

Short communication

La mano de DIOS...was the PIAMA intervention study intervened upon?

The PIAMA study evaluates whether application of mite impermeable mattress covers reduces exposure to mite allergen sufficiently to reduce the incidence of asthma and mite allergy. The study started in 1996. Baseline measurements of mite allergen levels were conducted on mattresses of newborn children and their parents, mostly in 1997. Mite allergen levels were surprisingly low in this study compared with previous studies among school children and infants. Mite allergen levels were measured again on mattresses in the PIAMA study in the years 2000/2001 when the children were 4 years old, and in a new study among 6–12 year old school children conducted in the fall of 2001. Data on winter climate were collected as well. In the winters of 1995/1996 and 1996/1997, which preceded and coincided with the PIAMA baseline measurements, temperatures had been extremely low, and precipitation had been extremely low as well. It is likely that these unusual winter weather conditions affected the baseline allergen levels in the PIAMA study so that the effect of the planned intervention (mite impermeable mattress covers) was considerably smaller than it could have been.

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When the famous Argentine soccer player Diego Maradona scored a goal by hand in a world cup match against England in 1986, he said afterward that it was the 'hand of god' that produced the goal. This story is about how divine interventions sometimes wreak havoc to a carefully planned epidemiologic study.

Over 10 years ago, we designed an intervention study to test whether allergen avoidance might help to reduce the incidence of asthma. There were almost no studies at the time to evaluate mite-allergen reduction as a tool to *prevent* asthma from developing in young children. A 'birth month' effect had been described showing increased pollen sensitization in children born just before the pollen season, and increased mite sensitization in children just before the peak mite season (1, 2). So, reduction of exposure especially during that period could be an important preventive strategy. We knew that dust mites depend on sufficiently high indoor air humidity levels, and that the cold winter weather in mountain areas, land climates and high latitude regions is so

effective in killing mites that mite allergen exposures in these regions are very low (3–7). The reason is that cold air can contain only very little water, and then relative humidity becomes very low when the outside air is heated in homes to room temperature. The 'Isle of Wight' study had just produced its first encouraging results (8), based on a multifaceted intervention programme that was especially heavy on the dietary side. We decided to design a classic randomized, placebo controlled intervention trial that could reasonably be blinded to study subjects and data collectors (9). The decision was to put mite impermeable covers on mattresses of the baby beds, and on the mattresses and pillows of the parental beds. Cotton placebo covers were used in the control group, and we included a second reference group, receiving no covers, to evaluate potential placebo effects. Furthermore, we included a large group of neonates of non-allergic mothers, without intervention, to be able to study the natural history of asthma and other childhood allergic diseases. The study is known as the Prevention and

Incidence of Asthma and Mite Allergy (PIAMA) study. This paper focuses on the mite allergen levels that were found in the PIAMA study, in relation to levels that were found in previously published studies, in a new study, and in relation to climate data.

Methods

Our studies of the early 1990s have been described before (6, 10). In 1990, about 500, 6–12-year-old school children participated in a case–control study on the relationship between allergen exposure and asthma. There was not much difference in mite allergen exposure between cases and controls, so that the subject selection has not influenced mean mite allergen levels found in this study. In 1993, we studied 103, 3–15 months old children selected for having an allergic or nonallergic mother. In this study, infants of allergic mothers had twice lower mite allergen levels in mattress dust, so that the study probably somewhat underestimated allergen levels that would have been found in a random sample.

The PIAMA study started data collection in the summer of 1996. When the children were 3-months old, dust samples were taken in the homes of the ‘intervention’ group, and in a random sample of homes of the ‘natural history’ study. This sampling period extended from the late fall of 1996 to the early spring of 1998. Samples were taken again at age 4. Methods of sampling and analysis, and results of the study up to age 1 have been published (11, 12). In all arms of the study, mite allergen levels were much lower than in our earlier studies (6, 10). Seasonal effects can account for only a small fraction of the difference as within the PIAMA study, Der p1 levels were only about 20% higher in the fall than in the rest of the year (12). We now report on data that were collected at age 4, and data that were collected in another study conducted in the fall of 2001 in a population of school-age children that was comparable with populations we studied before.

PIAMA study at age 4

Home visits took place between the summers of 2000 and the late fall of 2001. For the purpose of this paper, we focus on children participating in the ‘Natural History’ part, who received no mattress covers. Useable data were obtained from 315 homes.

School children's study in 2001

In the fall of 2001, a stratified random sample of school children (age 6–12 years) was investigated with the purpose to compare mite allergen levels to those in previous studies. Participants were recruited from schools in communities in Gelderland, which was also included in our 1990 study. A total of 100 participants were selected: 48 ‘cases’ with chronic respiratory symptoms, and 52 ‘controls’ without. Dust samples were taken from living room floors, child mattress, and child bedroom floor. Samples were extracted and analysed as described before.

