

## ORIGINAL ARTICLE

## Childhood Vaccination and Type 1 Diabetes

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## ABSTRACT

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**BACKGROUND**

A link between childhood vaccinations and the development of type 1 diabetes has been proposed.

**METHODS**

We evaluated a cohort comprising all children born in Denmark from January 1, 1990, through December 31, 2000, for whom detailed information on vaccinations and type 1 diabetes was available. Using Poisson regression models, we estimated rate ratios according to vaccination status, including the trend associated with the number of doses, among all children and in a subgroup of children who had siblings with type 1 diabetes. Given recent claims of clustering of cases of diabetes two to four years after vaccination, we also estimated rate ratios during the period after vaccination.

**RESULTS**

Type 1 diabetes was diagnosed in 681 children during 4,720,517 person-years of follow-up. The rate ratio for type 1 diabetes among children who received at least one dose of vaccine, as compared with unvaccinated children, was 0.91 (95 percent confidence interval, 0.74 to 1.12) for *Haemophilus influenzae* type b vaccine; 1.02 (95 percent confidence interval, 0.75 to 1.37) for diphtheria, tetanus, and inactivated poliovirus vaccine; 0.96 (95 percent confidence interval, 0.71 to 1.30) for diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine; 1.06 (95 percent confidence interval, 0.80 to 1.40) for whole-cell pertussis vaccine; 1.14 (95 percent confidence interval, 0.90 to 1.45) for measles, mumps, and rubella vaccine; and 1.08 (95 percent confidence interval, 0.74 to 1.57) for oral poliovirus vaccine. The development of type 1 diabetes in genetically predisposed children (defined as those who had siblings with type 1 diabetes) was not significantly associated with vaccination. Furthermore, there was no evidence of any clustering of cases two to four years after vaccination with any vaccine.

**CONCLUSIONS**

These results do not support a causal relation between childhood vaccination and type 1 diabetes.

THE INCIDENCE OF TYPE 1 DIABETES mellitus is increasing in developed countries.<sup>1</sup> This fact — taken together with the seasonal variation in the incidence of the disease, differences in incidence between genetically similar populations including monozygotic twins, and epidemiologic studies showing that migration changes the risk of type 1 diabetes according to the country of residence — suggests that environmental factors have an important role in the development of type 1 diabetes.<sup>2-4</sup>

A link between childhood vaccinations and the development of type 1 diabetes has been proposed for several reasons. First, there is a temporal association between the widespread introduction of general childhood immunizations and the increase in the incidence of type 1 diabetes in developed countries. Second, it has been observed that specific vaccines prevent type 1 diabetes in murine models and others induce it. And third, some findings suggest an association between infections and type 1 diabetes.<sup>2</sup> In particular, it has been hypothesized that any vaccination after two months of age increases a person's risk of type 1 diabetes and that early vaccination (in the first month of life) protects against type 1 diabetes.<sup>5-7</sup> Vaccination against *Haemophilus influenzae* type b has been singled out, with claims of clustering of cases of type 1 diabetes three to four years after vaccination.<sup>8</sup> This hypothesis has recently been expanded to include bacille Calmette–Guérin vaccine; measles, mumps, and rubella (MMR) vaccine; and pertussis vaccine.<sup>9</sup> However, the majority of the evidence does not provide support for these specific hypotheses or for any other association between type 1 diabetes and childhood vaccination, yet there have been few analytic studies.<sup>2,10,11</sup>

We evaluated the relation between type 1 diabetes and routinely administered childhood vaccines in a cohort comprising all children born in Denmark from 1990 through 2000, with longitudinal information on the type and the number of doses of vaccine received and the possible diagnosis of type 1 diabetes. Vaccines against *H. influenzae* type b, diphtheria, tetanus, poliovirus, pertussis, measles, mumps, and rubella were evaluated with respect to the development of type 1 diabetes among all children and among a subgroup of children who had a sibling with type 1 diabetes. In a further analysis, we examined the cohort to see whether there was an excess of cases of type 1 diabetes during specific periods after vaccination.

