

# Previous Exposure to Measles, Mumps, and Rubella—but Not Vaccination During Adolescence—Correlates to the Prevalence of Pancreatic and Thyroid Autoantibodies

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**ABSTRACT.** *Objective.* This study was designed to determine whether a relationship exists between previous exposure to measles, mumps, and rubella (MMR) by natural infection or vaccination or by new immunization with MMR vaccine, and either the presence or levels of autoantibodies against thyroid cell and pancreatic  $\beta$ -cell antigens.

*Methods.* Antibodies against MMR and autoantibodies against thyroglobulin, thyroid peroxidase, pancreas islet cells (ICA), islet cell surface, glutamic acid decarboxylase 65k autoantibodies, and insulin were studied before, and 3 months after, vaccination with combined MMR vaccine in 386 school children between 11 and 13 years of age.

*Results.* The vaccination changed neither the prevalence nor the level of autoantibodies. Children with rubella antibodies before vaccination had higher levels of ICA than did the rubella seronegative children. In contrast, thyroid autoantibody levels and prevalence were lower in children with antibodies against measles, mumps, or both before vaccination than in children without those antibodies.

*Conclusions.* Previous natural infection or vaccination against measles, mumps, or both seemed to have an inhibitory effect on the development of thyroid autoantibodies. In contrast, children with previous exposure to rubella had higher levels of ICA. No evidence was found that MMR vaccination during adolescence may trigger autoimmunity. *Pediatrics* 1999;104(1). URL: <http://www.pediatrics.org/cgi/content/full/104/1/e12>; autoantibodies, thyroiditis, type 1 diabetes mellitus, vaccination, virus.

ABBREVIATIONS. AIT, autoimmune thyroiditis; Tg-ab, thyroglobulin autoantibodies; TPO-ab, thyroid peroxidase autoantibodies; ICA, pancreas islet cell autoantibodies; GAD65Ab, glutamic acid decarboxylase autoantibodies; IAA, insulin autoantibodies; CRS, congenital rubella syndrome; ICSA, islet cell surface autoantibodies; GAD65Ab, glutamic acid decarboxylase 65k autoantibodies; MMR, measles, mumps, and rubella; JDF, Juvenile Diabetes Foundation; IgG, immunoglobulin G.

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In the majority of cases, children with autoimmune diseases such as autoimmune thyroiditis (AIT) or insulin-dependent type 1 diabetes mellitus are characterized by the absence of any first degree relative with the disease in question.<sup>1</sup> The prevalence of autoimmune markers associated with these disorders in children is higher than the prevalence of the respective diseases. It is unclear when and why autoantibodies are acquired and what induces the progress of disease in the individual patient. At clinical diagnosis of AIT, 93% to 95% of the patients have at least one of the thyroglobulin autoantibodies (Tg-ab) or thyroid peroxidase autoantibodies (TPO-ab).<sup>2,3</sup> Of patients with newly diagnosed type 1 diabetes mellitus, 80% to 90% have islet cell antibodies (ICA),<sup>4-8</sup> 70% to 80% have glutamic acid decarboxylase autoantibodies (GAD65Ab),<sup>9-12</sup> and 46% to 70% have insulin autoantibodies (IAA).<sup>13-16</sup> Virus and other environmental factors have been suggested to be initiators of the autoimmune reactions resulting in disease. Congenital rubella syndrome (CRS) has been reported to be associated with an increased risk of subsequent type 1 diabetes<sup>17,18</sup> or AIT.<sup>19</sup> Mumps,<sup>20,21</sup> coxsackie B3 and B4,<sup>22,23</sup> and cytomegalovirus<sup>24-26</sup> have also been suggested to be involved in the pathogenesis of type 1 diabetes.

