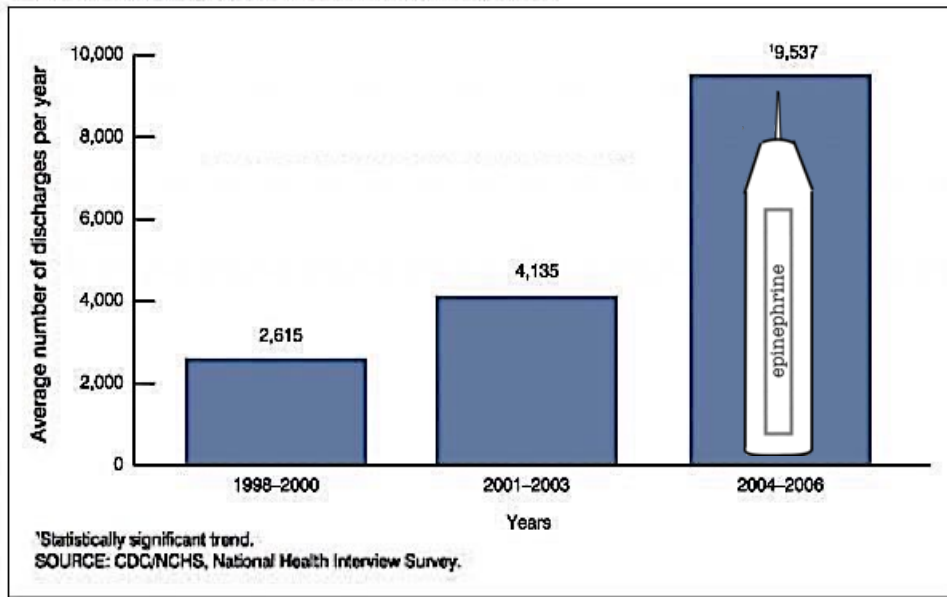
Respiratory allergies became increasingly “inclusive” as black Americans relocated to cities.



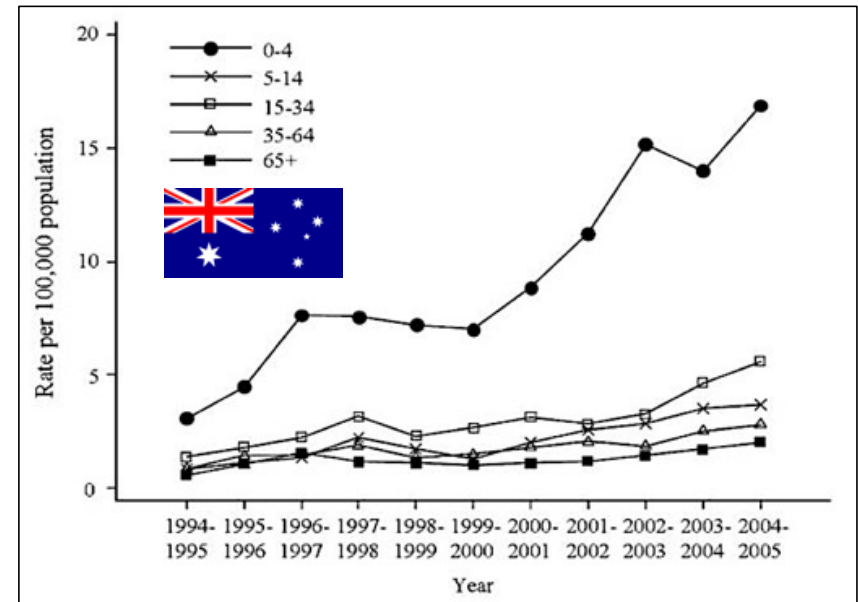
Thomas Platt-Mills in “The Allergy Epidemics: 1870–2010.” *J. Allergy Clin. Immunol.* July 2015 , 136(1): 3–13  
<https://pmc.ncbi.nlm.nih.gov/articles/PMC4617537/>

## 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 \*



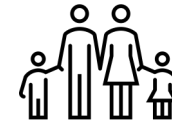
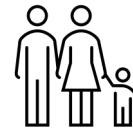
Food-induced hospital anaphylaxis admissions in Australia.\*\*



\* 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>






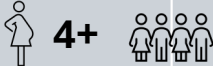

\*\* From Liew *et al.* (2009) "Anaphylaxis fatalities and admissions in Australia." *J. Allergy Clin. Immunol.* 123(2) 434-442.  
<https://pubmed.ncbi.nlm.nih.gov/19117599/>

## Epidemiologist David Strachan was the first to investigate the “hygiene hypothesis.”



...allergic diseases (may 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).

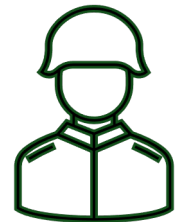
\*\* Adjusted for father's social class, housing tenure and shared household amenities in childhood, breast feeding, region of birth, and cigarette-smoking at 23 (n = 17,414).

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 cadets 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.*

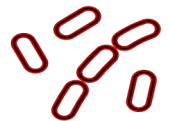
	Index of exposure to orofecal and foodborne infections			P value*
	0 (n=796)	1 (n=618)	2 or 3 (n=245)	
<b>Prevalence of sensitisation to allergens (weal <math>\geq 3</math> mm)</b>				
<i>Dermatophagoides pteronyssinus</i>	160 (20.1)	99 (16.0)	27 (11.0)	0.001
Cat	68 (8.5)	38 (6.1)	6 (2.4)	0.001
Mixed 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
<b>Respiratory allergic disease</b>				
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

