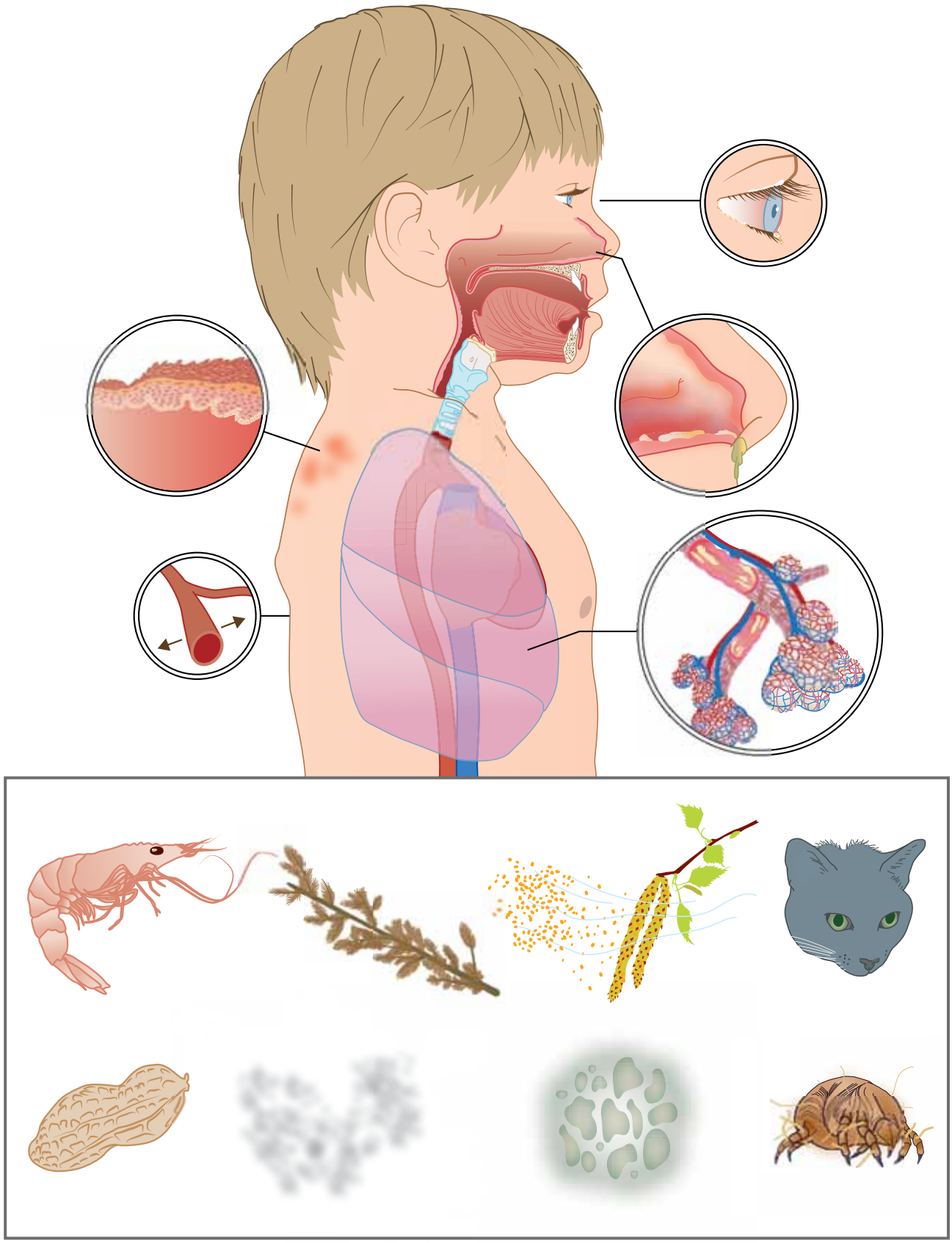


Tipping the allergy balance

The number of allergy sufferers has almost tripled in the last fifty years. We can only guess at the reason for this. The Allergy Consortium Wageningen helps patients to avoid allergens, and searches for ways to restore balance to overactive immune systems. **TEXT** ASTRID SMIT **ILLUSTRATIONS** MAARTJE KUNEN AND WAGENINGEN UR, JENNY VAN DRIEL