Comparison of Der p1 immunoassays

In 1990 and 1993, we used the no longer available EIA of ALK, whereas in the PIAMA study and the 2001 school children study EIA assays of Indoor Biotechnologies were applied. To assess comparability, duplicate aliquots of 20 house dust samples covering a wide range of *Der p1* levels of the 1990 study were analysed for *Der p1* using the Indoor Biotechnologies EIA. Extracts had been stored frozen at –20 °C.

Climate data

Daily temperature and precipitation data were obtained for the years 1988–2001 from the Royal National Meteorology Institute (<http://www.knmi.nl>). For the purpose of this paper, monthly mean temperature and precipitation were calculated for the December and January months of each winter.

Comparison of results

This analysis focuses on samples taken in the ‘Natural History’ part of the PIAMA study where no intervention took place. It is also restricted to Der p1, as Der f1 was not measured in our previous studies. Furthermore, the analysis compares results expressed in ng/g in order to make the comparison independent of possible differences in amounts of dust collected in the different studies.

Results

Table 1 and Fig. 1 show that that the baseline measurements in the PIAMA study (1997) were very low, on both the mattresses of the infants and the mattresses of the parents. Levels in 1993 (infants) were lower than in 1990 (school children), which may be related to age of the mattresses that were sampled, as this factor was shown to be related to mite allergen levels in both studies.

Table 1. Geometric mean Der p1 concentrations per gram mattress dust collected in different surveys in the Netherlands, 1990–2001

Year	Population	Number of homes	Der p1/g geometric mean	GSD
1990	6–12 year old	512	5075	4.0
1993	3–15 month old	103	2373	5.8
1997	3-month old PIAMA	928	586	2.9
1997	Parents of PIAMA	1009	687	5.8
2001	4-year old PIAMA	355	1495	4.0
2001	6–12 year old	100	2598	5.1

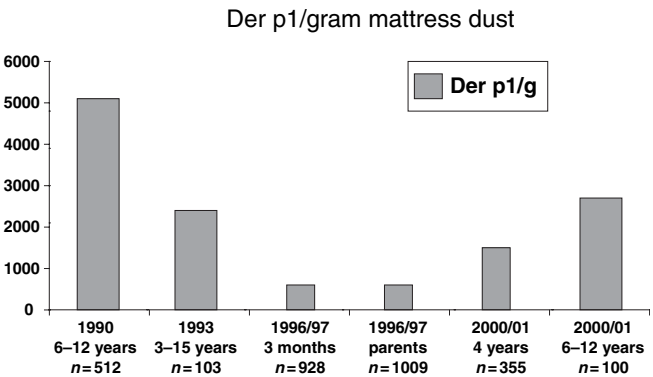


Figure 1. Geometric mean Der p1 levels per gram of dust collected from children's and parental mattresses in the Netherlands, 1990–2001.

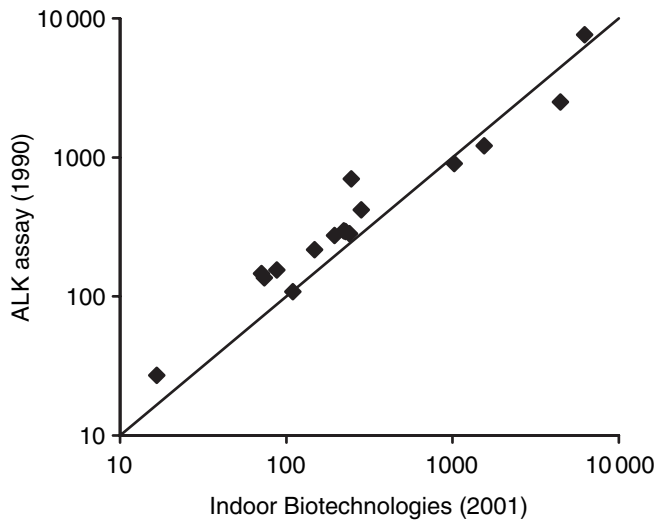


Figure 2. Der p1 concentration (ng/ml extraction solution) determined with the Indoor Biotechnologies assay vs the ALK assay. The Pearson correlation coefficient is 0.9.

Figure 2 shows that results obtained with the two assays were highly comparable. Figs 3 and 4 show that temperatures and precipitation in the winters of 1995/1996 and 1996/1997 (preceding and coinciding with the PIAMA baseline measurements) were very low compared with the preceding and following years.

