

MMR vaccination of children with egg allergy is safe

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ABSTRACT

INTRODUCTION: Measles, mumps and rubella (MMR) vaccination is part of the Danish Childhood Vaccination Programme. It is known that children may react with anaphylaxis to MMR vaccines containing traces of egg protein. In Denmark, national clinical guidelines recommend that children with egg allergy be referred to vaccination at a paediatric ward despite changed recommendations in other countries. The purpose of this study was to determine whether children with egg allergy presented with anaphylactic/allergic reactions to MMR vaccination and to discuss whether Danish recommendations should be upheld.

MATERIAL AND METHODS: Data collected through evaluation of the histories of children referred to the Paediatric Ward at Hillerød Hospital from 01.01.2008 to 28.02.2011 and coded according to action diagnosis and/or supplementary diagnosis in International Classification of Diseases 10 (ICD-10) for food allergy, oedema angioneurotica and tentative diagnosis as well as the procedure code for oral food challenge. A total of 32 patients were included, all were both sensitized to egg and had been MMR vaccinated.

RESULTS: The 32 patients had received a total of 41 doses of MMR vaccine. None of them had shown anaphylactic/allergic reactions to the MMR vaccines. 23% of the vaccines were given with considerable delay.

CONCLUSION: Based on our study, we conclude that the Priorix MMR vaccine may be administered just as safely to children diagnosed with egg allergy as to other children. We found no evidence in support of the current Danish recommendations. We therefore recommend that the Statens Serum Institut, the Danish Paediatric Society and/or the Danish Health and Medicines Authority reconsider these recommendations.

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The vaccine against measles, mumps and rubella (MMR) is part of the Danish Childhood Vaccination Programme. Initial vaccination is administered when a child is 15 months old, and revaccination is given at four years of age. Children who as of 1 April 2008 were older than four years are revaccinated when they are 12 years old [1]. It is known that children may react with anaphylaxis to MMR vaccines [2].

In Denmark, the MMR vaccine Priorix from GlaxoSmithKline Pharma – a lyophilized combination vaccine – is used. It may contain traces of egg protein as

measles virus and parotitis virus are cultivated in chicken embryo tissue culture [3]. Historically, concerns and discussions have been raised as to whether it was safe to give the vaccine to children with egg allergy and whether the vaccine should be administered at paediatric departments prepared to handle anaphylaxis. Reported anaphylactic reactions may have been caused by other ingredients such as gelatine [2]. Several studies have shown that there is no connection between egg allergy and anaphylactic reactions to MMR vaccination, which has led to changed recommendations in other countries [2, 4-8].

In Denmark, it is still recommended that children with egg allergy be referred to vaccination at a paediatric ward without a preceding skin prick test with the vaccine [9]. These precautions may cause parents to worry unnecessarily and may cause delay in or de-selection of MMR vaccination. A New Zealand study by Goodyear-Smith et al. demonstrated that children referred to MMR vaccination are vaccinated later than other children. This markedly increases the risk of contracting diseases, e.g. measles, and reduces the MMR immunisation of the population [10].

The purpose of our study was to investigate whether children diagnosed with egg allergy and referred to the Paediatric Ward at Hillerød Hospital have shown anaphylactic/allergic reactions to MMR vaccination and to discuss whether the Danish recommendations should be upheld.

MATERIAL AND METHODS

The study comprised data collected through evaluation of the histories of children referred to the Paediatric Ward at Hillerød Hospital from 01.01.2008 to 28.02.2011 and coded according to the following action and/or supplementary diagnoses in the International Classification of Diseases 10 (ICD-10) for suspected (DZ03.8+) or confirmed food allergy (DK52.2, DK52.2A) and oedema angioneurotica (DT78.3) as well as the procedure code for oral food challenges (ZZ4392M, ZZ4392N).

The histories were reviewed and 36 patients with egg allergy were identified. Missing information was supplemented with telephone calls to the child's general practitioner or to other practices/hospitals where the child had been treated as an outpatient. Patients were included if they had showed to be sensitized to egg in

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 TABLE 1

The diagnostic criteria. Primary diagnosis (confirmed sensitization): All patients confirmed sensitized to egg by positive skin prick test ≥ 3 mm and/or elevated egg-specific Immunoglobulin E antibodies ($>$ class 2).