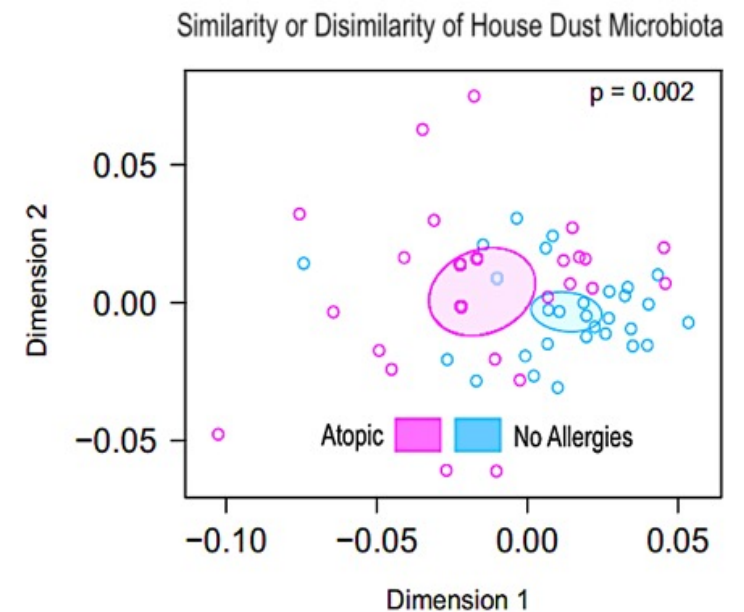
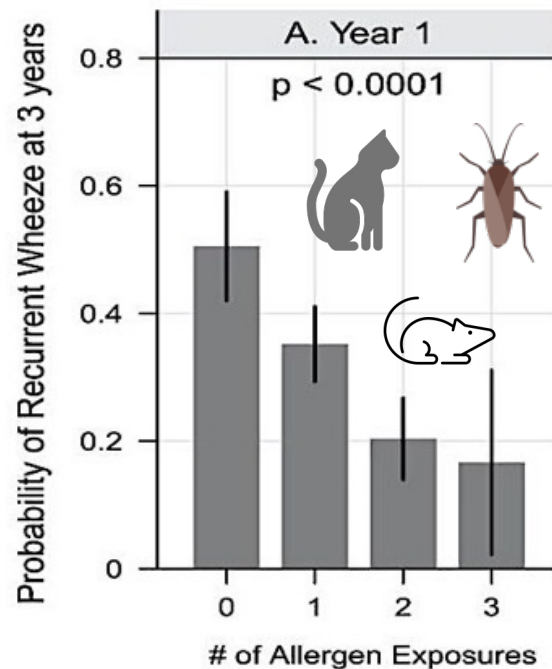
<https://pubmed.ncbi.nlm.nih.gov/10669445/>

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 differences in make-up of the bacteria in houses of children with allergies versus children with no allergy symptoms.



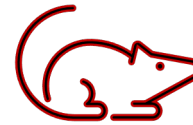
*Our observations raise the possibility that the optimal conditions to promote tolerance might be early-life antigenic exposure to allergen in conjunction with exposure to particular bacteria, such as those identified in this study.*



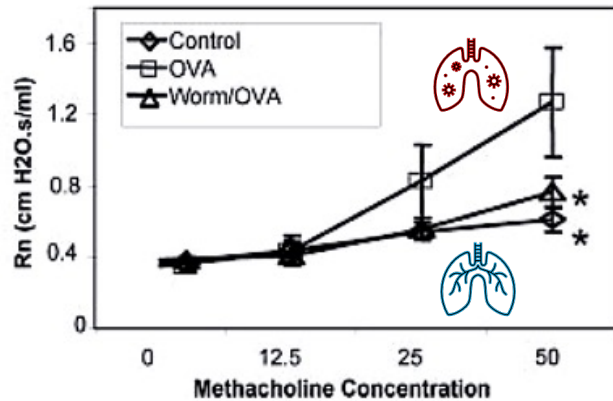
Lynch *et al.* "Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children." *Journal of Allergy and Clinical Immunology* (2014) 134(3): 593-601. [https://www.jacionline.org/article/S0091-6749\(14\)00593-4/fulltext](https://www.jacionline.org/article/S0091-6749(14)00593-4/fulltext)

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.

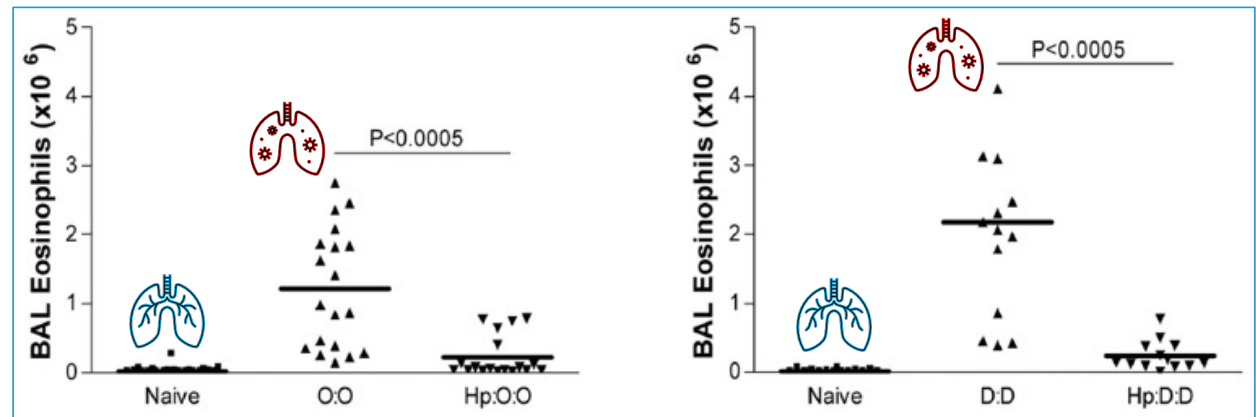


Bronchial Constriction in Response to Methacholine in Mice Challenged with Aerosolized Ovalbumin\*