If virus infection has an immunomodulatory effect, there is a possibility that vaccination may also induce autoimmunity, especially when live, attenuated virus is used, as in measles, mumps, and rubella (MMR) vaccination. In contrast to virus as initiating agents, a recent study showed that infections in early life may be associated with a reduced risk of type 1 diabetes.<sup>27</sup> Similarly, recently published epidemiologic data imply that BCG vaccination performed neonatally may be associated with lower risk of type 1 diabetes than later vaccination,<sup>28</sup> which in turn suggests that the timing of immunization with common pediatric vaccines may be an important determinant of the risk of developing type 1 diabetes.

The present study was designed to determine whether a relationship exists between previous exposure to measles, mumps, or rubella by natural infection or vaccination or new immunization with MMR vaccine, and either the presence or titers of autoantibodies against thyroid cell or pancreatic  $\beta$ -cell antigens.

**Subjects**

Blood samples were taken from 386 Swedish sixth-grade school children with a median age of 12 years (range 11–13 years). No child had overt type 1 diabetes or thyroid disease at the time of sampling. The families were interviewed about heredity for endocrine disease. Positive heredity was defined as the presence of disease in a sibling, parent, parental sibling, or grandparent. The general vaccination program in Sweden for this generation of children included vaccination against measles at the age of 18 months and then MMR vaccination at the age of 12 years. Serum sample volume permitted analyses of virus antibodies, thyroid autoantibodies, and glutamic acid decarboxylase 65k autoantibodies (GAD65Ab) in all 386 subjects, of ICA in 384 subjects, of IAA in 379 subjects, and of islet cell surface autoantibodies (ICSAs) in 366 subjects. Sera were sampled before and 3 months after MMR immunization (Virivac; Swedish Institute for Infectious Disease Control, Stockholm, Sweden) and stored at  $-20^{\circ}\text{C}$  until analyzed.

**Methods**

Tg-ab and TPO-ab were detected using a sensitive solid-phase immunosorbent radioassay based on binding the human  $^{125}\text{I}$ -labeled antigens to the autoantibody, as described previously.<sup>29</sup> If antibodies were present in a titer of  $\geq 5$ , the sample was considered positive. Dilution curves of positive sera (plotted with percent-bound activity of the labeled antigen on the  $y$  axis and the dilution on the  $x$  axis) showed a good conformity to the dilution curves of the standards from the Medical Research Council (research standard A 65/93 for Tg and No 66/387 for TPO).

ICA were analyzed using an indirect two-color immunofluorescence assay.<sup>30,31</sup> Results were expressed in Juvenile Diabetes Foundation (JDF) units.<sup>32</sup> If antibodies could be detected, the sample was considered positive. The laboratory at Malmö University Hospital, Malmö, Sweden, participates in the International Diabetes Workshop proficiency program.<sup>33</sup> In the 13th evaluation, our ICA assay manifested a sensitivity of 100% and a specificity of 100%.

IAA were measured with a competitive radioligand binding assay using monoiodinated insulin as the antigen and polyethylene-glycol as the precipitating agent.<sup>13</sup> IAA were considered to be present if precipitated radioactivity exceeded nonspecific binding and was suppressed significantly by the addition of excess unlabeled insulin. Levels of IAA were expressed in nanounits/milliliter, as described previously.<sup>15</sup> Values  $>3$  SD above the control mean were considered positive. Our laboratory participated in the international IAA proficiency program and obtained a sensitivity of 100% and a specificity of 100%.

GAD65Ab were analyzed using a radioligand assay as described previously in detail.<sup>34,35</sup> The upper limit of normal range was set at 3 SD above the control mean. A GAD65Ab index was calculated as described.<sup>35</sup> We participated in the international GAD65Ab proficiency program and obtained a sensitivity of 100% and a specificity of 100%.

ICSA were determined by radioimmunoassay.<sup>36</sup> Absorption tests showed the binding to be  $\beta$ -cell-specific. Interassay variation was 9.5%, and intraassay variation was 9.9%. For ICSA positivity, the specificity was 100% and the sensitivity was 70%, calculated as previously described.<sup>36</sup> Values of  $>2$  SD above the mean for healthy school children were regarded as positive.

