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# Clustering of Cases of Type 1 Diabetes Mellitus Occurring 2-4 Years After Vaccination is Consistent with Clustering After Infections and Progression to Type 1 Diabetes Mellitus in Autoantibody Positive Individuals

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## ABSTRACT

***Objective:*** **We previously analyzed data from a hemophilus vaccine trial and identified clusters of extra cases of type 1 diabetes mellitus (T1DM) caused by the vaccine that occurred between 36 and 48 months after immunization. Published reports indicate clustering of cases of T1DM occurring approximately 2-4 years after mumps infection. Others have reported a 2-4 year delay philus vaccine and T1DM to be established. The current findings indicate the there are also clusters of cases of T1DM occurring 2-4 years post-immunization with the pertussis, MMR, and BCG vaccine. The data are consistent with the occurrence of clusters following mumps infection and the progression to T1DM in patients with antipancreatic autoantibodies.**

**between the onset of autoantibodies and the development of T1DM. We attempted to determine whether similar clustering of cases of T1DM occurred after immunization with vaccines other than hemophilus.**

***Methods:*** **We searched MEDLINE and reviewed references from published papers to find databases on the incidence of T1DM and then searched MEDLINE to determine whether changes in immunization occurred in these regions during the times the incidence of DM was being recorded.**

***Results:*** **Distinct rises in the incidence of T1DM occurred 2-4 years following the introduction of the MMR and pertussis vaccines. A drop in the incidence of T1DM was detected between 3-4 years following discontinuation of pertussis and BCG vaccines.**

***Conclusion:*** **The identification of clusters of cases of T1DM occurring in consistent temporal time periods allowed a link between the hemo-**

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**KEY WORDS**

type 1 diabetes mellitus, vaccines, pertussis, BCG, measles, mumps, rubella

## INTRODUCTION

We previously performed animal studies that conclusively demonstrated a causal link between vaccines and diabetes mellitus (DM) in non-obese diabetic (NOD) mice[1]. Data from a large prospective clinical trial support a causal link between the hemophilus vaccine and type 1 (insulin dependent) DM (T1DM) in humans. In that study we found clusters of extra cases of T1DM starting approximately 38 months after immunization and lasting about 6 months[1].

Several different groups of authors have published papers by which reported clustering of cases of T1DM occurring 2-4 years after infection with mumps virus[2-5]. Sultz *et al*[2] published epidemiology data that there was a 3-4 year delay between epidemics of mumps and epidemics of T1DM. The authors described a median lag time of 3 years and a mean lag time of 3.8 years between infection with mumps and the development of T1DM. A group from Finland reported a 2-4 year delay between

mumps infection and the development of T1DM[3]. The authors also cite two older publications that reportedly contain a similar delay between mumps infection and the development of T1DM[4,5]. A study in Pittsburgh found rises of T1DM associated with epidemics of varicella infections[6]. The authors found there was a 2-3 year delay between the epidemics and the onset of T1DM.

Centers in many different parts of the world have prospectively followed the progression to DM in individuals with one or more autoantibodies. The delay between the detection of autoimmunity and the development of T1DM is very consistent between centers when looking at similar groups. The studies that are most analogous to the cases of vaccine-induced DM are in groups of people who have been prospectively followed prior to the development of autoantibodies. In these studies the median onset of DM following the onset of autoimmunity is roughly 3 years. There is also an ~2-year delay between the beginning of autoimmunity and the development of any significant number of

A German study prospectively followed children at risk for developing DM because of family history, from birth. Researchers screened blood at birth, 9 months, 2 years, and 5 years. They found that in children who had two autoantibodies by age 2 years, 50% developed DM by age 5, a median onset of approximately 36 months after detection of autoantibodies[11].

Numerous groups have followed the progression to DM in high-risk patients who have one or more autoantibodies present at the time of enrollment into the study. The median or mean progression time is often near 3-4 years. A group in Finland followed 701 individuals at high risk for T1DM, mean age 9.9 years. The authors found the median time between the enrollment in the study and the development of T1DM was 3.3 years, while the median follow-up time for the non-progressors was 10.3 years[8]. Almost all of those who were ICA positive at the beginning of the study and went on to develop DM did so within 5 years. A large US study[12] followed 7,834 high-risk people (median

cases of T1DM.

Researchers have been prospectively following a group of 765 initially non-diabetic siblings of patients with in Finland[7,8]. DM manifested after a mean time of 3.2 years from the detection of anti-islet cell antibodies (ICA) in those who were initially negative at the beginning of the study[7]. ICA had the highest sensitivity of any autoantibody with a sensitivity of 100%, and presence of persistent ICA had an actuarial risk of developing T1DM of 47%. The authors found that ICA had a lower predictive value in controls from the general population than in the siblings of patients with DM[9], which could indicate that those in the general population, as opposed to the siblings, are more likely to have genes that keep the ICA antibodies from destroying pancreatic islet cells. A second study from Finland prospectively followed 4,590 newborns with high and medium genetic risk for developing DM[10]. The authors found that with 95% of all autoantibodies associated with T1DM, including insulin autoantibodies (IAA), glutamic acid decarboxylase antibodies (GADA), and tyrosine phosphatase-like protein antibodies (IA-2), sero-conversion occurred in clusters -12 to 8 months around the time of ICA sero-conversion.

age 27.4 years) for the development of T1DM, with a median of 4.6 years of follow up. During the study 135 participants developed T1DM with a median age of 10.5 years and a median time between enrollment in the study and the development of T1DM of 2.8 years, similar to the Finnish study above. A group in Italy[13] followed 158 individuals, median age 45 years, with ICA for the development of T1DM. The mean time between enrollment in the study, being ICA positive, and the development of T1DM was 4.8 years. The investigators looked at factors associated with faster progression to development of T1DM in autoantibody-positive individuals. They found those with a family history of T1DM, family history of other autoimmune diseases and a younger age may progress to T1DM more quickly than others who had the same autoantibodies at the time of enrollment in their study.

