Thimerosal Exposure in Infants and Developmental Disorders: A Retrospective Cohort Study in the United Kingdom Does Not Support a Causal Association

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ABSTRACT. *Objective.* **After concerns about the possible toxicity of thimerosal-containing vaccines in the United States, this study was designed to investigate whether there is a relationship between the amount of thimerosal that an infant receives via diphtheria-tetanus-whole-cell pertussis (DTP) or diphtheria-tetanus (DT) vaccination at a young age and subsequent neurodevelopmental disorders.**

Methods. **A retrospective cohort study was performed using 109 863 children who were born from 1988 to 1997 and were registered in general practices in the United Kingdom that contributed to a research database. The disorders investigated were general developmental disorders, language or speech delay, tics, attention-deficit disorder, autism, unspecified developmental delays, behavior problems, encopresis, and enuresis. Exposure was defined according to the number of DTP/DT doses received by 3 and 4 months of age and also the cumulative age-specific DTP/DT exposure by 6 months. Each DTP/DT dose of vaccine contains 50 μg of thimerosal (25 μg of ethyl mercury). Hazard ratios (HRs) for the disorders were calculated per dose of DTP/DT vaccine or per unit of cumulative DTP/DT exposure.**

Results. **Only in 1 analysis for tics was there some evidence of a higher risk with increasing doses (Cox's HR: 1.50 per dose at 4 months; 95% confidence interval [CI]: 1.02–2.20). Statistically significant negative associations with increasing doses at 4 months were found for general developmental disorders (HR: 0.87; 95% CI: 0.81–0.93), unspecified developmental delay (HR: 0.80; 95% CI: 0.69–0.92), and attention-deficit disorder (HR: 0.79; 95% CI: 0.64–0.98). For the other disorders, there was no evidence of an association with thimerosal exposure.**

Conclusions. **With the possible exception of tics, there was no evidence that thimerosal exposure via DTP/DT vaccines causes neurodevelopmental disorders.** ***Pediatrics*** **2004;114:584–591;** ***cohort study, neurodevelopment, safety, thimerosal, thiomersal, vaccines.***

ABBREVIATIONS. Hg, mercury; WHO, World Health Organization; VSD, Vaccine Safety Datalink; CDC, Centers for Disease Control and Prevention; HMO, health maintenance organization; ADD, attention-deficit disorder; GPRD, General Practice Research Database; ICD, *International Classification of Diseases*; DTP, diphtheria-tetanus-whole-cell pertussis; DT, diphtheria, tetanus; GP, general practitioner; HR, hazard ratio; CI, confidence interval.

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Inorganic mercury (Hg) poses a potential risk of neurodevelopmental and renal toxicity in young children.[1,2] Cumulative exposure to an organic mercury–containing compound, methylmercury, can also produce neurologic or renal damage as it has a long half-life and can cross the blood-brain barrier, where it accumulates and is converted to inorganic mercury. Guidelines to limit cumulative exposure to methylmercury have been drawn up by various agencies and incorporate a wide margin of safety. The maximum daily dose specified by these different agencies varies by nearly 5-fold, the most stringent being the guideline of the Environmental Protection Agency in the United States that specifies a maximum daily exposure to Hg of 0.1 μg/kg extrapolated from data on methylmercury exposure. These guidelines are reproduced by Pichichero.[2]

Ethylmercury, a related organic mercury compound, is a constituent of thimerosal, an antibacterial agent used in certain nonlive vaccines. Ethylmercury has a much shorter half-life than methylmercury, being rapidly excreted via the stools after parenteral administration such that blood levels remain substantially below the safe threshold.[2] Nevertheless, the guidelines to limit cumulative methylmercury exposure have been translated to ethylmercury.[3] In the United States, increases during the 1990s in the number of childhood vaccines that contained thimerosal, which contains 49.6% Hg by weight, led to questions about safety because the maximum cumulative exposure in some US children was 187.5 μg Hg by 6 months of age, which would have exceeded the stringent Environmental Protection Agency limit. Although there is no evidence that this level of Hg exposure via ethylmercury was likely to or had actually caused any harm, a joint statement was issued by the American Academy of Pediatrics and the Public Health Service in 1999 recommending the removal of thimerosal from vaccines as soon as possible, as a precautionary measure.[4] Although the World Health Organization (WHO) supported in principle the move toward thimerosal-free vaccines, it nevertheless recommended that vaccines that contain thimerosal continue to be used in the meantime because the

known morbidity and mortality from vaccine-preventable diseases greatly outweighed any theoretical risk from ethylmercury.[5]