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\*\*

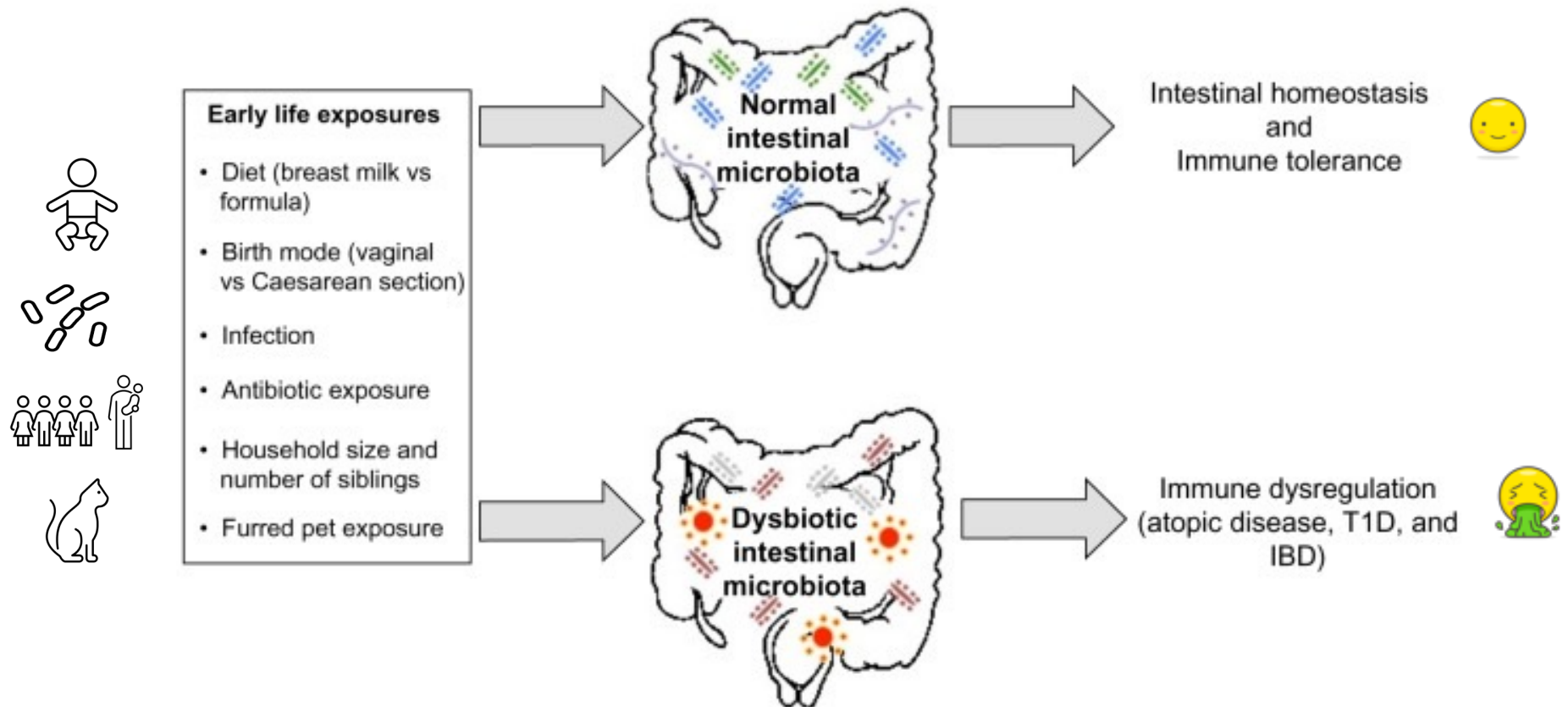


Naive = non-sensitized mice (control)  
 O:O or D:D = mice sensitized to ovalbumin or the dust mite allergen Der p 1  
 Hp = mice infected with worms prior to sensitization

\*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/>

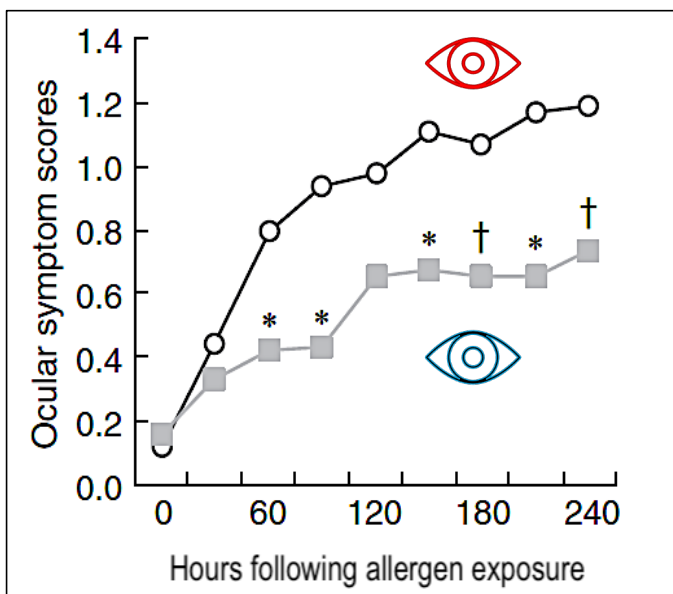
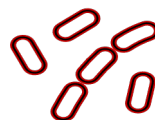
\*\*Wilson *et al.* "Suppression of Allergic Airway Inflammation by Helminth-induced Regulatory T-Cells." *J. of Exper. Medicine* (2005) 202(9): 1199-1212.  
<https://pubmed.ncbi.nlm.nih.gov/16275759/>

## 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						Sum
		day 0	day 1	day 2	day 3	day 4	day 5	
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*

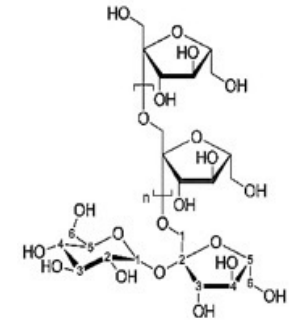
\*  $p < 0.05$ , difference in total counts vs placebo groups, Fisher's exact test.