We hypothesized that there may be a 2-4 year lag between exposure to a number of different agents causing insult to the islet cells and the development of T1DM. We attempted to determine whether clusters of cases of T1DM were detected 2-4 years after administration of vaccines other than the hemophilus vaccine.

## METHODS

MEDLINE was searched to locate publications on the incidence of T1DM in children age 0-14 years living in industrialized Western nations. Key words used in the MEDLINE search were *diabetes*, *insulin* and *incidence*. References listed in papers found in MEDLINE were used to find additional texts on the subject. We prospectively planned to include only papers on Caucasian populations from Western European countries, the United States, Canada, Australia, and New Zealand, because we felt the standards of living and medical care of the Caucasian populations in these countries were similar, and our previous studies had revealed an effect in children living in these countries. We limited our search to papers containing incidence data primarily from 1975 to the present and containing at least 100 patients with T1DM in the study population.

After we identified countries with data meeting the criteria mentioned above, a MEDLINE search was performed to determine whether changes in

that there were approximately 60,000-83,000 children born in Finland each year between 1965-1996[15].

## RESULTS

### Rise in the incidence of T1DM in Finland following introduction of more potent pertussis vaccine

The pertussis vaccine has been given in Finland according to a four-dose regimen starting at 3 months of age with the last booster dose given before 24 months[16]. The incidence of DM was stable in the 1-4 year-old age group in Finland from 1966-1977 at around 15 cases/100,000 per year. In November 1974, a large clinical trial was started in Finland testing a non-conjugated hemophilus vaccine against a non-conjugated meningococcal vaccine. The study vaccinated approximately 100,000 children between the ages of 3 months and 5 years, or about 25% of all children in Finland of this age[17]. Measles immunization was started in Finland

was performed to determine whether changes in immunization practices with the pertussis, diphtheria, tetanus, hepatitis B, polio, hepatitis A, chickenpox, measles, mumps and rubella, BCG, and influenza vaccines occurred during the time frame covered by the diabetes registry. We contacted several sources to determine the details of the discontinuation of the BCG vaccine in Denmark. These included the National Board of Health in Denmark, Statens Serum Institut, World Health Organization, and others.

**Statistical analyses**

Relative risks and other calculations were made using Epi 6 software (WHO). A 2x2 table with an uncorrected $\chi^2$ test was used. Taylor series 95% confidence limits were used. Figures on the relative risk were rounded to the nearest tenth. Regarding the BCG analysis, statistics pertaining to the decline in incidence of T1DM in Denmark were described earlier[14]. Spearman rank order correlation was performed using the software Statitistica and all 12 pairs of data points from Figure 2. Relative risks were calculated for Finnish populations assuming there were at least 60,000 children born each year. This is a conservative estimate based on data in 1975. The vaccine was offered to all children starting at 1 year of age. Immunization rates were about 70% nationally[18]. In 1976, the pertussis vaccine was made more antigenic by the addition of a second strain of bacteria[19]. Approximately 2-3 years after the addition of the more potent pertussis vaccine, a 52% rise in T1DM occurred[20]. The incidence rose to 23 cases/100,000 and remained stable from 1978-1986, with a relative risk of 1.52 ($1.34<RR<1.73$) (Fig. 1A).

A birth cohort analysis was performed comparing the cumulative incidence of T1DM in those born between 1976 and 1980 who received the new pertussis vaccine, to children born between 1973 and 1975, before the new pertussis vaccine was available. Many children in the latter group were eligible to receive the new pertussis vaccine as part of a booster dose at age 18-24 months. Children in the 1973-1975 cohort, based on their birth date, may have received the hemophilus/ meningococcal vaccine given in 1974[17]. All children would have been eligible to receive the measles vaccine but at different ages. Data on the cumulative incidence of T1DM in these cohorts was made available from an unrelated study[21]. The cumulative incidence in children aged 0-4 years in the two cohorts was