## METHODS

Since April 1968, people living in Denmark have been given a unique identification number in the Danish Civil Registration System.<sup>12</sup> Using this registry, we constructed a cohort of all children born in Denmark from January 1, 1990, through December 31, 2000. Using these unique personal identification numbers, we were able to link information on vaccinations, the diagnosis of type 1 diabetes, the presence or absence of siblings with type 1 diabetes, and potential confounders to the children in the cohort. The use of registries containing information on individual subjects was approved by the Danish Data Protection Agency.

### VACCINATIONS

During the study period (1990 through 2001), Denmark had a nationwide policy of vaccinating children against pertussis, measles, mumps, rubella, diphtheria, tetanus, poliovirus, and *H. influenzae* type b. Table 1 provides an overview of the vaccines and schedules used in this period. The dates of vaccination with the first, second, or third dose of the vaccines were obtained from the National Board of Health. We did not obtain information on the second dose of the MMR vaccine, since administration of the second dose is recommended at 12 years of age, or on the diphtheria–tetanus booster, since the booster was introduced in January 1996 and administration is recommended at 5 years of age. In Denmark childhood vaccinations are administered solely by general practitioners, who are reimbursed when they report these data to the National Board of Health. The National Board of Health has kept a register of these reports since 1990. Data on the MMR vaccine have been available only since September 1991, and thus, children born in 1990 were classified as having unknown MMR vaccine status.

### TYPE 1 DIABETES

Information on the diagnosis of type 1 diabetes from January 1, 1990, through December 31, 2001, was obtained from the Danish National Hospital Register.<sup>13</sup> From 1990 through 1993, Denmark used a modified version of the *International Classification of Diseases, 8th Revision* (ICD-8). From 1994 through 2001, the *International Classification of Diseases, 10th Revision*, was used. We used codes 249 and E10 (the code 249 does not exist in the standard World Health Organization version of the ICD-8) to iden-

**Table 1. Overview of Childhood Vaccines Used in Denmark from 1990 through 2001.**

| Vaccine   | Period Used                         | Schedule  | Composition  |
|---|-------------------------------------|---|--|
| <i>Haemophilus influenzae</i> type b                      | June 1993–1995<br>1996<br>1997–2001 | 5, 6, and 16 mo of age*<br>5, 6, and 15 mo of age<br>3, 5, and 12 mo of age | Capsular <i>H. influenzae</i> type B polysaccharide conjugated to tetanus toxoid           |
| Diphtheria, tetanus, and poliovirus†                      | 1990–1996                           | 5, 6, and 16 mo of age  | Diphtheria and tetanus toxoids and inactivated poliovirus                                  |
| Diphtheria, tetanus, acellular pertussis, and poliovirus† | 1997–2001                           | 3, 5, and 12 mo of age  | Diphtheria, tetanus, and pertussis toxoids and inactivated poliovirus                      |
| Whole-cell pertussis                                      | 1990–1996                           | 5 wk (½ dose), 9 wk, and 10 mo of age                                       | Inactivated whole-cell pertussis   |
| Measles, mumps, and rubella                               | 1990–2001                           | 15 mo of age and 12 yr of age   | Live, attenuated measles (Moraten), mumps (Jeryl Lynn), and rubella (Wistar RA 27/3) virus |
| Oral poliovirus   | 1990–2001                           | 2, 3, and 4 yr of age   | Live, attenuated poliovirus (trivalent)  |

\* Catch-up vaccination was initially offered to older children.

† The use of a diphtheria–tetanus booster at five years of age was introduced in January 1996.

tify all cases of type 1 diabetes. Beginning in 1995, visits to the emergency room and outpatient visits were included in the National Hospital Register.

#### HISTORY OF TYPE 1 DIABETES AMONG SIBLINGS

Information on a person's mother and father is potentially available for each person in the Danish Civil Registration System. We used this information to identify siblings. We defined siblings as children having the same mother. Information on the diagnosis of type 1 diabetes among siblings who were 0 to 14 years of age in the period from January 1, 1997, through December 31, 2001, was obtained from the Danish National Hospital Register, with the use of the above-mentioned diagnostic codes. Before January 1987, only one diabetes code (250) existed. Consequently, siblings who received a diagnosis of code 250 before January 1, 1987, and code 249 or E10 thereafter were considered to have type 1 diabetes.