Measles immunoglobulin G (IgG) antibodies were analyzed with the Behring Enzygnost Measles kit (Behring, Marburg, Germany), mumps IgG antibodies were analyzed with the Behring Enzygnost Parotitis kit (Behring), and rubella IgG antibodies were analyzed with the hemolysis in-gel test.<sup>37</sup> In a serum panel from the United Kingdom National External Quality Assessment Scheme for Microbiology, the hemolysis in-gel test manifested 100% sensitivity and 100% specificity.

**Statistical Analyses**

The  $\chi^2$  test was used for subgroup comparison of antibody positivity rates, and Fisher's exact test (two-tailed) was used for comparison of small groups. The Mann-Whitney  $U$  test was used for subgroup comparisons of antibody levels among groups, and Student's  $t$  test was used for comparison of antibody levels before and after vaccination.  $P$  values  $< .05$  were considered significant.

This study was approved by the ethics committee of the medical faculty at the University of Lund, Malmö, Sweden.

**RESULTS**

**Autoantibodies and Heredity for Thyroid Disease or Type 1 Diabetes**

Relationships between the prevalence of autoantibodies and heredity for thyroid disease or type 1 diabetes are presented in Table 1. Heredity was not a significant correlate of autoantibody prevalence.

**Autoantibodies and Virus Antibodies Before MMR Vaccination**

*Thyroid Autoantibodies (Table 2)*

*Tg-ab*

The prevalence of Tg-ab positivity in the measles seropositive subgroup was significantly lower than that in the measles seronegative group (12% [39/321] vs 23% [15/65];  $P = .03$ ), and the levels of the Tg-ab titers were significantly lower as well ( $P = .02$ ). The prevalence of Tg-ab was also lower in the mumps seropositive subgroup than in the corresponding seronegative subgroup (11% [26/241] vs 19% [28/145];  $P = .03$ ), as were the Tg-ab titers ( $P = .02$ ). No correlation was found between rubella antibodies and Tg-ab.

*TPO-ab*

The prevalence of TPO-ab positivity was significantly lower in the subgroup with IgG-antibodies against measles, mumps, or both than in the corresponding seronegative subgroup (5% [17/353] vs 15% [5/33];  $P = .03$ ), as were the TPO-ab titers ( $P = .02$ ). No correlation was found between rubella antibodies and TPO-ab.

*Tg-ab, TPO-ab, or Both*

At least one of the thyroid autoantibodies was found in 14% (49/353) of the children seropositive for measles, mumps, or both, compared with 33% (11/33) of the seronegative children ( $P = .007$ ).

*Pancreatic Islet  $\beta$ -Cell Autoantibodies*

*ICA*

The prevalence of ICA positivity was slightly higher in the subgroup with positive IgG tests for rubella than in the corresponding seronegative subgroup, although the difference was nonsignificant (4% [8/190] vs 1% [2/196];  $P = .06$ ), but ICA levels were significantly higher in the rubella seropositive

**TABLE 1.** Prevalences of Autoantibody Positivity in Subgroups With or Without Heredity for Thyroid Disease or Type 1 Diabetes\*

Heredity	<i>n</i>	Tg-ab (%)	TPO-ab (%)	ICA (%)	ICSA (%)	IAA (%)	GAD65Ab (%)
<b>Thyroid disease</b>							
Yes	66	9	3	4	2	0	0
No	320	15	6	2	4	1	1
<b>Type 1 diabetes</b>							
Yes	38	18	11	5	8	0	0
No	348	14	5	2	3	1	1

\* Heredity was defined as the presence of disease in a sibling, parent, parental sibling, or grandparent. No statistically significant association related to heredity was seen.