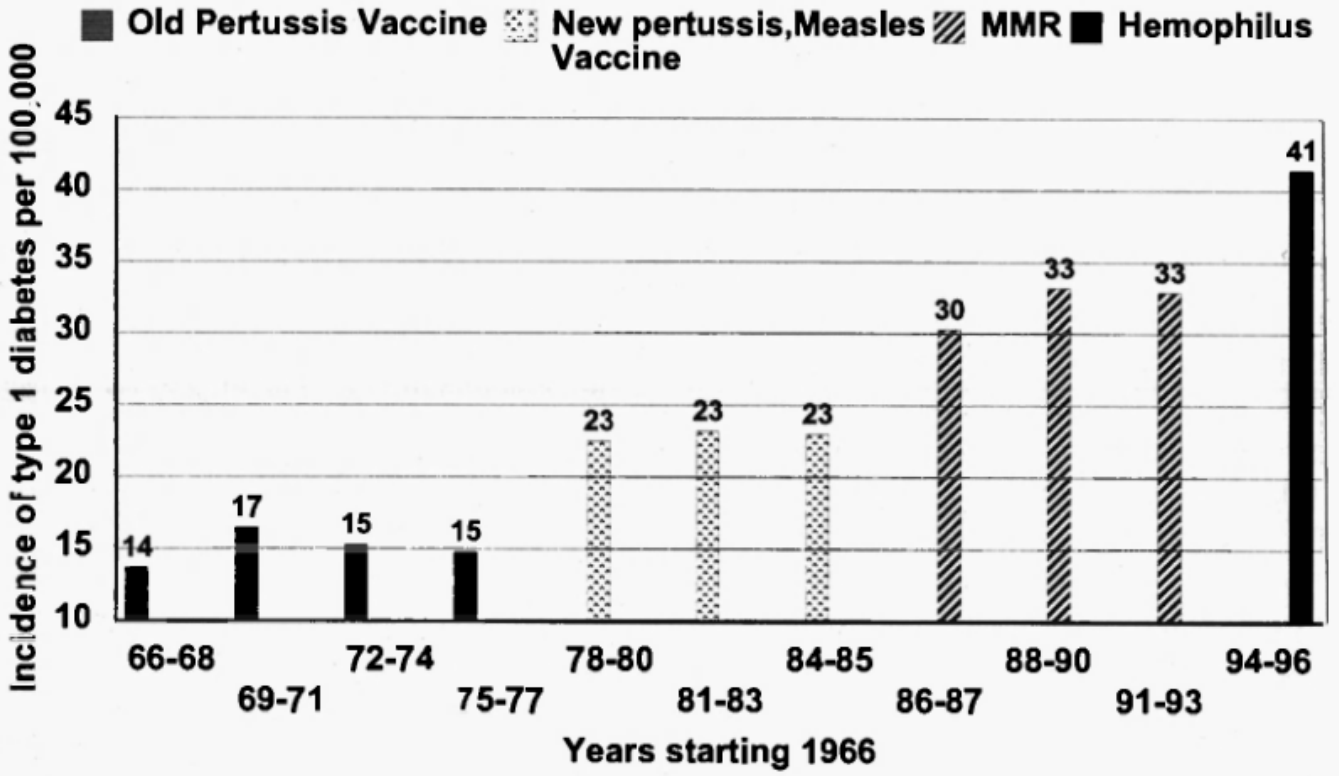


**Fig. 1A:** In 1976 the Finnish government started immunizing children with a more antigenic pertussis vaccine. The incidence of T1DM rose in children aged 1-4 years about 3 years after the introduction of this new vaccine. The vaccine regimen in Finland was altered to replace the measles vaccine with the measles-mumps-rubella vaccine and given at age 14 months. The incidence of T1DM which had been stable again rose in a step-like fashion several years after the introduction of the vaccine. Another step-like rise in the incidence of T1DM occurred after the introduction of the Hemophilus vaccine.

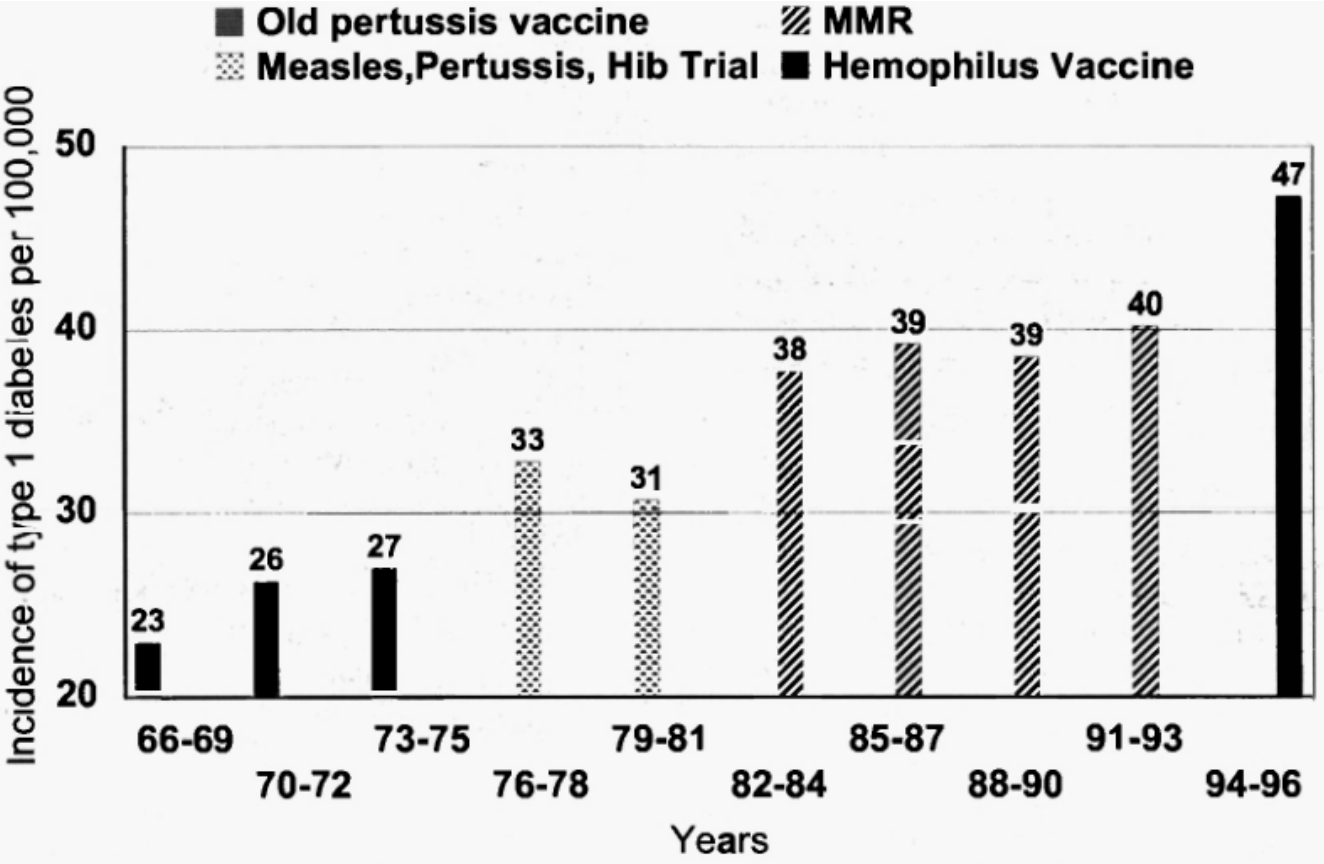


**Fig. 1B:** The incidence of T1DM in Finnish children age 5-9 was stable below an incidence of 27 patients/100,000 in the years 1966-1975. The incidence increased in a step-like manner in the years 1976-1981 after the introduction of a more potent pertussis vaccine and measles vaccine and children in a Hemophilus vaccine trial started to reach age 5 years. The incidence of T1DM rose in a step-like fashion again and formed a plateau from 1982 to 1993 after the introduction of the MMR vaccine. Another step-like rise in the incidence of T1DM occurred after the introduction of the Hemophilus vaccine.