#### POSSIBLE CONFOUNDING FACTORS

The following information on possible confounding factors was obtained from the Danish Civil Registration System, the Danish Medical Birth Registry,<sup>14</sup> and the National Hospital Register: the child's place of birth (Copenhagen; Copenhagen suburbs; an area with at least 100,000 population; an area with a population of 10,000 to 99,999; or an area with a population of less than 10,000), the child's birth weight (less than 2500 g, 2500 to 2999 g, 3000 to 3499 g, 3500 to 3999 g, or 4000 g or more),

the mother's country of birth (Denmark or other), and the mother's age at the birth of the child (less than 20 years, 20 to 24 years, 25 to 29 years, 30 to 34 years, 35 to 39 years, or 40 years or greater). The percentage of missing values for the variables of child's birth weight, child's place of birth, and mother's country of birth were 5.2 percent, 0.03 percent, and 0.5 percent, respectively.

#### STATISTICAL ANALYSIS

Children in the cohort were followed from birth until December 31, 2001, or until they received a diagnosis of type 1 diabetes, died, were lost to follow-up or emigrated, or reached 12 years of age, whichever occurred first. The resulting incidence rates for type 1 diabetes were analyzed with the use of Poisson regression (log-linear regression on the incidence rates with the use of the logarithms of the follow-up times as offsets), which yielded estimates of rate ratios according to vaccination status.<sup>15</sup> Vaccination status (the receipt of zero, one, two, or three doses of any vaccine) was considered a time-varying variable — that is, the children could contribute person-years in the cohort as both unvaccinated and vaccinated subjects. The presence of siblings with type 1 diabetes was also considered a time-varying variable. Thus, children contributed person-years as children who had a sibling with type 1 diabetes only after a sibling received a diagnosis of type 1 diabetes, and not before.

We estimated the dose–response relation between vaccination and the development of type 1

diabetes as the increase in the rate ratio per dose (or per 0.5 ml in the case of the whole-cell pertussis vaccine). We determined whether there was clustering of cases of type 1 diabetes in the period after vaccination by subdividing this period (the first, second, third, or fourth years after vaccination and more than four years after vaccination).

We adjusted all rate ratios for the child's sex, the child's age (in six-month intervals), and the calendar period (in one-year intervals). In an additional analysis, we further adjusted rate ratios for the receipt of other vaccines (children were categorized as either unvaccinated or vaccinated with at least one dose), with the exception that the diphtheria, tetanus, and inactivated poliovirus vaccine; the diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine; and whole-cell pertussis vaccine were not mutually adjusted for, owing to their strong intercorrelation. We also adjusted rate ratios for the potential confounding variables previously listed. In the analysis of the association between type 1 diabetes and vaccination among children who had siblings with type 1 diabetes, we also included the number of siblings as a time-varying variable.

Variables were identified as confounders in the analysis of the association between vaccination and type 1 diabetes if they changed the dose-specific rate ratios among all children by more than 10 percent. When adjusting for the potential confounding effect of variables with missing values, we used the method of single imputation, replacing a missing value with the most common value.

## RESULTS

A total of 739,694 children were included in our cohort. During 4,720,517 person-years of follow-up, we identified 681 cases of type 1 diabetes. Of these, 26 cases during 4208 person-years were among children who had a sibling with type 1 diabetes.

The follow-up of 16,421 children was prematurely terminated because of death in 5131 children, emigration in 11,057, or loss to follow-up in 233. The mean ( $\pm$ SD) age at the diagnosis of type 1 diabetes was  $5.2 \pm 2.8$  years. The mean age at the end of follow-up was  $6.4 \pm 3.2$  years.

Table 2 presents rate ratios for type 1 diabetes according to vaccination status among all children and children who had at least one sibling with type 1 diabetes. No association was found between vaccination and type 1 diabetes. The rate ratio for type 1 diabetes was 40.05 (95 percent confidence interval,

26.90 to 59.63) among children who had at least one sibling with type 1 diabetes, as compared with children who had no siblings with type 1 diabetes.