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

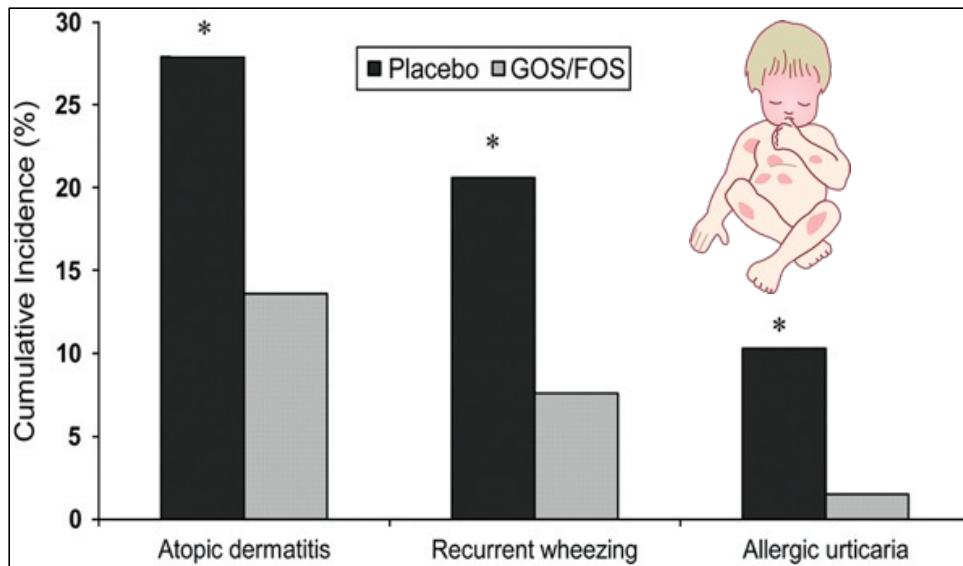
<https://pubmed.ncbi.nlm.nih.gov/17259812/>

In this experiment, babies with a parental history of atopy who consumed a supplemental “prebiotic” infant formula had less allergies and less infections than the placebo group.

This prebiotic (GOS/FOS) contained galacto- and fructo-oligosaccharides in ratios that approximated those of breast milk.



Cumulative incidence of allergic manifestations at the end of 2-y follow-up period in the placebo and GOS/FOS groups.



Episodes of infections and fever during the 2-y follow-up period in the placebo group (left) and GOS/FOS group (right)<sup>1</sup>

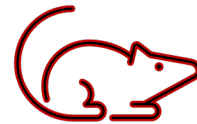
	episode/infant	
<i>n</i>	68	66
Physician-diagnosed infections		
Overall (any kind of infection)**	5.9 ± 4.1	4.1 ± 3.1
URTI <sup>†</sup>	3.2 ± 2.2	2.1 ± 1.8
Lower respiratory tract infections	1.3 ± 0.8	0.9 ± 1.1
Otitis media	0.7 ± 1.2	0.5 ± 1.0
Gastrointestinal infections	0.6 ± 0.9	0.4 ± 0.7
Urinary tract infections	0.1 ± 0.5	0.0 ± 0.0
Infections requiring antibiotic prescriptions*	2.7 ± 2.4	1.8 ± 2.3
Fever episodes recorded by parents <sup>‡</sup>	3.9 ± 2.5	2.2 ± 1.9

<sup>1</sup> Values are means ± SD. \*Different from placebo, *P* < 0.05, \*\**P* = 0.01, <sup>†</sup>*P* < 0.01, <sup>‡</sup>*P* < 0.0001.

Arslanoglu *et al.* “Early Dietary Intervention with a Mixture of Prebiotic Oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life.” *Journal of Nutrition* 2008 Jun;138(6):1091-1095 <https://pubmed.ncbi.nlm.nih.gov/18492839/>

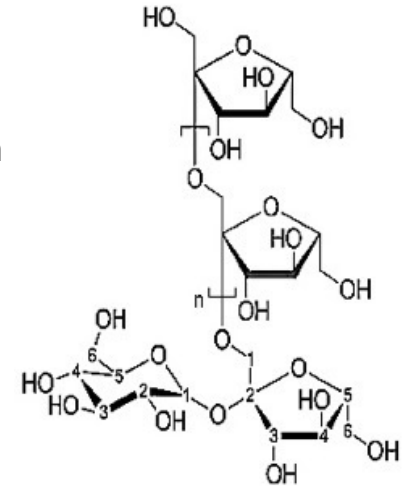
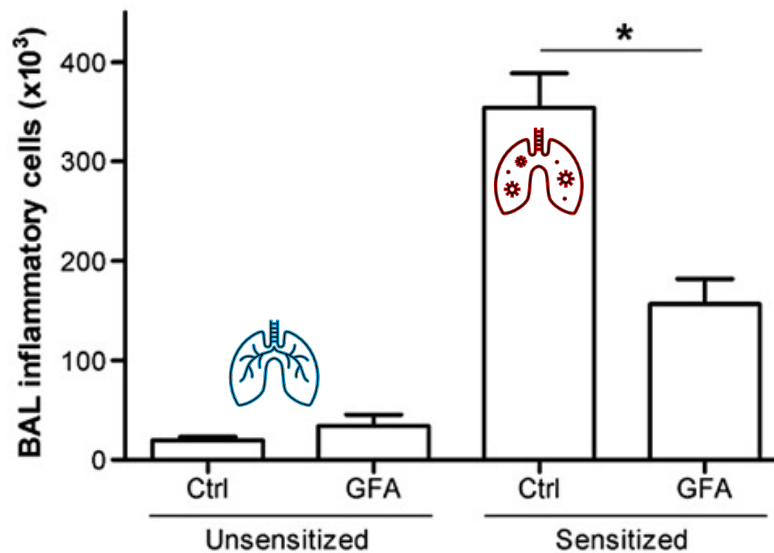
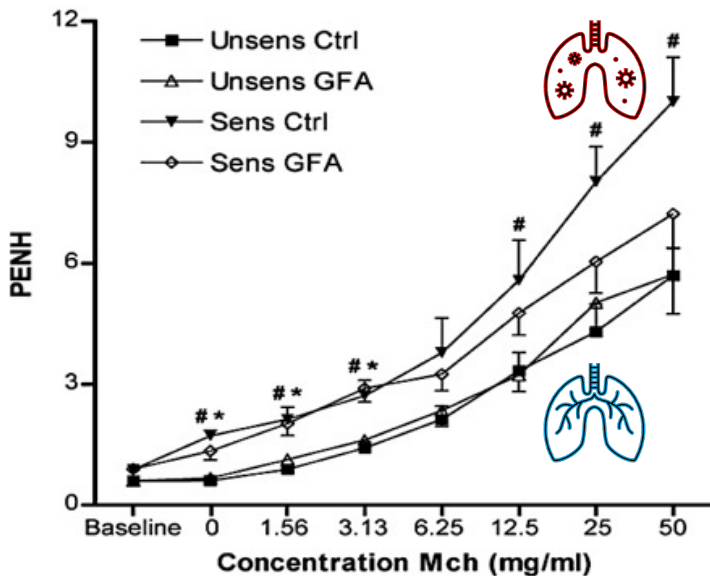
The symptoms of these sensitized mice significantly improved when they consumed a supplement containing oligosaccharides in ratios that approximated those of breast milk.