found to be 82 cases/100,000 and 102.9 cases/100,000, respectively ($p < 0.05$), relative risk 1.25.

**Decline in the incidence of T1DM during UK pertussis vaccine scare**

During the period of 1975-1979, immunization with the pertussis vaccine dropped in several countries, including the UK, following a published report that the pertussis vaccine caused brain damage in children[22]. In the UK, the acceptance rate of the pertussis vaccine fell from 77% in 1974 to 31% in 1978[23,24]. Data from Yorkshire[25] showed a drop in the incidence of T1DM in children aged 0-4 years which reached a trough in 1982, 3-4 years after the trough in immunization rate with the pertussis vaccine. The incidence of T1DM declined from 9.5 cases of T1DM/100,000 in 1979 to approximately 6.5 in 1982, and rose again to 9.8 in 1985. This is consistent with a relative risk of 1.46 (Spearman rank order correlation $p = 0.0082$ using all 12 pairs of data points) (Fig. 2). The rise in T1DM correlated with the rise in immunization rate. Between 1979 and 1986, the immunization rate went up 75% and the incidence of T1DM rose 85% from 1982-1989[24].

**Measles, mumps, rubella vaccine: Finland**

The vaccine regimen in Finland was altered by replacing the measles vaccine with the measles, mumps, rubella (MMR) vaccine at age 14 months and 6 years in 1982[21]. Analysis of incidence data in children aged 1-4 years shows the incidence of T1DM was stable at a yearly rate of about 23 cases/100,000 from 1977-1985[15] (Fig. 1A). The rate rose to 33 cases/100,000 starting in 1986, a relative risk of 1.40 ($1.25 < RR < 1.57$), and remained elevated. The delay in the rise of T1DM is consistent with a delay between exposure and the development of T1DM of about 2-4 years.

The incidence of T1DM also rose in the age group 5-9 years after the introduction of the MMR vaccine in 1982. The incidence of T1DM varied from 31-33 cases/100,000 between the years 1976 and 1981, but stabilized at approximately 39 cases

T1DM correlated with the rise in immunization and 1981, but stabilized at approximately 39 cases