In 2001, the preliminary results of an unpublished US cohort study that screened for associations between various neurodevelopmental and renal disorders and infant thimerosal exposure in vaccines were made available to an Institute of Medicine Immunization Safety Review.[6] This study used the computerized Vaccine Safety Datalink (VSD) developed by the Centers for Disease Control and Prevention (CDC) in association with 2 health maintenance organizations (HMOs).[7] The preliminary results suggested a possible trend between the level of ethylmercury exposure in the first few months of life and the following neurodevelopmental diagnoses: tics, attention-deficit disorder (ADD), language/speech delays, unspecified delays, and general neurodevelopmental delays. Although additional analyses were later conducted to control for confounding variables and to include more data, some disorders remained significant. Given the exploratory nature of this study, it was unclear whether these findings were real, a result of chance, or a result of uncontrolled confounding or bias. A subsequent, much smaller study by the CDC using another HMO data set did not confirm the first findings but had inadequate power to identify effects of the size seen in the first study.[6]

After review of the available evidence by the WHO Global Advisory Committee on Vaccine Safety, it was recommended that other studies be conducted to test the hypotheses raised by the VSD study.[8] The General Practice Research Database (GPRD) in the United Kingdom was identified as 1 of the few databases that were comparable to the HMO databases used in the VSD study.[9,10] In addition, the Avon Longitudinal Study of Pregnancy and Childhood in the United Kingdom was identified as a prospective cohort with information on vaccination and regular assessment of children's developmental progress. This cohort had the advantage of having data on many potential confounding variables, although it was not large enough to assess rare outcome conditions. The results of the analysis of this study are published together with this article.[11]

The GPRD holds data on all significant patient consultations, referrals, and prescribed medicines, including vaccines from 1988 from ~500 general practices in the United Kingdom. Together, these practices provide primary health care for 3.4 million patients (5.7% of the population). Preliminary analyses conducted by staff of the Morbidity and Health Care Team of the Office for National Statistics (which until 1999 managed the GPRD) using the *International Classification of Diseases* (ICD) codes for the outcomes of interest from the CDC study confirmed that the GPRD had sufficient power to test the hypotheses generated in the CDC study.

In the United Kingdom, the only vaccine that contains thimerosal and has been used routinely in the infant immunization program in the past 2 decades is diphtheria-tetanus-whole-cell pertussis (DTP) vaccine or diphtheria-tetanus (DT) vaccine and any combination vaccine that contains DTP or DT. These vaccines all contain 50 μg of thimerosal (25 μg of Hg) per dose. No other thimerosal-containing vaccines have been given routinely to United Kingdom children, so the cumulative Hg exposure by age can be readily obtained from the number of doses of DTP- or DT-containing vaccines given. Because the United Kingdom changed to an accelerated 2/3/4 month DTP immunization schedule in 1990 (replacing the former 3/5/10 month schedule) and because vaccinations are generally given on time in the United Kingdom, a substantial proportion of children in the GPRD cohort will have had a cumulative Hg exposure of 150 μg of thimerosal (75 μg of Hg) by 4 months of age. This level of Hg exposure, although lower than the maximum of 187.5 μg received in the United States by 6 months of age, is similar to the level received by ~3 to 4 months of age in the United States. It is also the same as the amount of thimerosal used by developing countries that follow the expanded immunization schedule.

METHODS

The GPRD Cohort

Information on all children who were born from 1988 to 1997 and had at least 2 years of continuous follow-up from birth in the GPRD was obtained from the Office for National Statistics. Data were available up to the end of 1999 in linked patient, medical, and prevention databases for 152 898 children. For quantifying thimerosal exposure by age, it was important that an exact date of birth (to the day) be available. The patient database had information only on year and month of birth, but we were able to obtain exact dates of birth for 109 863 children from the date at which procedures or measurements taken on the day of birth were recorded in the linked medical database. Additional data quality processing, mostly concerning the validity of the dates of birth, vaccination, or the date of recording of the neurodevelopmental problems, led to the exclusion of 2711 records (2.5% of the cohort), leaving 107 152 children for analysis (Fig 1).

For each child, information was available on date of birth, gender, date leaving the practice (if applicable), last date that data were obtained from the practice, dates of all vaccinations (along with vaccine code and dose number), and dates and Read or OXMIS codes for all medical events. Read and OXMIS are diagnostic coding schemes that are built into practice software and based respectively on ICD-9 and ICD-8 codes. We had no information enabling identification of the patient and no information on general practitioner (GP) practice, so the only potential confounding variables that could be allowed for were gender and year/month of birth.

Exclusion Criteria

Children with Read and OXMIS codes relating to a variety of prenatal, perinatal, and postnatal conditions that occurred before 6 months of age were excluded as were children who were recorded as having an outcome event in the first 6 months of life. These children were excluded from the main analysis because the presence of such a condition is likely to affect both vaccination and future neurodevelopmental outcomes. Examples of exclusions were birth asphyxia, Down syndrome, cerebral palsy, meningitis, encephalitis, and head injury. Children were also excluded when they received either hepatitis B or influenza vaccination in the first 6 months of life because such children are likely to be an atypical subgroup. Children who were born preterm (<37 weeks' gestation) are likely to be of low birth weight, and many stay small. Such infants might be more susceptible to standard doses of thimerosal. Preterm infants therefore were analyzed separately.