'It started when Marijn was about two', says Jiska Beelen about her son, who is now eight. 'At a particular time of year, somewhere in spring, he would start to scratch his face open, especially round his eyes. "Perhaps it's hay fever", a neighbour suggested. Our doctor thought that was unlikely. "Hay fever is most unusual in children under four", was his reaction. But it turned out that Marijn did have hay fever. Since then every spring – when the birch, poplars and grasses bloom – we go through the same thing. In May and June this year, when the weather was gorgeous, the hay fever was really bad. We had to sit inside with the doors and windows closed for days.' Marijn is not the only one. About 25 to 30 percent of the Dutch population is allergic to substances in the air or in food, says Harry Wichers, professor of Immunomodulation at Wageningen UR Food and Biobased Research. 'That's two to three times as many as fifty years ago.' The number of people with respiratory allergies, such as hay fever and asthma – the most common allergies – has risen in particular. And the sufferers are getting younger. Twenty to thirty years ago hay fever did not affect children until they reached 15. Now four-year-olds are affected, and in exceptional cases younger children too, like Marijn.

TOO CLEAN

Many factors are believed to be the cause. The most dominant seems to be the vastly improved levels of hygiene, Wichers thinks. Towards the end of the 1980s, the British scientist David Stachan introduced the idea that our lives are too clean. As a result, children are not exposed enough to fungi, bacteria, worms and parasites, so their developing immune system doesn't get a chance to toughen up. If it then encounters an alien substance in food or in the air, the immune system can go into overdrive. Jean-François Bach, a French scientist, suggests that it's also related to the intensive vaccination programmes in most western European countries, and the increasing use of antibiotics. He points to a graph which shows how the decline in infectious diseases such as measles, mumps and tuberculosis between the 1960s and 1980s was accompanied by an increase in asthma and auto-immune diseases – where the body turns against its own immune system – such as diabetes 1, Crohn's disease and multiple sclerosis.

But climate change (more pollen in the air as temperatures have risen), increased air pollution, changing infant nutrition (less breastfeeding, delayed introduction of solid food), the increase in the number of >

caesarean births (the birth canal is full of microbes), changing diets (more ready meals, more spicy and exotic food), lack of exercise and increased stress (which weakens the immune system) are all in the dock too.

NOT ENOUGH STUDIES

So there are plenty of suspects and many correlations, but scientists are still unable to pinpoint the culprits. The Netherlands Institute for Public Health and the Environment made a detailed survey of the literature on food allergies last year and was able to draw one clear conclusion: it is not at all certain which factors lead to an increased risk of food allergy. There are too few reliable studies and many of them contradict each other. When it comes to respiratory allergies you can draw the same conclusion, Wichers believes. 'We really don't know what causes them. We have our suspicions though, and that's why there's so much research being done.'

Nine institutes at Wageningen UR, united in the Allergy Consortium Wageningen, are engaged in allergy research. Their activities include helping allergy sufferers to avoid allergens, trying to make certain foods less allergenic, and searching for faster and better tests and diagnostic tools. In addition, they are trying to find out how an overactive immune system can be brought under control. These efforts have already led to some useful results.

Together with Leiden University Medical Center, the Environmental Systems Analysis Group at Wageningen University, part of Wageningen UR, developed the *AllergieRadar* for hay fever sufferers. This website is rather like the weather radar sites that show where rain is due, but instead of indicating rainfall it shows which pollens are prevalent, in what quantities, and how long they are likely to remain a problem. This gives hay fever sufferers a better idea of what they can expect.

Plant Research International, another part of Wageningen UR, has bred two apple varieties – Elise and Santana – for people who are mildly allergic to apples. The Food Process Engineering Group has developed wheat bread that people with gluten intolerance will be able to eat in the future. The gluten has been replaced by milk protein globules, which gives the bread a similar structure to that of ordinary bread. In addition, RIKILT (part of Wageningen UR) designed a test for rapid detection of twelve different allergens – in nuts, eggs and milk. This makes it much quicker and easier to check foods such as biscuits and chocolate for allergens.

