

## Leading articles

# MMR vaccine and allergy

Live measles and mumps vaccine viruses are cultured in chick embryo fibroblasts and may contain minute amounts of egg related antigens.<sup>1-3</sup> In view of this, there has been a longstanding debate on the safety of these vaccines in children with severe allergic reactions to egg. Initially it was believed that such children could safely receive the vaccine; Kamin *et al* in 1965<sup>4</sup> reported the safe administration of measles vaccine to 22 children with egg allergy confirmed by food challenges.

The concern was again raised in 1983 by Herman *et al* when they reported two children with allergy to egg white protein who had generalised urticaria, angio-oedema, and respiratory difficulty following immunisation with measles vaccine.<sup>3</sup> Serum IgE reactive with ovalbumin related antigens in the vaccine was demonstrated in both children. They also showed the presence of ovalbumin reacting protein in the vaccine.

They subsequently evaluated 24 children with egg allergy using skin prick testing with ovalbumin and measles vaccine. They found that children with severe reactions to egg were more likely to have a positive skin reaction on testing with the vaccine, and those who had a positive skin test had IgE antibodies reacting to ovalbumin. Non-allergic children had negative skin tests. From this they recommended that patients with severe reactions to egg white should be skin tested with dilute vaccine, first by scratch test and, if this is negative, by intradermal injection. If both were negative, the vaccine could be given as a single dose of 0.5 ml. If either were positive, they recommended that the vaccine be administered in slowly increasing increments of 0.05 ml, every 15 to 20 minutes. The 1991 *Red Book* published by the American Academy of Pediatrics recommended a similar policy for children with severe reactions to egg.

However further evidence suggesting that children allergic to eggs were at no greater risk continued to accumulate.<sup>4A-D</sup> By 1995, of 40 reported cases of anaphylaxis to measles/mumps/rubella (MMR) vaccine given as a single dose, only two involved children with egg allergy (the same two reported by Herman).<sup>1 3 5-10</sup> A review of 17 studies from 1963 to 1995 showed only (the same) two of 1227 patients who were allergic to eggs and had been given the vaccine had developed any symptoms suggestive of anaphylaxis<sup>11</sup>; this included many children with convincing history of severe allergic reactions to egg. Children with or without egg allergy could have positive skin tests using the vaccine and still be safely immunised.<sup>1 12-15</sup> Aicken *et al* carried out skin prick testing on 410 children allergic to eggs with the vaccine and subsequently vaccinated them with a standard single dose.<sup>12</sup> Five children had a positive skin prick test, none of whom developed a reaction following vaccination. Four children had a minor reaction to the vaccine, all of whom had negative skin tests. On the other hand, Baxter found that a positive skin prick test with the vaccine might increase the chance of a systemic reaction.<sup>16</sup> They performed a skin prick test followed by an intradermal test in 150 children allergic to eggs. Of these, 145 had negative skin prick and intradermal tests, and were given the vaccine without any significant immediate reactions. Of the five with positive skin tests, four had negative intradermal tests and were vaccinated safely. The fifth child devel-

### Key messages

- Anaphylaxis is an extremely rare but potentially fatal complication after any vaccination
- It is difficult to predict which children are likely to have a severe allergic reaction
- Many of the allergic reactions that occur after administration of gelatin containing vaccines in Japan appear to be due to IgE mediated or cell mediated immune responses to gelatin
- MMR vaccine is not advised in children with known severe systemic allergic reactions to gelatin or neomycin
- Children allergic to eggs (including those who have had anaphylactic reactions to egg) do not appear to be at greater risk for anaphylaxis to MMR vaccine than other children
- All vaccination must be carried out in settings with equipment to deal with anaphylaxis and by personnel trained in its recognition and management. Assuming these criteria are met, vaccinations do not have to take place in the presence of a doctor or on medical premises

oped a 15 mm local reaction and a systemic reaction including urticaria, irritability, and hypotension within 10 minutes of the intradermal test. Approximately half the patients who had an anaphylactic reaction to the vaccine (almost all of whom had no history of allergy to egg) when tested subsequently had positive skin tests.<sup>1 5 7 10 17</sup> This suggests that while it is not useful to skin prick test children with egg allergy and it would be impractical to skin prick test all children, a positive skin test may to some extent predict allergy to some component of the vaccine and may increase the risk of an allergic reaction.