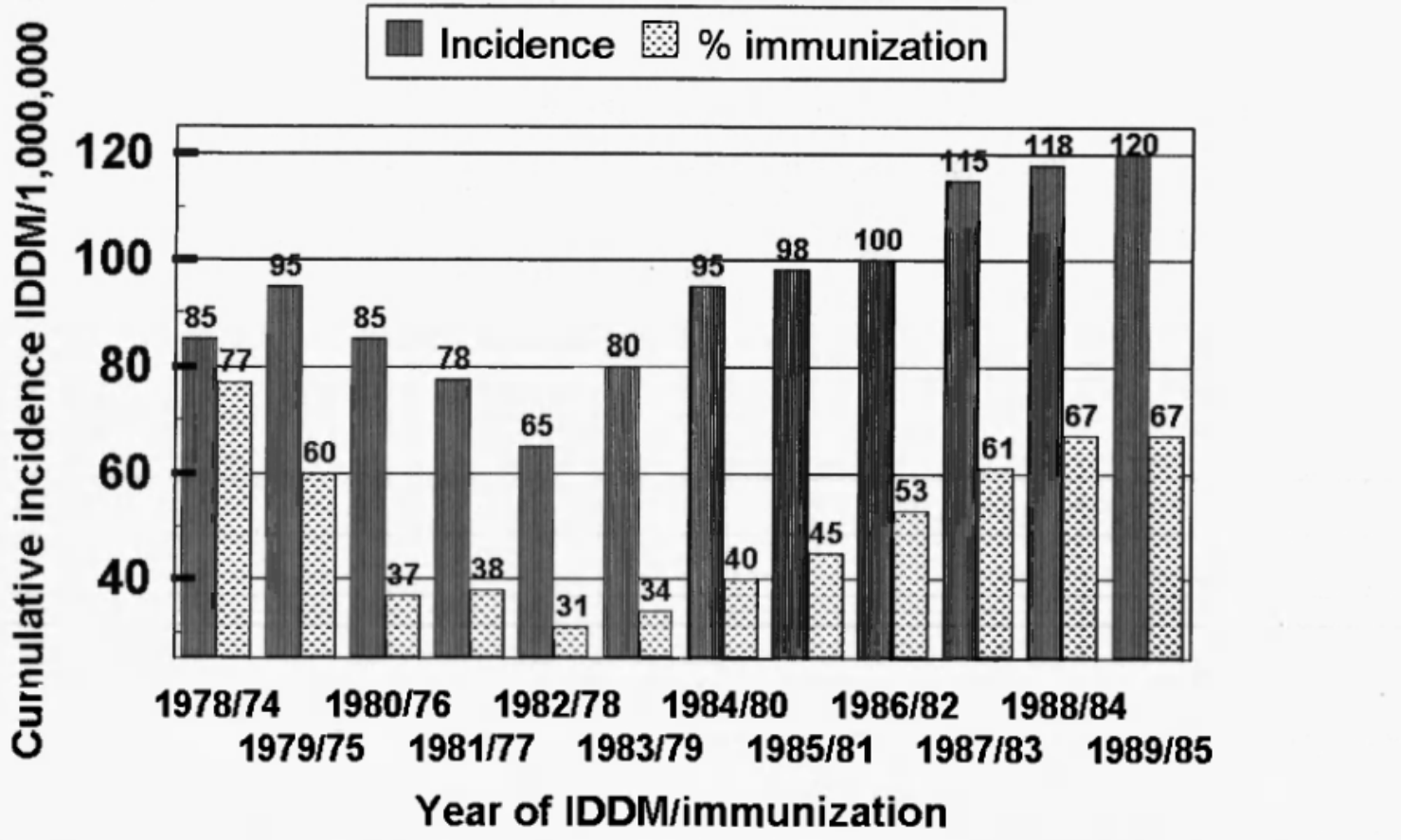


**Fig. 2:** During the period from 1974 to 1978 immunization with the pertussis vaccine dropped in the UK. Data from Yorkshire showed a drop in the incidence of T1DM in children aged 0-4 years that reached a trough in 1982, 4 years after the trough in immunization rates with the pertussis vaccine. The incidence of T1DM went from 9.5 patients with T1DM/100,000 in 1979 to approximately 6.5 in 1982 and back to 9.8 in 1985.

/100,000 from 1982-1993, relative risk 1.22 (1.11<RR<1.35) (Fig. 1B). The children born in 1976-1981 had received or been offered the measles vaccine. Comparison of the children exposed to the MMR vaccine, children living in the years 1982-1993, to children who were not exposed to the measles vaccine, children living in the years 1966-1975, indicates the incidence of T1DM had risen to 39 cases/100,000 from 26 cases/100,000, respectively, indicating a relative risk of 1.53 (1.39<RR<1.67).

**Measles, mumps, rubella vaccine: UK**

The measles vaccine was replaced by the MMR in the UK starting in 1988 and given to children around 18 months of age[26]. The yearly incidence in children[27] rose from approximately 10 cases per year to 15 cases per year, relative risk of 1.48 ($p = 0.01$), (1.09<RR<2) (Table 1). The rise in incidence of T1DM occurred approximately 2-3 years after the introduction of the vaccine.

**BCG vaccine**

The BCG vaccine was routinely given to school-children in Denmark starting at age 7 years. In 1989, the first county in Denmark officially stopped BCG immunization. BCG was removed from the list of government-funded vaccines in 1990, and other counties officially stopped BCG immunization between 1990 and 1992. However, BCG immunization may have declined prior to the official discontinuation. The last available data provided to the WHO indicate an 85% immunization rate in 1985[28]. No additional information on immunization rates was available.

Data on the incidence of T1DM in children aged 0-14 years in four counties in Denmark (Fyn, Ribe, Sønderjylland and Vejle) in the years 1989-1993 have been published[29]. Additional information on the incidence in the year 1994 was published separately[14] in a paper which also included information on the incidence of T1DM from 1989-1994 in 28 additional countries. The publication on the

**TABLE 1**

Effect of measles-mumps-rubella (MMR) vaccine on type 1 diabetes mellitus in children aged 0-4 years, UK

| | Year | Incidence | |
|---|---|---|---|
| | 1986 | 9 | |
| | 1987 | 7 | |
| | 1988 | 12 | |
| **Pre-MMR effect** | 1989 | 12 | AVG.: 10 |
| | 1990 | 16 | |
| | 1991 | 15 | |
| | 1992 | 14 | |
| **MMR effect** | 1993 | 14 | AVG.: 14.75 |
| | 1994 | 21 | |
| **HiB effect** | 1995 | 19 | |

Yearly population aged 0-4 years: 178,700.
Relative risk of 1.48 ($p = 0.01$) ($1.09 < RR < 2$).

**TABLE 2**

Effect of BCG vaccine on the incidence of type 1 diabetes mellitus in Denmark

| Year | Cases | Population | Incidence/100,000 | Source |
|---|---|---|---|---|
| 1989 | 44 | 230,524 | 18.6 | Published |
| 1990 | 47 | 228,535 | 19.8 | Published |
| 1991 | 38 | 227,063 | 16.6 | Published |
| 1992 | 34 | 226,580 | 14.9 | Published |
| 1993 | 38 | 228,172 | 16.8 | Published |
| 1994 | 20 | 227,000 | 8.8 | Calculated |

trends of T1DM in Europe[14] shows Denmark, and only Denmark out of 29 countries, had a statistically significant drop in the incidence of T1DM during the interval 1989-1994. The incidence of T1DM in Denmark dropped from 18.6 in 1989 to 8.8 in 1994 (Table 2). The incidence of T1DM

lasting 6 months or more[1]. There were insufficient data to determine whether clusters of T1DM occur after immunization with the polio, varicella, diphtheria, tetanus, hepatitis A, Lyme's disease, and influenza vaccines. We detected declines in the incidence of T1DM following discontinuation of

declined 9% per year during this 6-year interval ($p = 0.02$), assuming a linear decline[14]. The trough in the incidence of T1DM occurred about 4 years after the national BCG vaccination programme was stopped.

Estimates of the relative risk of the BCG varies from 2.1 to 1.6 depending on the method of calculation. If one uses the incidence data in 1994 (8.8 cases/100,000) as the unimmunized incidence, and the incidence data in 1989 (18.6 cases/100,000) as the immunized incidence, the relative risk is 2.17 ($1.28<RR<3.68$) ($p = 0.003$). The relative risk, based on the incidence of T1DM declining by 9% per year during the time frame 1989-1994[14], is 1.61 ($1/0.91^5$).