Discussion

Few investigators have systematically addressed changes in mite allergen concentrations over extended periods of time. A study from the UK (13) investigated mite allergen in the homes of 59 1–2-year-old children from October 1979 to March 1980, and then again in the homes of 65 children, then 11-years old, from February to April 1989. Geometric mean mattress Der p1 levels were 18 400 ng/g in the first study, and 10 600 ng/g in the second. Levels in living room and bedroom floor dust were not different between periods. In a study among adults in Germany, mattress samples were collected in the same homes from

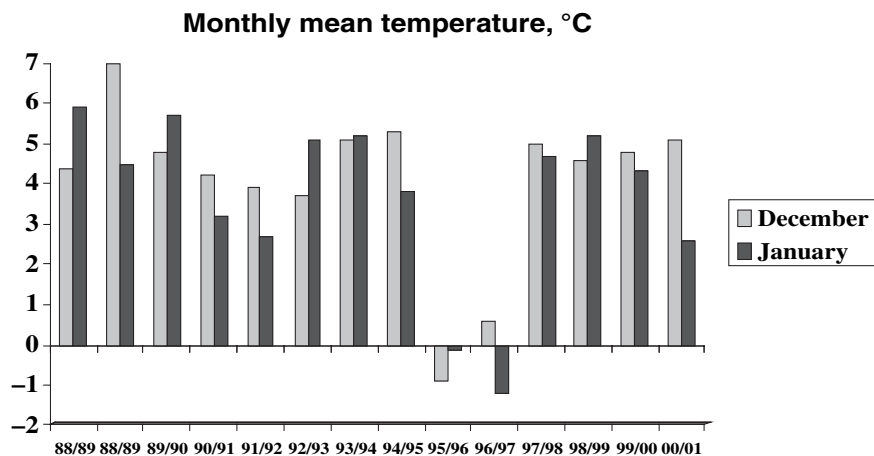


Figure 3. Mean monthly temperatures in the December and January months of the winters of 1988/1989–2000/2001 in the Netherlands (station De Bilt).

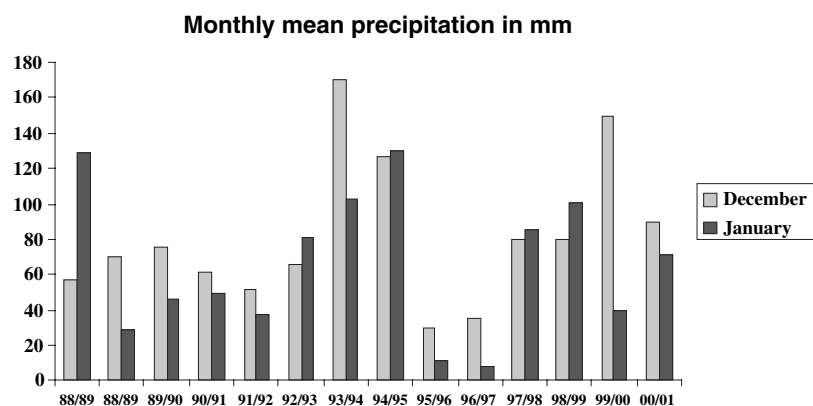


Figure 4. Mean monthly precipitation in the December and January months of the winters of 1988/1989–2000/2001 in the Netherlands (station De Bilt).

June 1995 to October 1996 (14). Sampling areas were relatively close to the Netherlands. In a companion paper, we show that Der p1 levels decreased in by a factor of about 2 after the first cold winter, and then again by a factor of about 2 after the second cold winter (15).

Our study groups were not completely comparable in age, selection or location. Nevertheless, previous work from the Netherlands and other countries has shown that it is difficult to identify strong determinants of mite allergen levels in mattresses, which can change levels by an order of magnitude (6, 12). By focusing our analysis on the PIAMA families from the 'Natural History' part of the study, potential bias introduced by effects of the intervention were avoided. In our earlier study among infants, we found that children of nonatopic parents had higher geometric mean Der p1 in mattress dust than children with an atopic mother (3331 vs 1610 ng/g)

(610 ng/g.). This could be a result of selective avoidance measures taken by atopic parents. However, when comparing these groups in the PIAMA study at baseline, we found that there was no difference for the children in these two categories or for the parental mattresses (12). Therefore, we propose that the large differences observed between the results of surveys in the Netherlands can be explained by the abnormal climatic conditions in the winters of 1995/1996 and 1996/1997.

So, was it 'La Mano de Dios' that manipulated the climatic conditions purposely during the crucial phase of our study? Or did we witness an experiment of nature that caused a most effective large-scale house dust mite allergen exposure reduction – and could this experiment of nature be further explored to find out what its effect has been on the health of children born in this very period?

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