Based on such evidence, the 1997 *Red Book* did not recommend skin testing in children allergic to eggs.<sup>18</sup> The Department of Health's *Green Book*,<sup>19</sup> while being generally reassuring, ends by saying that if there are any concerns, paediatric advice should be sought with a view to providing immunisation under controlled conditions in hospital. The product leaflet for MMR vaccine continues to prohibit vaccination of children who have history of anaphylactic, anaphylactoid or immediate reactions to eating eggs. Children with egg allergy are regularly referred for specialist advice and day case admission into hospital for MMR immunisation in our centre and, we believe, in most others—a significant use of time and resources.

Kelso *et al* in 1993 first suggested that some anaphylactic reactions to MMR may be the result of an allergic reaction to gelatin.<sup>10</sup> Hydrolysed gelatin, obtained from animal collagen, is used as a stabiliser in various vaccines including MMR, varicella, and diphtheria, tetanus, acellular pertussis (DTaP). Much of the recent work on gelatin allergy has come from Japan where there has been a recent increase in allergic reactions to MMR vaccine.<sup>20</sup> From 1994 to 1997 there were 366 reported cases of allergy to MMR vaccine in Japan, and 34 of these were anaphylactic reactions; from

1989 to 1993 there were no reports of anaphylactic reactions to the vaccine. Before 1993, the immunisation schedule in Japan consisted of a trivalent MMR vaccine followed by a series of DTaP vaccines. From 1994 onwards, this was changed to a series of DTaP followed by MMR vaccines given separately (monovalent MMR vaccines). Both monovalent and trivalent MMR preparations contain gelatin; however, not all DTaP contains gelatin. Among the subjects with adverse reactions, almost all (98%) had received the gelatin containing DTaP before the MMR. Nakayama *et al* used this data to postulate that prior injection with gelatin containing DTaP had sensitised the children to subsequent reactions to MMR vaccine.<sup>20</sup>

There is good immunological evidence suggesting that both immediate and delayed-type hypersensitivity reactions to vaccines containing gelatin result from gelatin allergy.<sup>21-23</sup> Sakaguchi *et al* found that 24 of 26 patients with immediate reactions to MMR vaccine had IgE antibody to gelatin.<sup>24</sup> In contrast, this antibody was not found in any of 26 age and sex matched controls who had not reacted to the vaccine. Kumagai *et al* showed that while patients with non-immediate reactions did not show IgE antibody to gelatin, many of them did show a cell mediated immune response to gelatin.<sup>25</sup> Administering gelatin to a sensitised individual by injection would pose the greatest risk for anaphylaxis.<sup>21</sup> Because gelatin used as a vaccine stabiliser may be of porcine origin whereas gelatin ingested in food may be of bovine origin, the absence of history of allergy to foods containing gelatin does not eliminate the possibility of a gelatin mediated reaction to vaccine.<sup>26</sup> Skin testing with the MMR vaccine of people with a history of systemic anaphylactic reactions following gelatin ingestion may be useful to identify those at risk for similar reactions to the vaccine; however, protocols for such testing or desensitisation have not been published.<sup>26-27</sup>

The only gelatin containing vaccine in use in UK is the MMR vaccine\*. Drug analysis prints (DAPs) produced by the Committee on Safety of Medicines/Medicines Control Agency (CSM/MCA) list all spontaneously reported reactions on the adverse drug reactions online information tracking database (ADROIT). The DAP for MMR vaccine states that eight cases of angio-oedema and 55 cases of anaphylaxis or anaphylactoid reactions have been received by the CSM/MCA in the period July 1963 to July 1999. No fatalities have been reported associated with allergic reactions. While this cannot be used to estimate the incidence of allergic reactions to the vaccine, there is no recent increase in the number of cases reported. Thus, unlike in Japan, allergy to the MMR vaccine does not seem to be an increasing problem in the UK.