## DISCUSSION

We found that there were clusters of extra cases of T1DM associated with the MMR, pertussis, and BCG vaccine that occurred 2-4 years following immunization. These data are consistent with data from a large clinical trial on the hemophilus vaccine that demonstrated clusters of extra cases of T1DM starting 38 months after immunization and pertussis and BCG vaccines, which are quite notable observations, since numerous papers have indicated the incidence of T1DM is rising throughout the world[14,30].

Our findings of clusters of T1DM after immunization are consistent with papers from several different groups indicating clusters of cases of T1DM occurring 2-4 years following mumps epidemics[2-5] and varicella epidemics[6]. The clustering of cases of T1DM occurring after vaccination is also consistent with studies on the progression of T1DM in autoantibody-positive individuals. In several prospective studies, the mean or median time between the detection of autoantibodies and the development of T1DM has been around 3 years[7-11].

The similarities in temporal delay between either infection or immunization and the onset of T1DM compared to the progression of autoantibody positive patients to develop T1DM may be explained by the ability of infections and vaccines to induce the development of autoantibodies. Natural infection with mumps has been linked to the development of ICA[31,32]. Immunization at birth with BCG vaccine has been associated with decreased risk of DM in humans[33] and has recently

been associated with decreased GAD65 and IA-2 autoantibodies[34]. The hemophilus vaccine, which has been shown to cause DM in humans[1], was evaluated in a case control study using autoantibodies in high-risk children[35]. While the case control study was small and the results were not statistically significant, the odds ratio was similar to that seen in the clinical trial with the hemophilus vaccine[1]. ICA were also found to develop in three of 239 10 year-old girls following rubella vaccination[36]. Furthermore, vaccines can cause DM in NOD mice, an animal model of T1DM[1]. Autoantibody titers, especially with antibodies to insulin, are strongly associated with the development of DM in mice[37].

While vaccines may induce T1DM through the induction of autoantibodies, proper studies have not been performed to address this. The studies to date have been too small to detect a statistically significant association. A German group[38] performed an almost identical study to that performed by Graves *et al.*[25]. The case control study involved 29 patients with a single autoantibody associated

showed abnormal glucose tolerance at the time of enrollment in the study had developed DM by 6 years compared to about 55% who had normal glucose tolerance at the beginning of the study[40]. This may explain our epidemiology data that indicated the hepatitis B vaccine was associated with rises in the incidence of T1DM starting about 1 year after immunization in New Zealand[33].

There are likely many cases of vaccine- or infection-induced T1DM in which the onset of DM occurs more than 4 years after immunization. In an analysis of a hemophilus vaccine clinical trial there were an extra six cases/100,000 that occurred between ages 7-10 years in the group receiving the booster dose of hemophilus vaccine at age 2 years of age compared to the controls[1]. These extra cases of T1DM occurred after the cluster. Prospective studies of autoantibody positive patients show that while most of the patients who progress to T1DM do so before 5 years there are patients who progress to T1DM up to 10 years later[7,8,12,13]. These findings are consistent with a delayed, or slowly progressive autoimmune disease, which appears more com-

29 patients with a single autoantibody associated with the development of T1DM, and 251 controls. Only four children actually developed DM. It is well known that a single autoantibody has very low specificity for predicting the development of T1DM[39]. Patients were followed for as little as 2 years after birth. The controls were not well matched by age to the cases. The controls appear to be older, thus likely to have received more vaccines solely because they are older. The study thus contains some of the same flaws as the study by Graves *et al.*

The 2-year delay between infection or immunization and the development of the cluster is consistent with a progressive autoimmune disease. The data suggest that in most individuals with a healthy pancreas it would take at least 2 years for autoimmunity to destroy enough islet cells for the person to become diabetic. In older groups containing individuals whose beta-cells may have been partially destroyed by prior insults, it would be expected that some individuals would develop DM soon after immunization or infection. Support for this theory is supplied by data from a US study that followed the development of T1DM in autoantibody positive patients. Over 90% of patients who

autoimmune disease, which appears more commonly in studies of older individuals. These findings are also consistent with blood tests showing many older individuals initially diagnosed as having type 2 DM have autoantibodies to their islet cells and actually have a latent autoimmune, T1DM. These individuals often require insulin years after their initial diagnosis[41,42]. It is not known why older individuals are likely to have a more slowly progressive disease. Data indicate individuals with the high-risk genes develop a rapidly progressive autoimmune disease resulting in T1DM very early in life, while others who have moderate-risk genes have a slower progressive autoimmune disease and develop T1DM later in life[10]. In the latter case the autoantibodies may be less cytotoxic or the islet cells may have enhanced repair mechanisms.

There may be differences between the ability of vaccines to induce T1DM and natural infections[43]. Vaccines often contain aluminum and other ingredients that differentiate them from natural infections. Immunization with killed vaccines instantaneously exposes the immune system to a large bolus of immunogen intramuscularly, while with natural infections the body is gradually exposed to increasing amounts of immunogen as

the organism crosses the mucous membrane and divides. Another difference between natural infections and vaccines is that exposure to natural infections occurred for hundreds of generations prior to the existence of insulin therapy. This would have allowed natural selection to take place, and the genes for susceptibility to DM following natural infections to be removed from the gene pool. This would explain why studies have found a certain infectious agent to be diabetogenic in some populations, and not in others. For example, this could explain discrepancies in studies showing effects and lack of effects by Coxsackie viruses.