To evaluate the possible independent effect of the components of the diphtheria, tetanus, and inactivated poliovirus vaccines, we combined receipt of diphtheria, tetanus, and inactivated poliovirus vaccine with receipt of diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine and found rate ratios of 0.80 after one dose (95 percent confidence interval, 0.42 to 1.51), 0.90 after two doses (95 percent confidence interval, 0.51 to 1.58), and 0.79 after three doses (95 percent confidence interval, 0.45 to 1.38). We estimated rate ratios of type 1 diabetes in the period after the first, second, and third doses of vaccine.

We evaluated the clustering hypothesis by determining whether the models that included terms for the dose-specific time since vaccination were significantly different from the models that included only dose-specific vaccination terms. We found no significant differences:  $P=0.57$  for diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine;  $P=0.67$  for diphtheria, tetanus, and inactivated poliovirus vaccine;  $P=0.68$  for *H. influenzae* type b vaccine;  $P=0.80$  for whole-cell pertussis vaccine;  $P=0.34$  for MMR vaccine; and  $P=0.11$  for oral poliovirus vaccine. Likewise, we found no increase in rate ratios in the three or four years after vaccination.

For example, the rate ratios were as follows in the third year after vaccination with the last dose: 0.99 for diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine (95 percent confidence interval, 0.60 to 1.63); 0.86 for diphtheria, tetanus, and inactivated poliovirus vaccine (95 percent confidence interval, 0.55 to 1.35); 0.86 for *H. influenzae* type b vaccine (95 percent confidence interval, 0.59 to 1.26); 1.20 for whole-cell pertussis vaccine (95 percent confidence interval, 0.78 to 1.84); 1.50 for MMR vaccine (95 percent confidence interval, 0.98 to 2.28); and 0.83 for oral poliovirus vaccine (95 percent confidence interval, 0.49 to 1.42).

We further evaluated whether the total number of vaccinations was a risk factor for type 1 diabetes. Children who received at least one vaccination were compared with children who received no vaccinations whatsoever, resulting in a rate ratio of 1.24 (95 percent confidence interval, 0.48 to 3.18). We compared children who received the maximal number of vaccinations in this study (13) with children who received no vaccinations and found a rate ratio

