

## Seeking a Silver Lining to Allergy Season

The temperature outside our offices in Midtown Manhattan is cooling down as of this writing. Labor Day has passed, summer is about to end, and autumn is around the corner – and for a growing number of us, that means allergy season.

Seasonal allergies seem to have gotten more intense in recent years, and some studies back up these anecdotal observations. Researchers say that around the country and all over the world, climate change has led to allergy seasons starting earlier and lasting longer. Along the way, pollen counts are getting higher throughout the season. That means increased misery for those with sensitive immune systems.

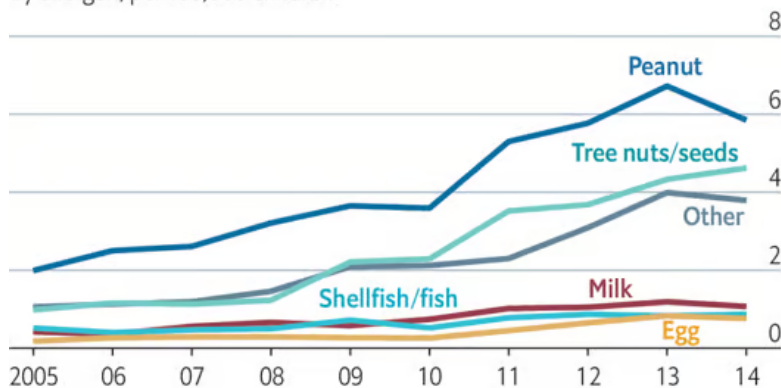
Yet perhaps more alarming is the spike in serious food allergies.

### Shock treatment

United States

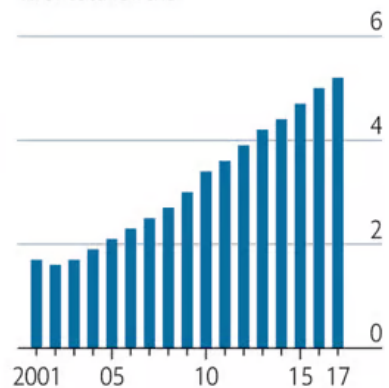
#### Emergency-department visits for food-induced anaphylaxis

By allergen, per 100,000 children



#### Peanut allergy incidence

% of total births



Sources: "National trends in emergency department visits and hospitalizations for food-induced anaphylaxis in US children" by Motosue et al., *Pediatric Allergy and Immunology* (2018); "Increased incidence and prevalence of peanut allergy in children and adolescents in the United States" by Lieberman et al., *Annals of Allergy, Asthma & Immunology* (2018)