MMR vaccine contains about 25 µg of neomycin sulfate. Contact hypersensitivity and systemic allergic reactions to neomycin are well known.<sup>28</sup> Kwittken *et al* reported the case of a 7 year old boy who developed anaphylactoid reaction after being given a 0.05 ml dose of the vaccine subcutaneously as part of a desensitisation protocol.<sup>29</sup> The child had a convincing history of contact hypersensitivity (but not systemic reaction) to neomycin in the past; however, no specific tests for neomycin sensitivity were done. Elliman and Dhanraj suggested that contact sensitivity to neomycin was not a contraindication to MMR vaccine.<sup>30</sup> They reported the case of a 3 year old girl who had developed swelling and erythema to ear drops containing neomycin and had subsequently been given the MMR vaccine as a 0.5 ml single intramuscular dose with no adverse effects. However, there is general agreement that children who

have had anaphylactic reactions to topical or systemic administration of neomycin should not be vaccinated.<sup>26</sup> While prevaccination screening should include a question about allergy to the vaccine, gelatin or neomycin, there will remain a small risk of severe allergic reaction in any child. Children with egg allergy do not appear to be at a greater risk than the general population.

In conclusion, anaphylaxis is a rare but potentially life threatening allergic complication of vaccination that must be anticipated in any vaccine recipient. All personnel involved in vaccinating children must be fully aware of this possibility and trained in its emergency management. Most severe reactions occur within a few minutes after the injection and it is extremely unlikely that a child who appears completely well 30 minutes after the vaccination will subsequently develop a severe reaction. Ideally children should be observed in a place equipped to deal with an anaphylactic reaction for at least this time period following vaccination. Any reports of reactions must be fully documented. Severe or unusual reactions must be reported to the CSM by the "yellow card system"; and if possible investigated by IgE RAST and/or skin tests to determine which component of the vaccine was responsible for the allergy.

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\*Information published by the Department of Health on 2 December 1999 indicates that diphtheria tetanus acellular pertussis combined vaccines will shortly be introduced into the UK primary schedule. It may prove that some of these vaccines contain gelatin.

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## Public health

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# Sustainable development, human induced global climate change, and the health of children

In this short article we introduce the concept of sustainable development and its significance to child health using climate change as an example. Environmental issues, in the long term, are as important to children's health as smoking, accidents, and poor parenting are in the short term, yet have hitherto had little publicity or discussion within paediatric circles.

What is happening to children's health in the world? In the developed world cardiovascular disease, diabetes, cancer, and dental disease are all on the increase, while in the developing world malnutrition, infectious disease, and injuries are still rife. At present, inequalities of health and wealth—both within and between nations—appear to be increasing,<sup>1</sup> with an adverse impact on children's health. The Ottawa charter for health promotion states that the fundamental conditions for health are peace, shelter, education, food, income, a stable ecosystem, sustainable resources, social justice, and equity.<sup>2</sup> The evidence for the connections among the environment, the economy, and social change are compelling and any change within one inevitably affects the others.

### Climate change

For the first time in history, the economic activity of the human population has become so vast that it is beginning to change the gaseous composition of the lower and middle atmospheres. This is now called human induced global climate change (HIGCC), which in turn will have a significant impact on a future generation of children. There seems no doubt that climate change is a genuine phenomenon.<sup>3</sup> The main cause of climate change is the greenhouse effect, which is related to the massive increase in use of fossil fuels with consequent liberation of CO<sub>2</sub> into the atmosphere. Before man started burning oil and coal and gas, the atmosphere contained about 280 parts CO<sub>2</sub> per million—now the figure is about 360 ppm. Methane concentrations are now more than double what they were in the pre-industrial age. Nine of the 10 hottest years on record have occurred since 1993.<sup>4</sup> Global average surface temperatures have increased by 0.3–0.6°C since the late 19th century.<sup>5</sup> This is a statistically significant trend, which, if it continues, will lead to a rise in temperature

between 3–5°C by the year 2100; this is now accepted by most of the international scientific community, which has concluded that an anthropogenic influence on the global climate is discernible.<sup>6</sup> This increase contrasts with a global temperature increase since the last ice age (10 000 years ago) of about 5°C.<sup>5</sup> Human beings have further interfered with the equilibrium by destroying large areas of vegetation, mainly forest, which acts as a carbon sink by trapping carbon dioxide in plant carbohydrates.<sup>7</sup>

### EFFECT OF CLIMATE ON HUMAN HEALTH

Extremes of temperature affect people directly, leading to excess mortality in both hot and cold spells. Eventually the indirect effects of greater warmth: increased vector borne disease—estimates of 60% of the world population being exposed to malaria by the latter half of this century<sup>8</sup>—increased natural disasters,<sup>9</sup> rising sea level<sup>10</sup> (and population displacement), and increased pollution, will have a far larger impact on health than the direct effects.