**Table 2. Rate Ratio for Type 1 Diabetes among Vaccinated Children as Compared with Unvaccinated Children.\***

| Vaccine  | All Children       |              |                      | Children with at Least 1 Sibling with Type 1 Diabetes |              |                      |
|--|--------------------|--------------|----------------------|---|--------------|----------------------|
|  | Person-yr at Risk† | No. of Cases | Rate Ratio (95% CI)‡ | Person-yr at Risk                                     | No. of Cases | Rate Ratio (95% CI)§ |
| <i>Haemophilus influenza</i> type b                                  |                    |              |                      |   |              |                      |
| Unvaccinated   | 1,596,918          | 211          | 1.00¶                | 1419  | 7            | 1.00¶                |
| 1 Dose   | 835,833            | 123          | 0.87 (0.69–1.09)     | 799   | 7            | 1.62 (0.57–4.63)     |
| 2 Doses  | 850,946            | 114          | 0.97 (0.73–1.29)     | 709   | 2            | 0.66 (0.14–3.19)     |
| 3 Doses  | 1,436,820          | 233          | 0.99 (0.75–1.30)     | 1281  | 10           | 1.69 (0.63–4.54)     |
| At least 1 dose  |                    |              | 0.91 (0.74–1.12)     |   |              | 1.38 (0.58–3.31)     |
| Increase in rate ratio per dose                                      |                    |              | 1.00 (0.91–1.10)     |   |              | 1.13 (0.82–1.55)     |
| Diphtheria, tetanus, and inactivated poliovirus                      |                    |              |                      |   |              |                      |
| Unvaccinated   | 1,110,803          | 110          | 1.00¶                | 258   | 1            | 1.00¶                |
| 1 Dose   | 276,557            | 33           | 1.02 (0.66–1.57)     | 1092  | 8            | 1.93 (0.12–31.17)    |
| 2 Doses  | 1,134,823          | 178          | 1.07 (0.79–1.46)     | 2136  | 16           | 3.22 (0.40–26.02)    |
| 3 Doses  | 2,198,334          | 360          | 0.95 (0.69–1.30)     | 723   | 1            | 2.92 (0.38–22.32)    |
| At least 1 dose  |                    |              | 1.02 (0.75–1.37)     |   |              | 3.03 (0.41–22.63)    |
| Increase in rate ratio per dose                                      |                    |              | 0.97 (0.88–1.06)     |   |              | 1.25 (0.78–1.99)     |
| Diphtheria, tetanus, acellular pertussis, and inactivated poliovirus |                    |              |                      |   |              |                      |
| Unvaccinated   | 3,734,846          | 552          | 1.00¶                | 3437  | 21           | 1.00¶                |
| 1 Dose   | 296,026            | 39           | 0.96 (0.66–1.39)     | 258   | 4            | 3.02 (1.02–8.91)     |
| 2 Doses  | 242,792            | 24           | 0.93 (0.57–1.53)     | 167   | 0            |                      |
| 3 Doses  | 446,854            | 66           | 0.97 (0.67–1.41)     | 347   | 1            | 0.58 (0.08–4.38)     |
| At least 1 dose  |                    |              | 0.96 (0.71–1.30)     |   |              | 1.36 (0.50–3.70)     |
| Increase in rate ratio per dose                                      |                    |              | 0.99 (0.87–1.12)     |   |              | 0.93 (0.56–1.56)     |
| Whole-cell pertussis   |                    |              |                      |   |              |                      |
| Unvaccinated   | 995,949            | 109          | 1.00¶                | 721   | 2            | 1.00¶                |
| 1 Dose   | 382,317            | 54           | 1.24 (0.85–1.79)     | 349   | 8            | 1.59 (0.22–11.41)    |
| 2 Doses  | 1,383,584          | 194          | 1.02 (0.76–1.37)     | 1298  | 14           | 1.58 (0.33–7.53)     |
| 3 Doses  | 1,958,668          | 324          | 1.04 (0.77–1.41)     | 1841  | 2            | 1.74 (0.39–7.76)     |
| At least 1 dose  |                    |              | 1.06 (0.80–1.40)     |   |              | 1.68 (0.39–7.19)     |
| Increase in rate ratio per 0.5 ml of vaccine                         |                    |              | 0.99 (0.94–1.04)     |   |              | 1.14 (0.76–1.73)     |
| Measles, mumps, and rubella  |                    |              |                      |   |              |                      |
| Unvaccinated   | 1,373,401          | 124          | 1.00¶                | 1053  | 6            | 1.00¶                |
| 1 Dose   | 2,934,287          | 499          | 1.14 (0.90–1.45)     | 2795  | 20           | 0.86 (0.34–2.14)     |
| Unknown  | 412,830            | 58           | 1.04 (0.71–1.52)     | 361   | 0            |                      |
| Oral poliovirus  |                    |              |                      |   |              |                      |
| Unvaccinated   | 1,655,931          | 137          | 1.00¶                | 1030  | 2            | 1.00¶                |
| 1 Dose   | 742,807            | 95           | 1.06 (0.71–1.59)     | 591   | 3            | 1.87 (0.31–11.36)    |
| 2 Doses  | 825,780            | 137          | 1.07 (0.69–1.65)     | 837   | 5            | 1.68 (0.32–8.90)     |
| 3 Doses  | 1,496,000          | 312          | 1.12 (0.73–1.72)     | 1750  | 16           | 2.24 (0.50–10.06)    |
| At least 1 dose  |                    |              | 1.08 (0.74–1.57)     |   |              | 2.01 (0.46–8.71)     |
| Increase in rate ratio per dose                                      |                    |              | 1.04 (0.91–1.18)     |   |              | 1.24 (0.83–1.87)     |

\* CI denotes confidence interval.

† Values for person-years at risk have been rounded.

‡ Rate ratios were adjusted for age, calendar period, and child's sex.

§ Rate ratios were adjusted for age, calendar period, child's sex, and the number of siblings.

¶ This group served as the reference group.

|| Children received only one dose of measles, mumps, and rubella vaccine during the study period because administration of the second dose of vaccine is not recommended until 12 years of age.

of 1.32 (95 percent confidence interval, 0.42 to 4.10). We calculated the trend for the number of vaccinations received and found an increase in the rate ratio per vaccination of 1.00 (95 percent confidence interval, 0.96 to 1.05).