**TABLE 2.** Virus Immunity and Thyroid Autoantibodies Before Vaccination

Virusimmunity	Result	<i>n</i>	Tg-ab % ( <i>n</i> )	TPO-ab % ( <i>n</i> )	Tg-ab, TPO-ab, or both % ( <i>n</i> )
Measles (1)	Pos	321	12 (39)	5 (16)	13 (43)
	Neg	65	23 (15)*	9 (6)	26 (17)
Mumps (2)	Pos	241	11 (26)	4 (10)	12 (29)
	Neg	145	19 (28)*	8 (12)	21 (31)
Rubella (3)	Pos	190	12 (22)	6 (12)	13 (25)
	Neg	196	16 (32)	5 (10)	18 (35)
1, 2, or both	Pos	353	13 (45)	5 (17)	14 (49)
	Neg	33	27 (9)	15 (5)*	33 (11)**
1, 2, 3, or combination	Pos	364	13 (48)	11 (19)	15 (53)
	Neg	21	29 (6)	14 (3)	33 (7)*

Statistically significant differences between the virus seropositive and seronegative groups are denoted by asterisks: \* ( $P < .05$ ) or \*\* ( $P < .01$ ).

If thyroid autoantibodies were present in a titer of 5 or more, the sample was considered positive.

subgroup (mean 5.9 JDF units vs mean 1.6 JDF units;  $P < .05$ , Mann-Whitney  $U$  test). There was no difference in the prevalence of ICA positivity among the subgroups seropositive versus seronegative for either measles or mumps.

#### GAD65Ab, IAA, or ICSA

There was no difference in the prevalence of GAD65Ab, IAA, or ICSA positivity among the subgroups seropositive for mumps, measles, or rubella versus the corresponding seronegative subgroup.

#### Virus Antibodies Before and After MMR Vaccination

The pre-MMR and post-MMR vaccination prevalences of IgG antibody positivity in reference to MMR are given in Table 3. All subjects became seropositive after vaccination with the exception of 5% (19/386) who remained seronegative against the mumps antigen. There was no significant gender-related difference in the pattern of viral antibody positivity.

#### Autoantibodies Before and After MMR Vaccination

The pre-MMR and post-MMR vaccination autoantibody positivity prevalences are shown in Table 4. No significant difference was found in the prevalence of positivity in reference to any of the autoantibodies before versus after vaccination. MMR vaccination did not affect either the prevalence of autoantibody positivity or the levels of autoantibodies.

### DISCUSSION

This study showed both the prevalence of thyroid autoantibody positivity and the titers to be lower among individuals with IgG antibodies against measles, mumps, or both, acquired by previous exposure attributable to either natural infection or vaccination. We also found the levels of ICA to be higher in the

**TABLE 3.** Percentages of Children Seropositive for Measles, Mumps, or Rubella, Before and After MMR Vaccination

	Before (%)	After (%)
Measles	321/386 (83)	386/386 (100)
Mumps	241/386 (62)	367/386 (95)
Rubella	190/386 (49)	385/386 (100)

No child seropositive before vaccination converted to seronegativity.

**TABLE 4.** Prevalence of Autoantibody Seropositivity in Children Before and After MMR Vaccination

	Before (%)	After (%)	Before and After (%)
Tg-ab	54/386 (14)	56/386 (15)	52/386 (13)
TPO-ab	22/386 (6)	23/386 (6)	18/386 (5)
ICA	10/384 (3)	10/384 (3)	10/384 (3)
ICSA	13/366 (3)	13/366 (3)	5/366 (1)
IAA	4/379 (1)	4/379 (1)	2/379 (1)
GAD65Ab	5/386 (1)	5/386 (1)	5/386 (1)

rubella IgG-positive than in the rubella-negative subgroup. MMR vaccination had no effect on the prevalence of either thyroid or islet autoantibody positivity (ICA, IAA, GAD65Ab, or ICSA). Heredity for AIT or type 1 diabetes did not correlate to the prevalence of the respective autoantibodies.