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

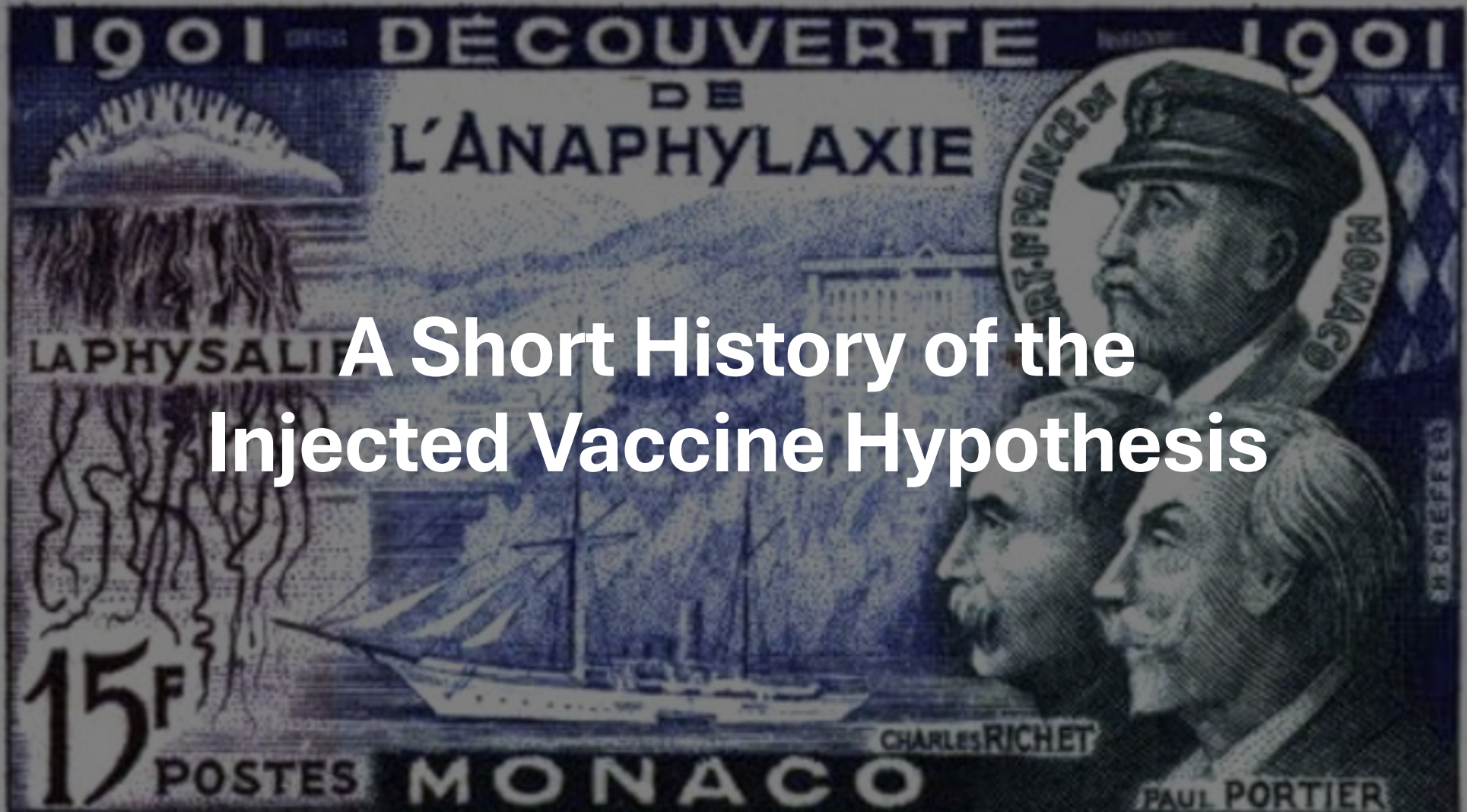
Lung Inflammation in Mice Challenged with Ovalbumin (GFA= mice on the prebiotic diet)



GFA = a combination of galactooligosaccharides, fructooligosaccharides, and acidic pectin-derived oligosaccharides

Vos *et al.* "Dietary supplementation with specific oligosaccharide mixtures decreases parameters of allergic asthma in mice." *International Immunopharmacology* 7 (2007) 1582-1587. <https://pubmed.ncbi.nlm.nih.gov/17920536/>

# A Short History 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.



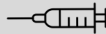









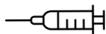



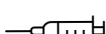
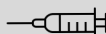