## DISCUSSION

Diverse causal mechanisms have been proposed to explain a possible link between childhood vaccination and type 1 diabetes,<sup>16</sup> but the available evidence

is weak.<sup>2,10,11</sup> However, the process of detecting associations between vaccination and rare or long-term outcomes is complicated, and many negative studies have been statistically underpowered or have suffered from a lack of unvaccinated subjects. Issues that call into question vaccine safety have the potential to jeopardize vaccination programs; for these programs to retain the confidence of both the public and health professionals, continued safety evaluations are becoming an increasingly important part of public health procedures.

On the basis of ecologic evaluations, Classen and Classen have claimed that vaccination is associated with an increased risk of type 1 diabetes two to four years after vaccination.<sup>8,9</sup> We tested this hypothesis directly by examining data on individual subjects in a population-based cohort study. We found no support for the existence of a causal relation between type 1 diabetes and childhood vaccination overall or at any time after vaccination.

We speculated that any association between vaccination and type 1 diabetes would be more pronounced among children who were genetically predisposed to diabetes. Although we found that the risk of type 1 diabetes increased among children who had one or more siblings with diabetes, there was no apparent association between diabetes and vaccination among such children. However, the lack of statistical significance and inconsistency limit the conclusions that can be drawn from this analysis. If we consider the results for at least one dose of vaccine, the diphtheria, tetanus, and inactivated poliovirus vaccine and the oral poliovirus vaccine stand out, with rate ratios of 3.03 (95 percent confidence interval, 0.41 to 22.63) and 2.01 (95 percent confidence interval, 0.46 to 8.71), respectively. However, these increases are clearly based on reference groups that included only one and two unvaccinated children in the case of diphtheria, tetanus, and inactivated poliovirus vaccine and oral poliovirus vaccine, respectively. In a previous study, Hummel et al. evaluated the risk of developing islet autoantibodies during the first two years of life among children who had a parent with type 1 diabetes and found no association with vaccination.<sup>17</sup> A novel aspect of our study is the evaluation of the association between vaccination and type 1 diabetes among genetically predisposed children older than two years.

We identified cases of type 1 diabetes from discharge diagnoses in the National Hospital Register. Nielsen et al. evaluated the quality of data in this

registry with respect to type 1 diabetes and found that in the period from 1987 to 1993, the specificity of the diagnosis was 96 percent and the completeness of the data was 91 percent.<sup>18</sup> Svensson et al. estimated the incidence of type 1 diabetes in Denmark from 1996 through 2000 on the basis of data in a national diabetes registry initiated in 1996.<sup>19</sup> Among children from birth to four years of age, the incidence was 12.73 per 100,000 person-years, and among children five to nine years of age, the incidence was 19.36 per 100,000 person-years. During the same period, we found similar rates of type 1 diabetes — 13.37 per 100,000 person-years among children from birth to four years of age and 18.12 per 100,000 person-years among children five to nine years of age. Consequently, the validity and completeness of the data on type 1 diabetes that we used are unlikely to be a cause for concern. Our main priority was obtaining a large cohort with a sufficient period of follow-up, and thus we chose the National Hospital Register, which allowed us to start our follow-up in 1990, rather than in 1996, as would have been the case had we used the national diabetes registry.

Analytic epidemiologic studies of a possible association between vaccination and type 1 diabetes are rare. Three case-control studies — one from Sweden,<sup>20</sup> a multicenter study by the Europe and Diabetes study group,<sup>21</sup> and one from the United States<sup>22</sup> — found no adverse effect of childhood vaccination on type 1 diabetes. In a recent review of the safety of immunization,<sup>23</sup> the Institute of Medicine recommended that existing vaccine surveillance systems be used in combination with disease registries to explore the association between immunization and type 1 diabetes. The advantage of our study is that we were able to evaluate the association between childhood vaccinations and type 1 diabetes in a nationwide cohort with longitudinal, individual-level information on vaccinations and type 1 diabetes. The use of a nationwide cohort and the independent and prospective ascertainment of vaccination history and the diagnosis of type 1 diabetes eliminate concern regarding selection bias and recall bias, commonly found in other types of post-licensure studies of vaccination safety. In conclusion, there appears to be no support for any causal relation between childhood vaccination and type 1 diabetes.

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