The relationship found between thyroid autoantibody (Tg-ab + TPO-ab) negativity and the presence of virus antibodies suggest that previous virus exposure may reduce autoreactivity. The opposite view is often taken, and it is a popular hypothesis that previous infection induces autoreactivity by means of molecular mimicry.<sup>38</sup> Our data, which suggest that the absence of any marker for previous virus infection is associated with increases both in the prevalence of thyroid autoantibody positivity and in the antibody titers, are novel. Although long-term follow-up is needed to determine whether the noninfected children with autoantibodies will develop thyroid disease subsequently, it is open to speculation whether infections with mumps or measles may result in polyclonal activation, which generates regulatory T cells that prevent the survival of autoreactive T cells. To the best of our knowledge, there have been no epidemiologic investigations of the relationship between early MMR infections or vaccination and thyroid disease. At present, we can only speculate that the lower prevalence of thyroid antibody positivity among virus antibody-positive 12-year-old children will be associated with a lower incidence of autoimmune thyroid disease later in life.

In contrast, in type 1 diabetes, a protective effect of early virus infection has been suggested by findings in an epidemiologic investigation.<sup>27</sup> Similarly, a case-control study showed the relative risk of developing type 1 diabetes to be reduced in children vaccinated against measles.<sup>39</sup>

Although the evidence of virus infection before the clinical onset of type 1 diabetes is substantial, the mechanisms by which virus may cause injury to endocrine cells are not understood fully. The prevalence of type 1 diabetes among individuals with CRS is high (12%–20%),<sup>40,41</sup> although the diabetes may take 5 to 20 years to manifest.<sup>18,42</sup> Other autoimmune manifestations in CRS include AIT and Addison's disease.<sup>19</sup> In addition, as with CRS, enterovirus infection during pregnancy is a risk factor for type 1 diabetes in the child.<sup>43</sup>

Early reports were published of the occurrence of type 1 diabetes during acute mumps infection or in the recovery phase,<sup>20,21</sup> and more recently there have been reports of increasing prevalences of ICA positivity and even type 1 diabetes after vaccination against mumps.<sup>44,45</sup> Some type 1 diabetes patients have increased levels of specific virus antibodies (eg, coxsackie B-IgM<sup>22,23</sup> and rubella<sup>46,40</sup>) and PCR-detected coxsackie B3 or B4 genome was reported to be increased among newly diagnosed type 1 diabetes patients.<sup>47</sup> Coxsackie virus antigens have also been observed in the islets of Langerhans.<sup>48</sup> At least one rubella antigen has been shown to react with sera from patients with newly diagnosed type 1 diabetes.<sup>49</sup>

However, direct causative effects have been difficult to verify, and islet autoantibodies may already be present in cord blood from children who later develop type 1 diabetes,<sup>50</sup> suggesting that the islet autoreactivity developed before virus infection. Recent analysis of islets from new onset type 1 diabetic children failed to detect virus DNA or RNA.<sup>51,52</sup> The difficulty in identifying viruses as etiologic agents in autoimmune disease may be partly explained by our finding that autoreactivity may be modulated by previous virus exposure.

Similar to a previous finding of an increased prevalence of ICSA positivity among cases of CRS,<sup>53</sup> we found rubella-seropositive children to have higher ICA levels than do rubella-seronegative children. This finding may imply the existence of a link between rubella and islet cell autoimmunity but does not constitute an argument against rubella vaccination, because the value of vaccination for protecting children from CRS is undisputed. A transient increase in the prevalence of ICA positivity, occurring 6 weeks after rubella vaccination but no longer apparent 18 months later, has been reported.<sup>54</sup> However, in our study, as in other studies,<sup>55,56</sup> the prevalence of ICA positivity was unaffected by MMR vaccination and inconsistent with mumps vaccination being an initiator of type 1 diabetes. However, age at vaccination may possibly be an important factor.

Because we found no difference between pre-MMR and post-MMR vaccination prevalences of autoantibody positivity or in the respective autoantibody titers, our study yielded no evidence that MMR vaccination may trigger autoimmunity in children. Moreover, the lower prevalence of thyroid autoantibody positivity and the lower thyroid autoantibody titers in the subgroup manifesting IgG-antibody positivity in reference to measles and mumps, compared

with the corresponding seronegative subgroup, suggest that virus immunization may have a protective effect against thyroid autoimmunity.

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