In 1906 Clemens Von Pirquet concluded that **immunity and sensitization are two sides of the immune response** and coined the term “**allergy**” to describe this “**altered reactivity**” to antigens. He based this on his clinical observations of adverse reactions to serum therapy and vaccine boosters. 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)
<u>1</u>	2023	Ovalbumin 	Mouse 	Injection with alum as the adjuvant. 	<p>Responses to ingestion challenge:</p> <ul style="list-style-type: none"> <li>Scratching, sneezing, and nasal rubbing. </li> <li>IgE levels in plasma.</li> <li>Eosinophil levels in lungs.</li> </ul>
<u>2</u>	2022	Ragweed pollen 	Mouse 	Intranasal application of 6 doses over 21 days under anesthesia.	<p>Responses to inhalation challenge:</p> <ul style="list-style-type: none"> <li>Eosinophil and neutrophils in lungs.</li> <li>Inflammation of lungs.</li> <li>Airway resistance of lungs. </li> </ul>
<u>3</u>	2018	Whey protein 	Mouse 	Intragastric application with cholera toxin as the adjuvant.	<p>Responses to ingestion challenge:</p> <ul style="list-style-type: none"> <li>Digging frequency.</li> <li>IgE levels in plasma.</li> <li>Mast cell activity in brain and intestine. </li> <li>5-hydroxymethylcytosine reactivity in amygdala.</li> </ul>
<u>4</u>	2003	Dust mites 	Mouse 	Injection with alum as the adjuvant. 	<p>Responses to inhalation challenge:</p> <ul style="list-style-type: none"> <li>IgE levels in plasma.</li> <li>Eosinophil levels in blood.</li> <li>Cytokine levels in lungs.</li> <li>Airway resistance of lungs. </li> </ul>
<u>5</u>	1960	Ovalbumin 	Guinea pig	<ul style="list-style-type: none"> <li>Injection with 0.5 % phenol as solvent.</li> <li>Passive sensitization via injection with rabbit antisera. </li> </ul>	Histamine release by lung tissue cultured <i>in vitro</i> after the addition of antigen to the culture media.
<u>6</u>	1937	<ul style="list-style-type: none"> <li>Picryl chloride</li> <li>2,4-Dinitrochlorobenzene</li> </ul>	Guinea pig	Injection with saline as the solvent. 	<ul style="list-style-type: none"> <li>Anaphylaxis and death in response to reinjection.</li> <li>Redness and swelling upon application to skin.</li> </ul>
<u>7</u>	1903	Horse plasma	Rabbit	Injection of blood plasma. 	Edema, necrosis, and death in response to reinjection.

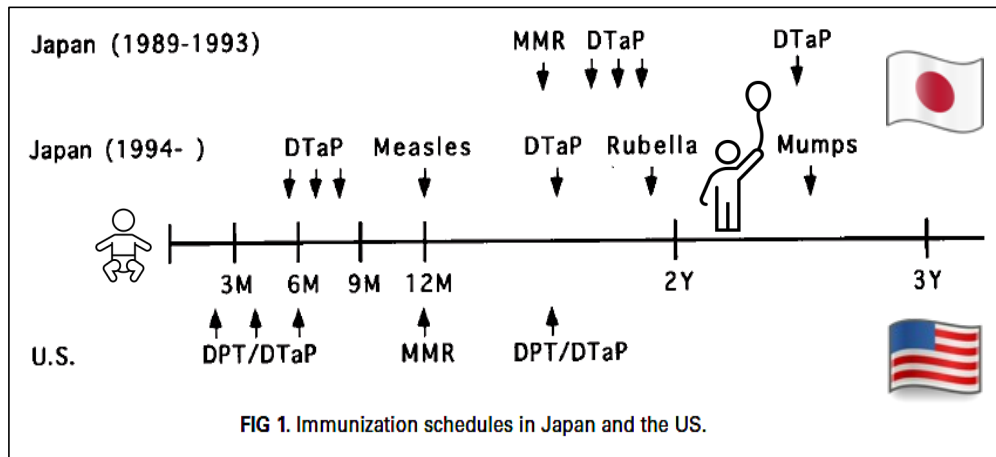
A sudden spike in gelatin allergies Japanese infants in the 1990's was traced to a change in the schedule whereby a gelatin-containing DTaP was given at a much earlier age.



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.\*

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 😊

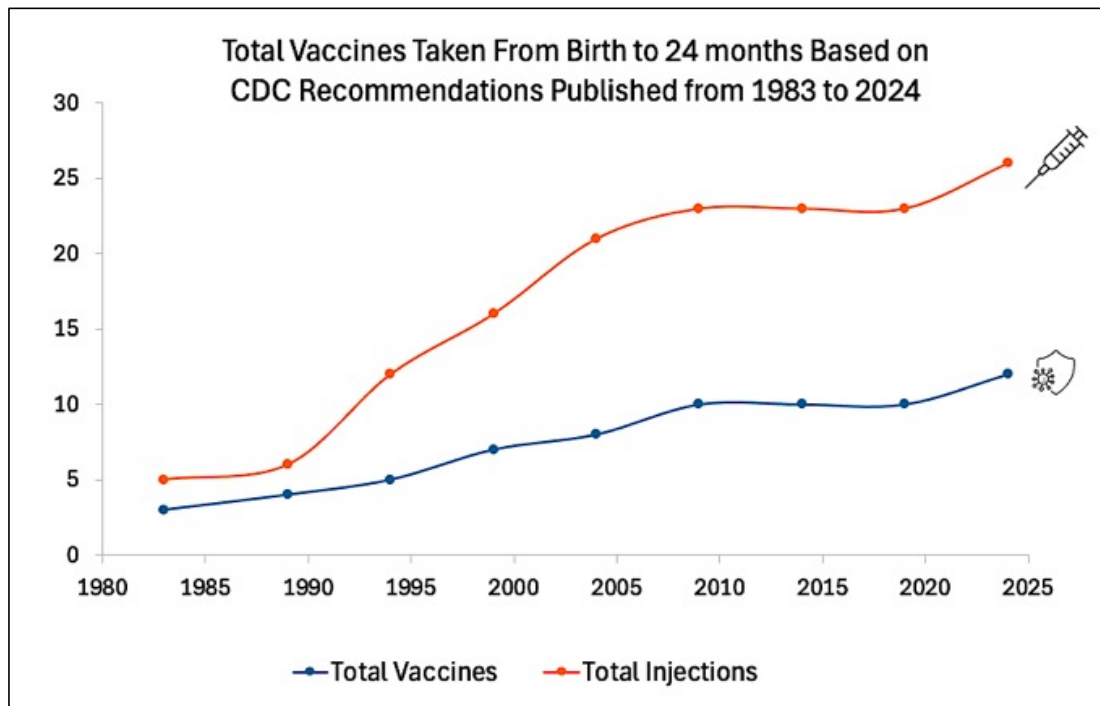
Significant relationship between histories of vaccination with gelatin-containing DTaP vaccine and anti-gelatin IgE production ( $P < 0.001$ ).