The current findings of clusters following immunization are compatible with smaller published studies which are too small and not powered to detect the findings we describe. Our data indicate the MMR vaccine is associated with a relative risk of between 1.43 and 1.5: 1.43 (Finland, age 1-4 years), 1.5 (Finland, age 5-9 years), 1.5 (UK, age 0-4 years) over a 4-5 year interval. A large case control study in the US[44] found the MMR vaccine was associated with an odds ratio of 1.43 or 1.36, children not receiving MMR vaccine (born 1973-1975) was 113.5 cases/100,000 compared to the incidence in children receiving the MMR vaccine which was 121.7 cases/100,000, a relative risk of 1.07. Our results differ from those of Hyoty *et al.* in part because in the latter study, children were not followed for a full 4 years following immunization, which decreases the relative risk. The children immunized at age 1 year were followed for about 3 years, until age 4 years, while children immunized at age 6 years were only followed for less than 3 years following immunization.

Blom *et al.*[46] presented data that the MMR vaccine may be associated with a protective effect for T1DM, odds ratio 0.69, with confidence interval between 0.48 and 0.98. The presumed mechanism is that immunization with the live attenuated virus protected children from natural infections with the virulent natural viruses. The authors did not look specifically at those children who were not immunized and did not get infected since these people may be at an increased risk of developing T1DM. This study is extremely difficult to interpret because

depending on compensation of confounding variables. A European multicenter case control study[45] indicated the measles, mumps, and rubella vaccines are associated with odds ratios of 1.02, 1, and 1.18, respectively. The same study, using multivariate analysis, found that the vaccines were associated with odds ratios of 1.1, 1.03, and 1.27, respectively. The combined effect would be an odds ratio of 1.44 (1.1*1.03*1.27) adjusting for confounding variables, or 1.2 (1.02*1*1.18) without adjustments. Neither study was powered to reach statistical significance.

A birth cohort study was performed by Hyoty *et al.* looking at the effect of the MMR vaccine on the incidence of T1DM in Finland[21]. Children immunized at age 1 year were followed for development of T1DM from birth to age 4 years. The cumulative incidence of T1DM in children not receiving MMR (born 1973-1975) was 82 cases/100,000 compared to the incidence in children receiving MMR (born 1981-1983) which was 110.6 cases/100,000, a relative risk of 1.35. Children immunized at age 6 years with the MMR vaccine were followed for the development of T1DM between ages 7 and 9 years. The cumulative incidence of T1DM in it did not evaluate the confounding effects of other vaccines. For example, 86% of children with DM who were asked to participate entered the study, whereas only 67% of controls who were asked to participate did so. The result is that the actual controls that entered the study may not have been well matched to the actual group of children with DM who entered the study.

Our data indicate a statistical and clinically significant decline in the incidence of T1DM following the discontinuation of the BCG vaccine in Denmark. This decline in incidence is very significant since Denmark is the only country out of the 29 to show a statistically significant decline during this time frame[14]. The estimate of a relative risk of 2.17 associated with the BCG vaccine in Denmark is remarkably close to the published relative risk of 1.74 based on ecological data[33] comparing the incidence of T1DM in Western European countries which did not give the BCG vaccine to countries that gave the vaccine at school age.

The results from Denmark are also remarkably close to an odds ratio of 2.0 based on data from a Canadian case control study[47,48]. This paper from

Montreal[48] contains two separate case control studies, series A and B. Series B analyzed cases of T1DM in 0-18 year-olds prospectively enrolled between 1982 and 1986. Series A pertains to a retrospective analysis of children aged 7 years or older. The authors concluded that there was no effect of the BCG vaccine on the development of T1DM. The analysis was flawed, however, because it did not consider the effect of the timing of the first dose of BCG vaccine on the development of T1DM. Immunization with BCG at birth is associated with a decreased risk of T1DM, while immunization starting at school age is associated with an increased risk of T1DM[33]. Sufficient data were not available from this paper to determine how many children immunized in the first year of life were actually immunized in the first month of life. However, analysis of cases and controls indicates the BCG immunization is associated with an increased risk of T1DM when started after 1 year of life. Series B analyzed 249 patients with T1DM and 431 matched controls age 0 through 18 years. The authors found 14 of 249 diabetics had

associated with an increased risk of T1DM. Our studies found the pertussis vaccine is associated with a relative risk of 1.5 (Finland, age 1-4 years) and 1.46 (UK, age 0-4 years). The potential effect of the pertussis vaccine may be larger if one considers that the UK study underestimates the effect of the pertussis vaccine because the relative risk assumes the pertussis vaccination rate went from 100% to 0% when in fact it went from 77% to 31%. The Finnish study may have also underestimated the effect of the pertussis vaccine because the study measured the effect of switching from a weaker vaccine to a more potent vaccine. The Finnish study was confounded by the start of measles immunization in Finland in 1975. The birth cohort analysis, however, indicates that the measles vaccine is unlikely to explain the majority of the effect seen because children in the 1973-1975 as well as the 1976-1980 birth cohort both received the measles vaccine. Several case control studies[45,46] indicate the measles vaccine alone is not associated with a relative risk greater than 1.1.

The effect of the diphtheria-tetanus-pertussis

received BCG immunization after 1 year of life versus 12 of 431 controls, odds ratio 2 ($p = 0.06$). Data from Series A were incomplete and not easily analyzable.

Dahlquist and Gothefors[49] published Swedish data and concluded that the BCG vaccine does not alter the incidence of T1DM. Re-analysis of the data[33,50] indicates that immunization at birth with BCG is associated with a clinically significant reduction in T1DM. The concern with the analysis of the results of the study by Dahlquist and Gothefors is that it fails to acknowledge that the smallpox vaccine was discontinued in 1976 in Sweden, while the BCG vaccine was discontinued in 1975. The smallpox vaccine was administered in Sweden primarily at 2 months or 9 months of age[51,52] as compared to the BCG vaccine which was administered at birth. Data from rodent and human studies[1] show that vaccines administered starting after 2 months of life increase the incidence of T1DM, thus having the opposite effect of administering vaccines at birth[33]. The Swedish BCG data need to be analyzed in such a way as to compensate for the confounding effect of the smallpox vaccine.