Working on restoring equilibrium in an overactive immune system – immunomodulation – requires more long-term work. Nevertheless, Wichers, who heads this project together with Huub Savelkoul, the head of the Cell Biology and Immunology Group at Wageningen University, is optimistic that products will be developed that will benefit allergy sufferers. 'We think we're going to be able to readjust the immune system in the right direction, so that people react less strongly to allergens and hopefully even overcome their allergies.'

SEESAW

Wichers reaches for a piece of paper and draws part of the immune system. It resembles a seesaw, with Th1 cells on one side and Th2 cells on the other. In a mature system, these immune cells – which keep the unwelcome intruders out through a complex system – are supposed to be in equilibrium, Wichers explains. A baby, however, has more Th2 cells than Th1 cells, so the seesaw tips towards the Th2 side. If a young child catches enough infections from all sorts of different pathogens, more Th1 cells are produced, the seesaw achieves balance and the immune system reacts in the right way to intruders in the future.

'If a child is not exposed to enough infections, the immune system will continue to tip to the Th2 cell side and the risk of developing allergies is greater, we think', says Wichers. 'The Th2 cells are overactive and therefore they also attack the wrong – innocent – intruders.'

The solution is to restore balance to the seesaw, Wichers says: 'But not by exposing people to infections they didn't have as children. Hygiene is a good thing, and has helped us come a long way. No, we are planning on re-educating the immune system through a controlled use of dirt'. 'We think we can do this by using parts of fungi and other microbes, and also using bacteria such as *Lactobacillus* and *Bifidobacterium*, both of which are used in probiotic drinks.'

A number of studies indicate that these microbial components or bacteria have favourable effects on allergies. A Japanese study has shown that people who are allergic to cedar pollen obtain relief from certain microbial sugars; a Chinese study has demonstrated that fungal proteins help reduce dust mite allergy in mice. And a Finnish study has proved that the incidence of eczema is reduced by half in children that are given probiotics in their bottle-feed and whose mothers had also been given probiotics two weeks before giving >

'We really don't know what causes allergies'

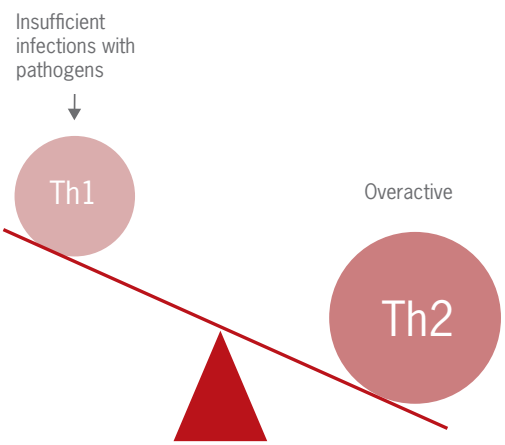
ALLERGY

Overactive

An allergic reaction is an excessive response by the immune system to harmless substances in the environment, such as pollen in the air or proteins in bread. After the initial contact with the substance the body starts making antibodies. After repeated contact the allergic reaction kicks in: the minute these substances, now called allergens, enter the body of an allergic person, antibodies spring into action and bring the 'intruder' into contact with 'mast cells'. These then produce substances such as histamines to eliminate the intruder. It is the histamines that cause the allergic reactions: a runny nose, puffy eyes, diarrhoea, vomiting or eczema.

Immune system

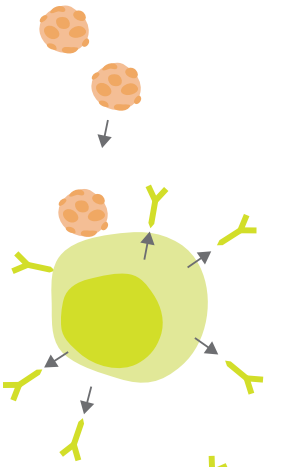
In a mature immune system the immune cells Th1 and Th2 are in balance. In babies there are more Th2 cells than Th1 cells. As the child is exposed to enough infections with everyday pathogens, the Th1 cells multiply and bring the system in balance. However, if there is not enough exposure to infections, the immune system remains dominated by Th2 cells. These cells are overactive and prone to attacking the wrong – harmless – intruders.