\* 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](https://www.jstage.jst.go.jp/article/yoken/53/5/53_JJID.2000.189/pdf/-char/en)

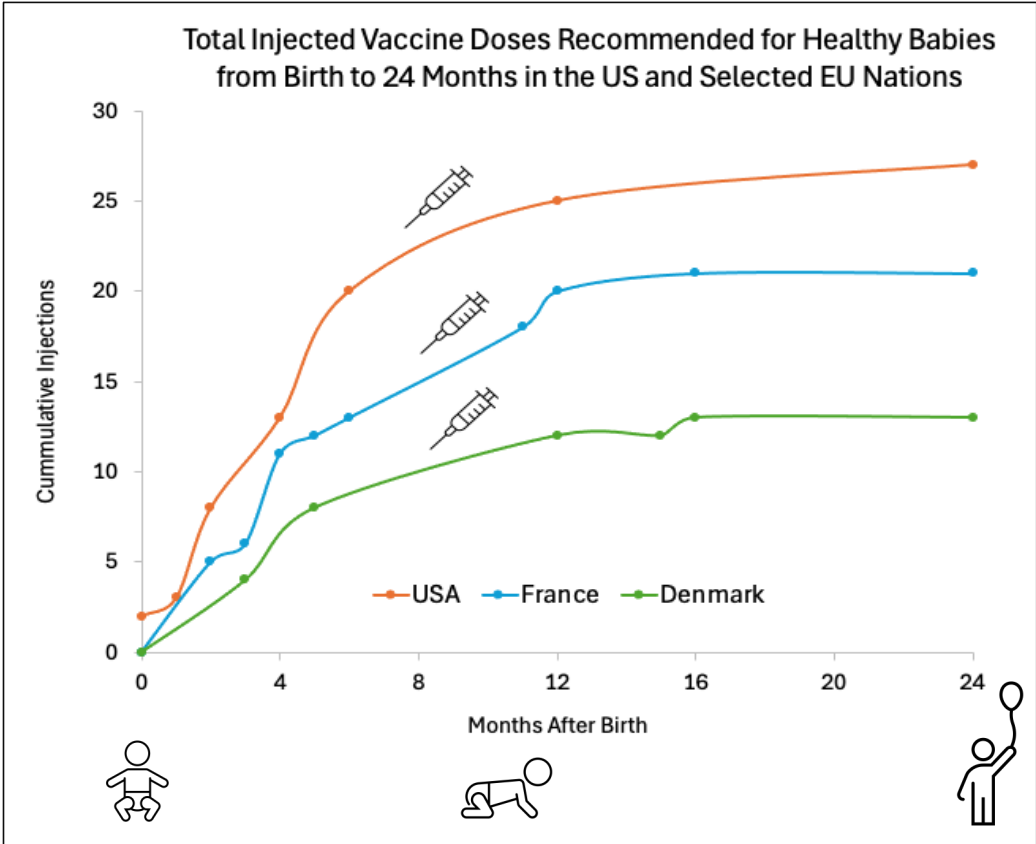
The “National Childhood Vaccine Injury Act of 1986” provided liability protection to manufacturers of all products listed on the US childhood immunization schedule.

This may have played a role in the *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](https://www.cdc.gov/vaccines/hcp/imz-schedules/resources.html?CDC_AAref_Val=https://www.cdc.gov/vaccines/schedules/hcp/schedule-related-resources.html)

This may also explain why US 2-year-olds accumulate more injections than their EU counterparts.

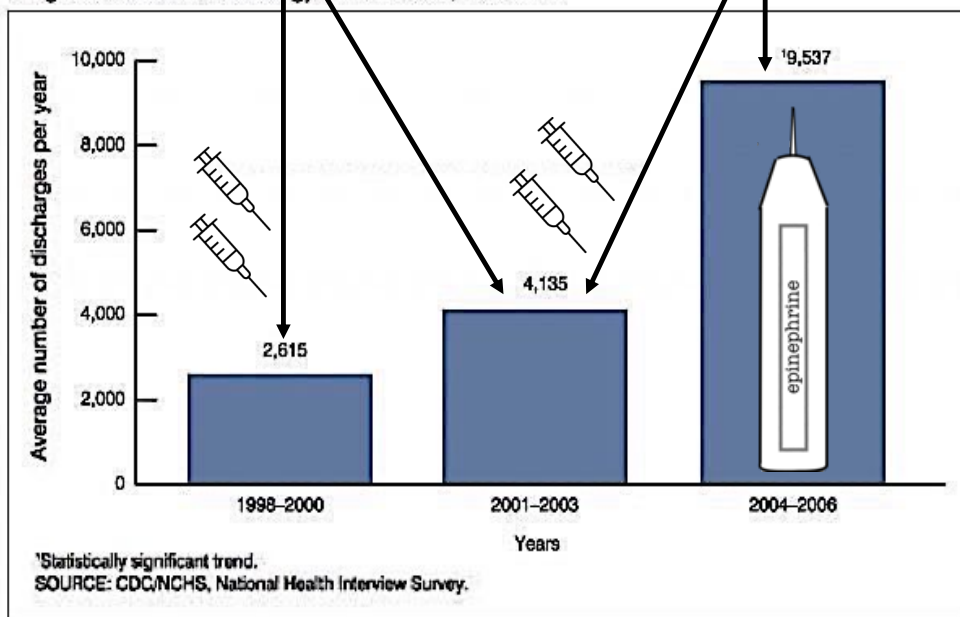


Data sources: The CDC Immunization Schedule-Related Resources for Healthcare Providers. [https://www.cdc.gov/vaccines/hcp/imz-schedules/resources.html?CDC\\_AAref\\_Val=https://www.cdc.gov/vaccines/schedules/hcp/schedule-related-resources.html](https://www.cdc.gov/vaccines/hcp/imz-schedules/resources.html?CDC_AAref_Val=https://www.cdc.gov/vaccines/schedules/hcp/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