### FOOD PRODUCTION AND NUTRITION

Worldwide, total production of food is likely to remain constant but the production of food is likely to favour the higher latitudes with developing countries around the equator suffering most. Many communities that rely on traditional agriculture may lack the resources and adaptability to switch to alternative crops and production methods. One study has forecast the additional number of hungry people attributable to climate change by the year 2060 to be between 40 and 300 million.<sup>11</sup> Children would be the group most severely affected by food shortages.

### SEA LEVEL

A projected increase of 0.2–1.0 m by 2100 is the current best estimate of sea level change.<sup>10</sup> This is two or three times greater than the change in the last century. Over half the world's population lives within 60 km of the sea. Delta areas are most likely to be affected many of which are densely populated. At today's population level an increase of 0.5 m would approximately double the number of people who suffer flooding annually—currently around 46 million. The rise in sea level would be compounded by

extreme weather events, particularly floods and storms in coastal areas.

#### INFECTIOUS DISEASES

All vector borne diseases are predicted to increase as a result of warming and changed rainfall. It is estimated that the current 45% of the world's population who live in zones of potential malaria transmission would increase to around 60% in the next 100 years.<sup>12</sup> Children are particularly susceptible to malaria.

#### SPECIFIC IMPACT ON CHILD HEALTH

The health impacts of environmental change will affect all age groups but children are among the most vulnerable to these effects. Some of these are noticeable now, namely the postulated effects of motor vehicle pollution in contributing to asthma and respiratory problems,<sup>13 14</sup> the effect of lead poisoning on neurological development, the effects of ozone depletion on skin cancer, and the indirect effect of the growth of road traffic on patterns of children's exercise,<sup>15</sup> prevalence of obesity, and pedestrian injury rates.

#### Sustainable development

The concept of sustainable development was first discussed by the World Commission on Environment and Development in its report *Our common future* in 1987.<sup>16</sup> Their definition was "...development that fulfils the needs of the present generation without endangering the needs of future generations". In essence it stipulates that no environmental burdens, such as the build up of greenhouse gases, pollution of seas and rivers, unmanageable amounts of waste, and loss of natural habitats, should be inherited by future generations—thus establishing the principle of intergenerational equity. A useful concept is the "ecological footprint": the surface area required to feed and absorb the waste of a person, group or city. The footprint of London equals the UK's entire area of productive land, around 125 times London's surface area, a total of 19.7 million hectares. European citizens average a footprint of three hectares each, North Americans require between four and five, yet worldwide only one and a half hectares of productive land is available per person.<sup>17</sup> At the United Nations Earth Summit in Rio de Janeiro in 1992, over 150 countries signed up to a global action plan for the 21st century—*Agenda 21*. They announced the Rio Declaration of Environment and Development,<sup>18</sup> the first principle of which states that "...human beings are at the centre of concerns for sustainable development. They are entitled to a healthy and productive life in harmony with nature". Sustainable development attempts to improve the quality of human life, while living within the carrying capacity of supporting ecosystems. The objectives of sustainable development are to ensure the quality of life both for people now and for generations to come. In this sense it is rooted in responsibility and justice for others—can we accept that the developed nations currently use 50 times more energy per person than the developing nations; that the 57.5 million people added to the northern hemisphere population during this decade will add more greenhouse gases to the atmosphere than the roughly 900 million added to the southern hemisphere; that global warming is likely to lead to a rise in sea level which will displace 30 million people living in low lying areas in India alone? The debate over the relative importance of population control in developing countries (is there a need for a "one child world"?<sup>19</sup>) and reduction of consumption in the rich developed countries was well covered in a recent special issue of the *BMJ* (9 October 1999). There has been a measure of agreement internationally that action must be taken, and at