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Symptoms ^a + positive oral food challenge	9
Symptoms ^a with confirmed correlation with exposure to egg, but no positive oral food challenge at the time of vaccination	17
Sensitized but never exposed to egg	6
Total	32

a) Urticaria, gastrointestinal symptoms, asthmatic symptoms, angio-oedema, rash/dermatitis, anaphylactic shock, rhino-conjunctivitis.

skin prick test or positive to specific immunoglobulin E (IgE) to egg and had been MMR vaccinated. Patients for whom sufficient documentation was unavailable were excluded.

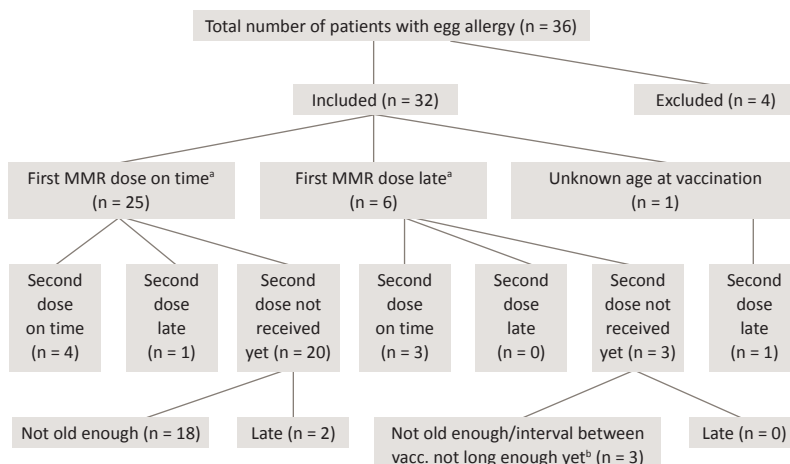
Trial registration: not relevant.

RESULTS

A total of 36 patients with egg allergy were identified. Four patients with egg allergy were excluded for the following reasons: lack of information concerning MMR vaccination (two patients) and insufficient diagnostic criteria (two patients). The average age at the time of diagnosis was < 1 year. Of the 32 included patients, ten had showed sensitivity to egg both in a skin prick test and based on positive specific IgE to egg (IgE class > 2), 18 in skin prick test only, and four based on positive specific IgE only.

 FIGURE 1

MMR vaccination status.



a) First vaccination (recommended at 15 months of age) given at 0-2 years of age.

b) Recommended 2.5 year interval between first and second vaccination.

The diagnostic criteria are presented in **Table 1**. Oral challenge with egg was carried out 18 times in all on a total of 12 patients. Eleven were positive, one was inconclusive and six were negative in patients who had all shown definite allergic reactions to egg. Of the 12 patients, nine were positive. The three patients with negative oral challenges had all been challenged following the first MMR vaccination. At the time of vaccination, a definite positive anamnesis of reaction to egg existed for these three patients. Five patients presented with asthmatic symptoms when provoked with egg, three patients showed no asthmatic symptoms, and in four cases information was missing from the medical history.

A total of 15 patients had chronic asthma as comorbidity, 14 showed no symptoms of asthma and in three cases there was no information of existing asthma symptoms.

The 32 patients had been given a total of 41 doses of MMR vaccine. The distribution is presented in **Figure 1**.

One of the 32 patients developed a small wheal at the site of the injection. There were no reports of late reactions.

Of 43 potential MMR vaccinations, ten were delayed with respect to the SSI's recommended vaccination interval of 2.5 years. Thus, 23% of the MMR vaccines were given with a significant delay.

The first dose of MMR vaccine had been given in general practice in six cases and at a paediatric ward in 24 cases, whereas the place of vaccination was unspecified in two cases. In the six cases in which the first MMR vaccination was delayed, the place of vaccination was a paediatric ward. At the time of observation, a total of nine second doses of MMR vaccine had been given, three in general practice and six at a paediatric ward.

DISCUSSION

The Priorix vaccine used in Denmark consists of living attenuated measles virus (Schwarz), living attenuated mumps virus (RIT 4385, derived by Jeryl Lynn) and living attenuated rubella virus (Wistar RA 27/3), and it may therefore contain egg protein [3]. It is thus recommended that patients who are allergic to egg be vaccinated at a paediatric ward [9]. Approximately two thirds of our patients had been vaccinated at a paediatric ward.