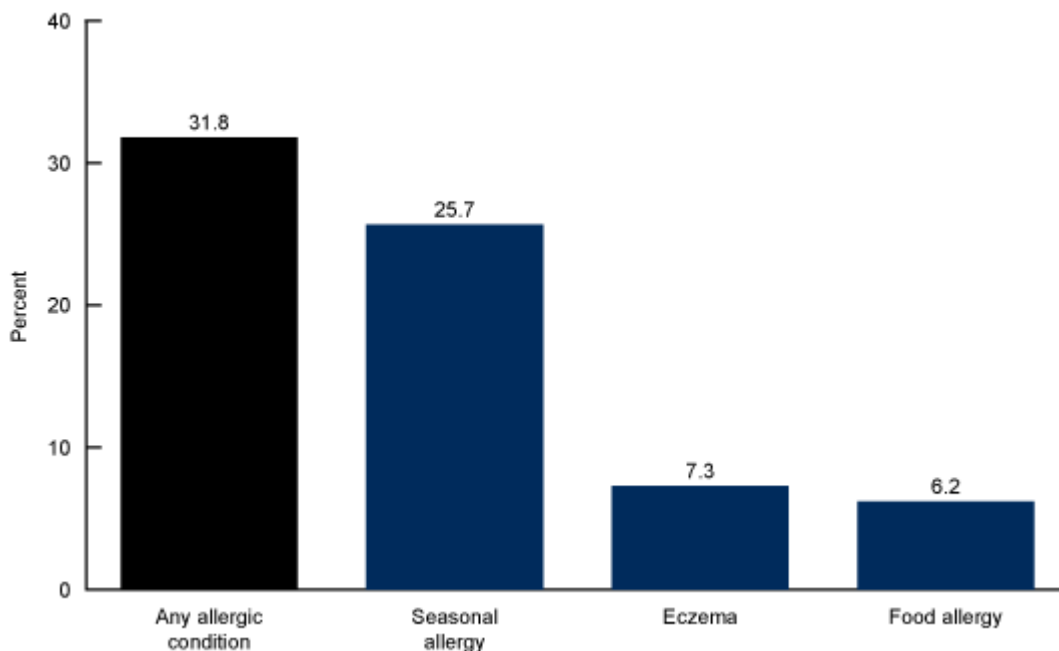
The Economist

While it was never unusual to encounter or hear about food allergies that might trigger mild reactions such as mild rashes or stomach discomfort, it is now becoming increasingly common for the consumption of foods containing nuts, shellfish, dairy, eggs, wheat, or other foods to trigger reactions so severe they require a visit to the emergency room – and in some cases, cause death.

The reason for this spike remains unknown, though not for a lack of research. Scientists have many competing theories. Some believe that a growing emphasis on personal hygiene and household sterility has increased the likelihood of people developing overly sensitive immune systems, perhaps by changing our respective microbiomes. (A microbiome is the combined genetic material of the microorganisms, many of which are beneficial, that live on our skin and in our bodies.)

Others suggest that some aspect of the modern diet is to blame for having changed our microbiomes. There's quite a bit of disagreement about what, in particular, about our diets might have caused this change. Researchers variously hypothesize that processed foods, additives, produce variants bred for hardiness and shelf life, or the changing levels of fat, fiber, or sugar consumption are to blame. Still others blame an increase in the number and concentration of environmental pollutants or contaminants, or changes in the urban environment.

Regardless, seasonal and food allergies are affecting an increasing share of children and adults. Federal data suggest that nearly 32% of American adults have a seasonal or food allergy, or eczema (a skin condition that has an allergy-related component).



SOURCE: CDC, National Center for Health Statistics, National Health Interview Survey, 2021.

### What is an allergy?

In essence, an allergy is a harmful immune-system response to a foreign substance that is otherwise harmless or nearly so. At present, allergies can not be cured. Instead, treatments focus on either allergen immunotherapy – conditioning patients' immune systems on an ongoing basis so that allergic reactions are minimized, or reducing allergic reactions.

The human immune system reacts to pathogens and foreign substances that it deems to be a threat by producing antibodies, also known as immunoglobulin. The most common type of antibody is Immunoglobulin G or IgG. It works by binding itself to pathogens and foreign substances, thus preventing them from attaching themselves to cells. IgGs also mark pathogens so that white blood cells can destroy them.

The antibody responsible for allergic reactions is Immunoglobulin E (IgE). It responds to perceived pathogens by causing cells to produce histamines, which in turn cause various inflammatory reactions. Each type of IgE responds to a specific allergen.

Histamines can cause blood vessels to dilate and become more permeable to white blood cells, trigger respiratory muscle contractions (coughing, sneezing, etc.), and stimulate the production of mucus and other fluids that can trap and flush out unwanted substances. Often, such reactions are useful in helping the body fight off pathogens and recover from illness. But not always.

### **The treatment of allergies**

Over-the-counter responses to allergic reactions tend to focus on antihistamines. They work by binding to histamine receptors, thus preventing histamines from doing so and triggering the unwanted symptoms.

A longer-lasting approach involves allergen immunotherapy. This works on similar principles as vaccines, training the patient's immune system to respond to allergens by producing IgGs rather than IgEs.

The most common form of allergen immunotherapy involves regular allergy shots. Such treatments work by repeatedly and deliberately introducing a specific allergen extract to the body in small but increasing doses, followed by several years of maintenance injections. This can create a lasting tolerance to the allergen in question. More recently, oral versions of the allergy-shot regimen have been introduced, as have sublingual (under the tongue) regimens. Allergen immunotherapy is customized to each individual by their physician.

### **Anti-IgE Antibodies**

Researchers have also begun experimenting with anti-IgE antibodies, which seek to bind with specific IgEs before they can trigger allergy symptoms. Several such antibodies are currently approved for use as treatments for asthma and chronic hives

Examples of such treatments include Omalizumab, currently marketed under the Xolair brand name by Novartis as a treatment for allergic asthma and chronic hives. Researchers believe Xolair could also be used to treat allergies to foods like peanuts and environmental particles like pollen, dust, dander, and mold. Another Novartis drug candidate, Ligelizumab, is also in late-stage clinical trials for similar indications.