Our results indicate pertussis immunization is

(DTP) vaccine on T1DM was studied in Sweden[46]. The study involved comparing the incidence of T1DM in birth cohorts that received a DTP vaccine lacking an aluminum adjuvant, 1977 and 1978 birth cohorts, to birth cohorts receiving a DT vaccine containing an aluminum adjuvant, birth cohorts 1980 and 1981. Both groups appeared to have similar rates of T1DM. The analysis was flawed because the MMR vaccine was started at about the same time that the pertussis vaccine was discontinued in Sweden[46]. The 1977 and 1978 birth cohorts received the pertussis vaccine but did not receive the MMR vaccine at age 18 months. The 1980 and 1981 birth cohorts did not receive the pertussis vaccine but did receive the MMR vaccine at age 18 months as well as an aluminum-based adjuvant that the 1977 and 1978 birth cohort did not receive. The results indicate the pertussis vaccine had an effect similar to the aluminum adjuvant and the MMR vaccine. Based on this study, it is not possible to compare the effect of the aluminum adjuvant to the pertussis vaccine. It is likely that both the aluminum adjuvant and the pertussis vaccine increase the risk of DM because both are immune stimulants[43]. If the aluminum

adjuvant increases the risk of T1DM, then the pertussis vaccine has an effect on T1DM which is greater than that of the MMR vaccine.

A seven-center collaborative study looking for an association between vaccines and the development of T1DM[45] reported the pertussis vaccine was associated with a statistically non-significant relative risk of 0.89 (0.71-1.12). The study involved 900 children with DM and 2,302 controls. Data from one center, Austria, were published separately[54]. The vaccinated group in the Austrian center was comprised of those with complete immunization, while the unimmunized group was comprised of people who did not complete the recommended number of shots for a given vaccine. Data on the hemophilus vaccine from Finland[55] indicate that there is likely to be little difference expected in the incidence of T1DM between those receiving three and those receiving four doses of the HiB vaccine since the majority of the effect on T1DM occurs with the first shot. Furthermore, prediabetics may experience more severe acute adverse events following immunization because of their

to cause autoimmune diseases including DM have been extensively reviewed recently[43]. In this paper the role of macrophages in causing T1DM was reviewed. Data published since the release of this paper was written further support the role of macrophages in the development of T1DM and explains why many vaccines will cause DM in a measurable number of recipients. Pancreatic islet cells are now known to secrete a number of chemotactic factors for macrophages[58-62]. It appears that some of the chemotactic factors have secondary biological functions and are actually involved in controlling insulin release[62]. Release of some of these chemotactic factors has been shown to be associated with the destruction of human pancreatic islet cells in islet cell transplants[61] and early onset DM[59]. The production of the chemotactic factors by the islet cells also explains why vaccines, which activate macrophages, would be expected to destroy islet cells. The macrophages, activated by vaccines, circulate in the blood and are induced to migrate to the islet cells, by the chemotactic factors, where they kill islet cells and induce autoimmunity. These

hyperactive macrophages[36,37], thus they may be less likely to complete immunization than people who do not have a propensity for T1DM. Using a case control design similar to that used by the Austrians would give the erroneous interpretation that vaccines are protective against T1DM.

A US case control study[44] found the acellular pertussis vaccine associated with an odds ratio of 0.92 or 1.12, depending on the which regression analysis they used. The whole cell pertussis vaccine was associated with odds ratios of 0.23 and 0.28, depending on the regression analysis. About 30% of children received both the whole cell pertussis vaccine and the acellular pertussis vaccine. Very few children received the acellular pertussis vaccine alone. The data were incomplete, however, since the authors did not show the rates for pertussis immunized versus not pertussis immunized, only the subgroup analysis described above. The study also had the shortcomings of several of the papers above: insufficient power, no adjustment for confounding vaccines, and the possibility of biases due to the likelihood that DM-prone children could have more severe acute vaccine reactions.

Mechanisms by which vaccines have been proven

latest findings explain an observation by Goto *et al.*[63]. They described experiments showing that injections of guinea-pigs with several different vaccines containing aluminum adjuvant caused inflammation of the pancreas[63]. The amount of inflammation in the pancreas correlated with inflammation at the injection site.

The current results will help make it easier to detect associations between vaccines and T1DM. In the past there have been discrepancies in results of studies as to whether vaccines were associated with an increased risk of T1DM. Some of the discrepancy can be explained by the study design used. Our ability to detect an association between vaccines and T1DM can be attributed to our controlling of confounding effects of more than one vaccine and controlling for the timing of immunization. One of the biggest reasons why many others have not demonstrated an association between vaccines and T1DM is lack of power. By narrowing the study interval to just the time of the cluster, one can increase the power of the study, as was shown with the hemophilus vaccine[1]. In the current study the relative risk would increase to greater than 2 if the interval of study were limited to only include

the interval between 2 and 4 years after immunization when the extra cases of T1DM occurred. The relative risk would be smaller if the interval of follow up is extended beyond 4 years. The relative risk would also be decreased if the interval of follow up is shortened so it does not include all the extra cases of T1DM occurring in the cluster spanning the interval 2-4 years after immunization.

The identification of clusters of cases of T1DM occurring in consistent temporal time periods allowed the link between the hemophilus vaccine and T1DM to be established. The current findings indicate that there are also clusters of cases of T1DM occurring 2-4 years post-immunization with the pertussis, MMR, and BCG vaccine. The data are consistent with the occurrence of clusters following mumps infection and the progression to T1DM in patients with antipancreatic autoantibodies. It is hoped that the discovery of these clusters will help speed the discovery of diabetogenic agents and further the understanding of the pathophysiology of T1DM.

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