## Did these additions to the vaccine schedule play a role in these spikes in childhood anaphylaxis?

***Varicella & IPV recommended in 1999***    ***PVC & Influenza recommended in 2004***

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




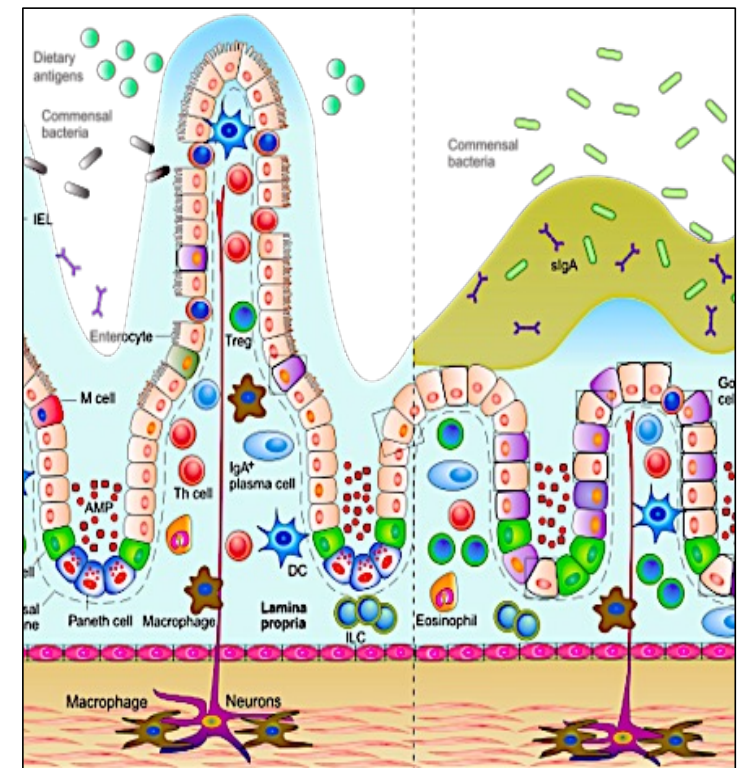
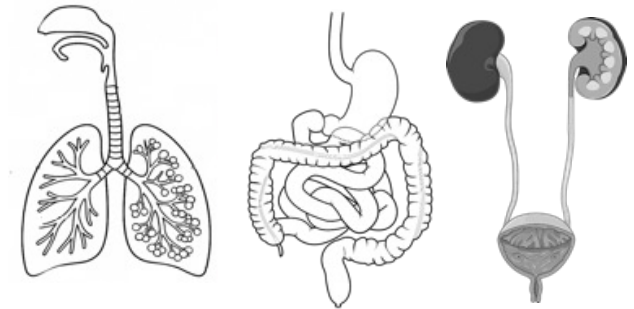
CDC (2008) "Food Allergy Among U.S. Children: Trends in Prevalence and Hospitalizations." NCHS Data Brief No. 10, October 2008  
<https://www.cdc.gov/nchs/products/databriefs/db10.htm>

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](https://www.cdc.gov/vaccines/hcp/imz-schedules/resources.html?CDC_AAref_Val=https://www.cdc.gov/vaccines/schedules/hcp/schedule-related-resources.html)

## Are we overlooking the significance of *mucosal* immunity?

- Mucosal surfaces exceed skin surfaces by 200X.
- Over 90% of infections enter via mucosal surfaces. 
- The majority of lymphocytes reside in the mucosa and the resident T & B cells are more efficient at stopping infections and discerning pathogens from the other particles.
- Mucosal lymphocytes and antibodies are less likely to activate systemic inflammation.



Should we rethink the way vaccines are applied?

What are the implications for the childhood immunization schedule when the experimental animals are sensitized with injected vaccines?

Today's Panel  
*Frontiers in Probiotics*

**2029 International Allergy Conference**  
*Honoring 100 years since the passing of Clemens von Pirquet*

Tomorrow's Panel  
*Cutting Edge Prebiotics*



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

<b>Total vaccines recommended by the CDC from birth to 24 months</b>									
<b>Vaccine name</b>	<b>1983</b>	<b>1989</b>	<b>1994</b>	<b>1999</b>	<b>2004</b>	<b>2009</b>	<b>2014</b>	<b>2019</b>	<b>2024</b>
<b>DTP</b>	4	4	4						
<b>DTaP</b>				4	4	4	4	4	4
<b>OPV</b>	3*	3*	3*						
<b>IPV</b>				3	3	3	3	3	3
<b>MMR</b>	1	1	1	1	1	1	1	1	1
<b>HbCV</b>		1							
<b>Hib</b>			4	4	4	4	4	4	4
<b>Hep B</b>			3	3	3	3	3	3	3
<b>Varicella</b>				1	1	1	1	1	1
<b>PVC</b>					4	4	4	4	4
<b>Influenza</b>					1	1	1	1	1
<b>Hep A</b>						2	2	2	2
<b>Rotavirus</b>				3*		3*	2*	2*	2*
<b>COVID-19</b>									1
<b>RSV</b>									2
<b>Total Vaccines</b>	3	4	5	7	8	10	10	10	12
<b>Total Doses</b>	8	9	15	19	21	26	25	25	28
<b>Total Injections</b>	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](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.

<b>Vaccine recommendations for healthy children from birth to 24 months.</b>																			
	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.	18 mo.	18 mo.	24 mo.
<b>USA</b>	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				
	Varicella														1				
	Hep A														1				1
	<b>Total Injections</b>		2	1	5		5		7						5		1		
<b>Cummulative Injections</b>		2	3	8		13		20						25		26			27
<b>Denmark</b>	DTaP				1		1							1					
	Hib				1		1							1					
	PCV				1		1							1					
	IPV				1		1							1					
	MMR																1		
	<b>Total Injections</b>				4		4								4			1	
<b>Cummulative Injections</b>				4		8								12			13		
<b>France</b>	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					
	MMR													1			1		
<b>Total Injections</b>			5	1	5	1	1					5	2			1			
<b>Cummulative Injections</b>			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](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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## Acknowledgements:



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