Allergic reaction type I

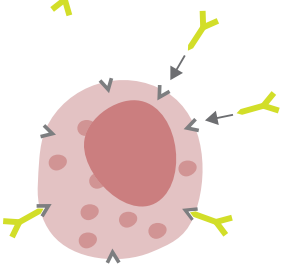
1

At the first contact with 'intruders', plasma cells make antibodies



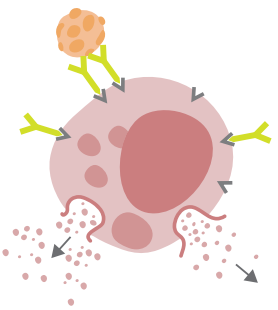
2

The antibodies attach themselves to mast cells



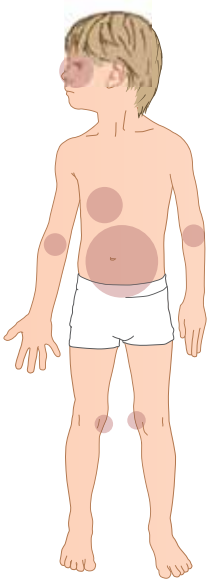
3

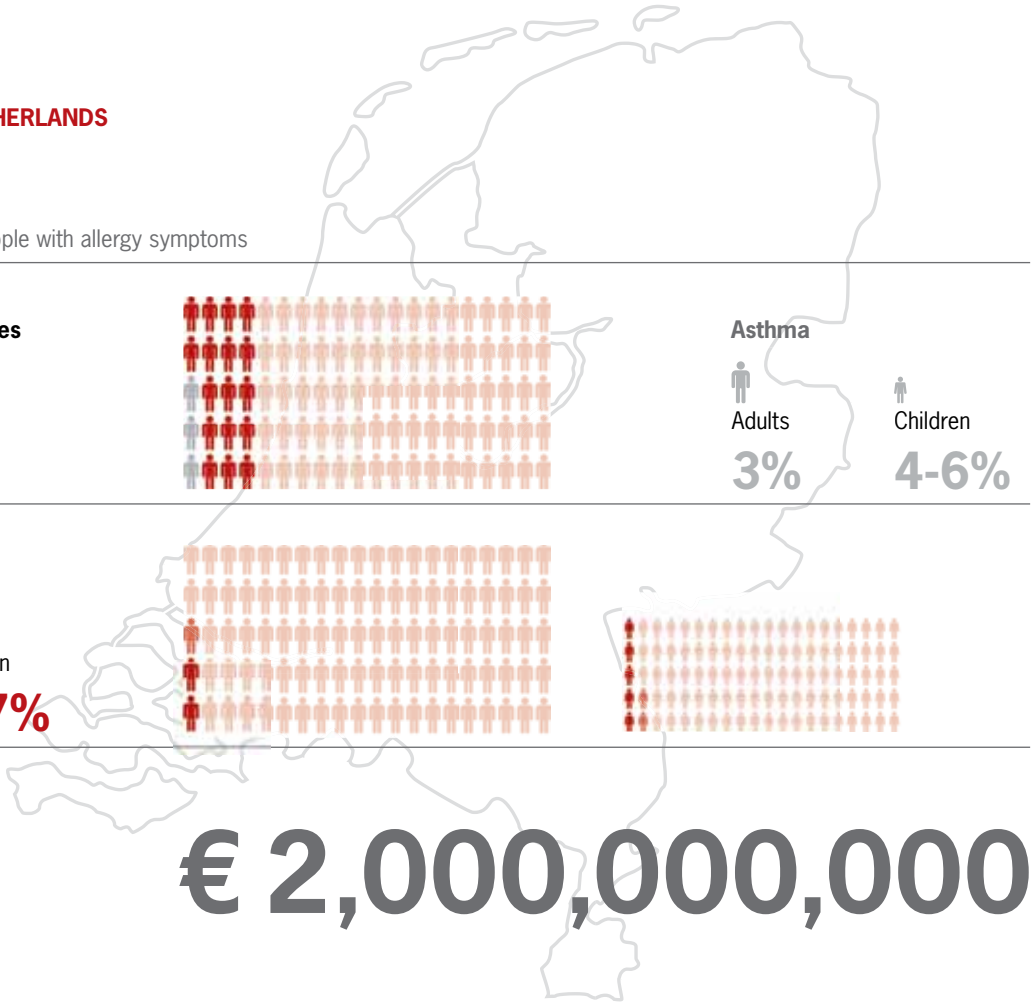
When the next contact with 'intruders' takes place, they attach themselves to the mast cells via the antibodies. The mast cells release their contents – histamines and other hormones – onto the intruders