All of the 32 patients had been vaccinated with MMR vaccine without developing anaphylactic or allergic reactions, regardless of the severity of their egg allergy, except for one patient who developed a small urticarial wheal at the site of injection and was treated with antihistamine. There were no reports of late reactions. Several of the patients presented with anaphylactic reactions including respiratory distress and Quincke's

oedema when exposed to egg, and several showed symptoms of chronic asthma. Co-morbidity in the form of severe bronchial asthma is a risk factor that may lower the threshold of egg protein required to cause anaphylaxis [5]. Several of the patients suffered from severe chronic asthma, but none of them reacted to the vaccine.

Earlier reports have described anaphylactic reactions to MMR vaccination, but most of these relate to children who were not allergic to egg [2]. This suggests that other allergens than egg protein, such as gelatine, present at high concentration in the vaccine may cause the described anaphylactic reactions [5, 6].

Skin prick testing with MMR vaccine prior to vaccination has been used in an effort to predict hypersensitivity to the vaccine, but it has proven an invalid screening method to determine which patients are at risk [11].

A total of 23% of the MMR vaccines were given with delay. The number may be higher, since only the year and not the patients' exact age at the time of vaccination were recorded due to the design of the study. One patient was not MMR-vaccinated until the year in which he turned 15 years old. Low vaccination coverage results in insufficient immunity of the population and increases the risk of new measles epidemics. It was mainly patients referred to a paediatric ward for vaccination who were vaccinated with delay.

Vaccines against influenza, influenza A, yellow fever and Central European encephalitis may also contain egg protein [12]. Whether influenza A vaccination of children with egg allergy can take place in general practice may be important in future epidemics, where referral to a paediatric ward is likely to delay potential vaccination and to cause parent concern, the result of which may be that their children are not vaccinated and remain at risk of infection. A prospective registration of all patients with verified egg allergy who fulfil all clinical criteria for vaccination with influenza A vaccine may be considered. In an American study, Chung EY et al demonstrated that persons allergic to egg may be safely vaccinated with influenza vaccine by giving the vaccine in two increasing doses [13] and, in a Canadian study, Gagnon R et al found that it was safe to give influenza A vaccine to persons allergic to egg [14], although these findings are, of course, subject to the specific type of vaccine and methods of production.

CONCLUSION

Based on our study, we cannot say anything about the relative risk that children with egg allergy may react with anaphylaxis to MMR vaccination, but our study supports the findings of foreign studies showing that the amount of egg protein in the MMR vaccine is not high enough to cause an IgE mediated allergic reaction in children with



MMR vaccination.
Source: James Gathany

egg allergy [5]. In the present Danish material, which includes patients with a severe reaction to egg, no reaction to MMR vaccination was shown. However, it is necessary to bear in mind that different methods of production of different vaccines may lead to different amounts of egg protein in the final vaccine [4]. Prior life-threatening reaction to exposure to egg as well as co-morbidity with severe asthma bronchiale are risk factors that may lower the threshold value of egg protein required to cause anaphylaxis [5]. Several of the patients suffered from severe chronic asthma, but none of these patients reacted to the vaccine.

Based on our study, we conclude that the Priorix MMR vaccine may be administered just as safely to children diagnosed with egg allergy as to other children while observing standard vaccine safety precautions in general practice, but that an assessment based on the risk of anaphylaxis must be made based on the anamnesis of the individual patient and the choice of vaccine.

If children are to be referred for MMR vaccination at a paediatric ward, this should be done early enough for the children to receive vaccination at the recommended age, and not at the time when they typically appear for vaccination in general practice. Low vaccination coverage results in insufficient immunity of the population and increases the risk of new measles epidemics.

Based on other existing articles and our study, we found no evidence in support of the current Danish recommendations and if they are maintained, there will be a continuous, high risk of delayed vaccinations. We thus believe that the SSI, the Danish Paediatric Society and/or the Danish Health and Medicines Authority should reconsider whether children with egg allergy may be vaccinated with MMR vaccine in general practice.

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CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk.

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