#### A practical personal agenda might include

*Energy*—insulating and draught proofing your home, reducing thermostat settings, using low energy light bulbs, and switching off appliances when not in use

*Waste*—reusing containers, buy loose not packaged products, complain about overpackaging, composting green waste, and recycling bottles, paper, plastic

*Transport*—avoiding unnecessary car travel, walking or cycling to work, sharing car journeys, using a compact energy saving car, driving at moderate speeds, lobbying for better public transport, teleconferencing rather than meeting

*Purchasing power*—buying local goods or recycled products, buying repairable goods, avoiding disposable products, using local shops, buying local holidays or supporting ecotourism

*Food*—growing your own, buying local food, buying organic food, buying Fair Trade goods, reducing meat intake

*Leisure*—joining local environmental and wildlife groups, supporting Local Agenda 21 initiatives

*Family planning*—no more than one child per adult

*National*—support the government's targets for CO<sub>2</sub> reduction and lobby for maintaining this commitment together with the introduction of green taxes (polluter pays)

the world conference on sustainable development in Kyoto, Japan in 1997,<sup>20</sup> a target of 8% reduction of 1990 emissions of CO<sub>2</sub> by 2010 was set for the European Union countries, 7% for the USA, and 6% for Japan and Canada. The UK government has taken a lead and has set itself a target of 20% reduction. The means of meeting this target will be by home energy efficiency programmes, increased business energy efficiency, increased road vehicle efficiency, and reduced road traffic.

#### Local Agenda 21 (LA 21)

Agenda 21 recognises that success depends on action at a local level and that local authorities have a vital role to play: all are expected to have a clear strategy in place by the year 2000. These strategies could include protection of the environment by minimising waste, meeting social needs by ensuring access to good food at low cost, and promoting economic success by encouraging access to local facilities in ways which make less use of the car.

What is the role of paediatricians in sustainable development? Paediatricians have four roles to play in relation to sustainable development and child health:

- to educate themselves and to ensure that this subject becomes part of the teaching and training of paediatricians
- to advocate for the principles of sustainable development both locally and nationally
- to set a personal example by adopting the principles of sustainable development in their own lifestyles
- to develop appropriate research methods to assess the health impact of policy decisions on children.<sup>21</sup>

#### Conclusion

The fact that an individual's health and quality of life depend to a great extent on the physical, social, and economic environment in which they live is hardly controversial. Not only can we intuitively recognise this as being true but there is an increasing weight of scientific evidence attempting to explain patterns of health inequality in terms of social, economic, and geographical factors. The more

the health impact of social and economic policies is recognised, the more obvious the importance of sustainable development will become. By adopting a sustainable development philosophy in our personal and work lives, we begin to change the way we and others think about “progress”, and the values upon which society is based. The concept and philosophy of sustainable development is possibly the most important concept to emerge at the end of 20th century. We believe that if all people, from the individual to the transglobal international company, understood and took decisions based on sustainable development principles, they would significantly reduce inequalities within and between today’s and future generations, improve the quality of their own lives, and preserve the planet earth for our children.

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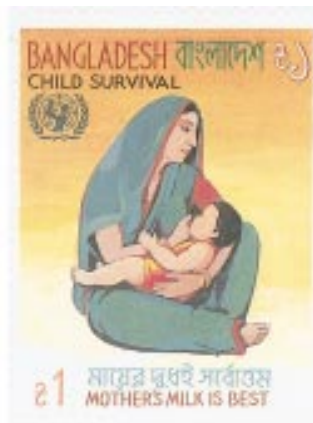
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## STAMPS IN PAEDIATRICS

### Breast feeding

Breast feeding is one of the major themes promoted and publicised on stamps with a paediatric interest. Although the total number of paediatric stamps is very small, infant feeding commands a relatively high proportion of these. The 1974 stamp from Central African Republic was issued to commemorate the 26th anniversary of the World Health

Organisation and the 1985 stamp from Bangladesh for the UNICEF Child Survival Campaign. The latter is inscribed in Bengali and English to reach as wide a population as possible. The best example of a pictorial message displaying the promotion of breast versus bottle feeding is shown in the St Vincent stamp of 1987.



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