4

The released histamines and other hormones cause allergic reactions





birth, compared with a group given a placebo. The problem is that there have been negative as well as positive results. Probiotics in particular – which have been the subject of much research – are yielding a diffuse and unclear picture. At the start of June this year, Yvonne Vissers, who is doing PhD research under Wichers and Savelkoul, announced that she had obtained positive results with probiotics. One strain of *Lactobacillus* is suitable for reducing markers, substances that indicate hay fever, Vissers wrote in her dissertation. But this conclusion – which had been formulated in a press release as: Probiotics can help wipe out allergies – came under heavy fire from Hans van Maanen, a columnist in the national newspaper *de Volkskrant*. Van Maanen believes that the groups of test subjects in Vissers' research were too disparate to warrant the conclusions she drew. But Wichers argues that Visser's conclusion is much more nuanced. Moreover, the results have been published in peer-reviewed scientific journals and seven experts approved her dissertation.

The effect of probiotics on allergies is not only a source of controversy between journalists and the scientific community, but among academics themselves too.

Wichers: 'I think that in future we have to select the bacteria strains we use more carefully. Five years ago we thought that all strains were pretty much the same, but we now know this is not the case. In my opinion, this explains the contradictory results.'

Wichers is convinced the future lies in immunomodulation. 'But we still have a long way to go.' If immunomodulation does turn out to work, this form of therapy has one big advantage. 'It's likely to be effective against a broad spectrum of allergens because you intervene at a very fundamental level in the immune system. And that's good news for patients, because they usually react to more than one allergen.' The disadvantage for allergy sufferers – and the advantage for manufacturers – is that they may well have to take immunomodulators for the rest of their lives. The minute they stop, the immune system's seesaw will tip out of balance again.

TRICKY BREEDING

Wichers reckons that immunomodulation has more to offer than technological solu-

CROSS-ALLERGIES

If allergic to:		Risk of an allergic reaction to at least one of the following:				Risk (%)
A pulse	Peanut	Other pulses	Peas	Lentils	Beans	5%
A nut	Walnut	Other nuts	Brazil nut	Cashew	Hazelnut	37%
A fish	Salmon	Other fish	Swordfish	Sole		50%
A shellfish	Shrimp	Other shellfish	Crab	Lobster		75%
A grain	Wheat	Other grains	Barley	Rye		20%
Cow's milk		Goat's milk	Goat			92%
Cow's milk		Horse's milk	Horse			4%
Pollen	Birch, ambrosia	Fruit, vegetables	Apple	Peach	Melon	55%
Latex	Latex gloves	Fruit	kiwi	Banana	Avocado	35%

Sources: National Public Health Compass of the RIVM, Health Council, Allergy Consortium Wageningen

> **'We want to re-educate the immune system through a controlled use of dirt'**

tions such as breeding new varieties of allergenic food crops. 'Apples are really the only product that is easy to breed, because they only contain one allergen, and the allergy is a mild one that is not life threatening. Most other foods that humans are allergic to contain a set of allergens. That makes breeding tricky. Other methods of getting rid of allergens such as heating are not effective. Most allergens are impossible to destroy.'

Margreet van Putten, who obtained her PhD last year in the Marketing and Consumer Behaviour Group at Wageningen University, part of Wageningen UR, agrees that eliminating allergens from foods is unlikely to work, but for a different reason: allergy sufferers are extremely cautious. They are not prepared to risk trying a product that may contain minuscule traces of allergens, and therefore tend to avoid new products like this. Only people with mild allergies are likely to benefit from these.

For the time being, Marijn's parents resort to a homeopathic remedy. 'We manage to keep his hay fever under control with this, which helps us to get through the season without too much trouble', says his mother. 'But we'd welcome other solutions.' She looks outside. 'We live opposite a park with lots of birch trees.

I can imagine that at times some hay fever sufferers feel like taking an axe to the trees or would like to move house. It's really hard going sometimes.' ■