### **Cytokine Therapies**

Cytokines are proteins produced by many components of the immune system, helping to trigger and regulate immune responses and cell growth. Cytokines – particularly a type known as interleukins – play a role in signaling IgE production, and thus in triggering allergic reactions. Researchers have achieved success in treating or mitigating allergic reactions by using agonists to stimulate the function of some cytokines and using antagonists to inhibit the function of others. Dupilumab, developed by Sanofi and Regeneron (marketed as Dupixent), is an example of a cytokine allergy therapy. It works to inhibit the function of the cytokines IL-4 and IL-13, which cause inflammatory responses associated with eczema, asthma, and sinus allergies.

[As a side note, cytokines played a significant role in COVID-19 fatalities, many of which were caused by an out-of-control over-release of pro-inflammatory cytokines in response to the coronavirus. Suppressing the cytokines in question is thus key to the reduction of COVID-19 fatalities.]

### **Adjuvants**

Adjuvants are formulations that are used alongside other immunotherapies to improve efficacy. They are often used to improve the efficacy of vaccines, for example. A number of pharmaceutical companies are investigating adjuvants like TLR4 and TLR7 agonists as potential adjuncts to improve the efficacy of allergy immunotherapies.

### **DNA and mRNA Vaccines**

With the success of the various mRNA vaccines during the COVID-19 pandemic, researchers have turned their attention to other potential applications of gene-based technology. As with mRNA vaccines, DNA vaccines use genetic material to train the immune system. This has potential applications in allergy treatment and prevention. As of this writing, no DNA or mRNA vaccines for the treatment of allergies has entered late-stage clinical trials. Nevertheless, privately held Immunomic Therapeutics recently developed a DNA vaccine that shows promise in providing protection against allergic symptoms triggered by Japanese red cedar pollen. Astellas Pharmaceutical, a subsidiary of Japanese conglomerate Mitsubishi UFJ, has licensed the technology for use in the development of a peanut-allergy vaccine.

### ***Companies Active in the Development and Production of Allergy Treatments***

#### **Novartis (\$NVS)**

The healthcare giant markets Zolair, an anti-IgE antibody that has already been approved for the treatment of allergic asthma and chronic hives; the FDA has given Zolair Breakthrough Therapy Designation, fast-tracking trials to determine whether it might also be useful in treating allergies to foods like peanuts and allergies caused by pollen, dander, and mold. The company also has a diverse array of other allergy treatments in its pipeline.

#### **Sanofi (\$SNY)**

France's Sanofi markets and continues to develop a wide range of potential treatments for allergies, including adjuvants (TLR7 agonists), DNA vaccines, anti-IgE antibodies, and cytokine therapies. The company jointly developed (with Regeneron \$REGN) a cytokine-based treatment called dupilumab (Dupixent) that has been approved to treat eczema, asthma, and chronic rhinosinusitis. Sanofi also sells the popular over-the-counter allergy medications Allegra, Nasacort, and Xyzal.

#### **ALK-Abello (\$AKBLF)**

Denmark's ALK-Abello is wholly focused on the manufacture and development of allergy immunotherapy products. This includes sublingual immunotherapy drops and tablets to treat allergies to dust mites and to grass and ragweed pollen, as well as a range of allergy tests and allergy shots related to pollens, molds, animals, and insect bites.

#### **Aimmune Therapeutics, owned by Nestle SA (\$NSRGY)**

As of this writing, Aimmune has the only FDA-approved peanut-allergy oral immunotherapy treatment on the market, Palforzia, which seeks to mitigate the severity of allergic reactions to accidental exposure. It also has a multi-nut allergy medication in clinical trials and an anti-IgE antibody in early development.

### **DBV Technologies (\$DBVT)**

DBV is a French biopharmaceutical technology company focused on the development of allergy treatments and related products, mostly through its Viaskin patch technology. The company is in late-stage clinical trials for treatments for peanut and cow's milk allergies based on this technology. The company also hopes to develop allergy tests based on its patch technology.

As allergies become increasingly more common for both children and adults, it is reasonable to assume that demand for more effective allergy treatments will grow. The companies identified above are all working to meet this anticipated trend, but they are subject to the significant risks associated with pharmaceutical development. As usual, Signal From Noise should serve as a starting point for further research before making an investment, rather than as a source of stock recommendations.

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