Exposure Variables

Hg exposure for each child was defined according to the number of DTP/DT doses received at 3 months (93 days) and 4 months

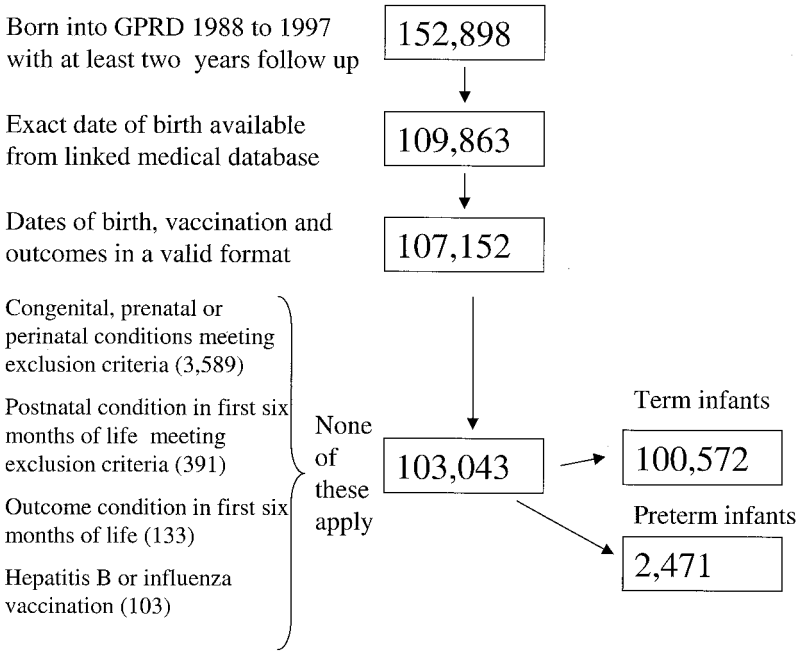

Fig 1. Selection of the GPRD cohort.

(124 days) of age. These ages were chosen to give a wide distribution for the number of children who received 0 to 3 doses of DTP/DT. A continuous variable (HgAll) that aimed to capture the age-specific Hg exposure up to 6 months (183 days) of age was also created. This variable was created to circumvent the problem of choosing age cut-offs and also to provide greater study power. HgAll was created from the age in days at the 3 DTP/DT doses as follows:

HgAll = [(183 − age at dose 1) + (183 − age at dose 2) + (183 − age at dose 3)]/40

When a dose was not given or was given later than 183 days of age, for the purpose of the above calculation, the age was set to 183 days. The higher the value of HgAll, the earlier the 3 doses of DTP/DT were given and the child thus was exposed to a higher dose of mercury at a younger age. The arbitrary division by 40 was to ensure that when calculating hazard ratios (HRs), 1 unit of HgAll was of a meaningful size. One unit of HgAll corresponds to a combined difference of 40 days (while under the age of 183 days) in the age at which DTP/DT is given. For example, a child who received dose 1 at 60 days, dose 2 at 88 days, and dose 3 at 116 days would have an HgAll value of 7.125, whereas a child who received doses 1 and 2 by the same age but dose 3 at 156 days would have an HgAll value of 6.125.

Outcome Events

The outcome events of most interest were OXMIS and Read codes relating to general neurodevelopmental disorders (a composite category that comprised the following ICD-9 codes: 299 [childhood psychoses including autism], 300.3 [obsessive-compulsive disorders], 307 [specific psychopathological syndromes], 312.0 [unsocialized disturbance conduct, aggressive], 313 [emotional disturbance], 314 [hyperkinetic syndrome], 315 [specific delays in development], 317–319 [mental retardation], and V40 [mental and behavioral problems]) and other individual conditions as follows: unspecified development delays, tics, ADD and language or speech delay, enuresis, encopresis, autism, and nonspecific behavioral problems. The ICD-9 codes relating to these outcomes are shown in Table 1.

Statistical Methods

The data were analyzed by Cox proportional hazards survival analysis in the statistical package S-Plus.[12] Survival for each child was taken as the number of days from age 183 days to the age at the first mention of each predefined outcome of interest. If for a particular outcome no event occurred, then survival was taken as being greater than the time to the end of follow-up. HRs with 95% confidence intervals (CIs) and two-sided *P* values were calculated for the effect of thimerosal exposure. The effect of the number of doses received by 3 and 4 months of age was quantified by the trend in hazard per dose. When the trend was significant, the HRs for 1, 2, and 3 doses at 4 months compared with the baseline of 0 doses were also calculated. A HR >1 is consistent with the hypothesis that early Hg exposure is associated with an increased risk of a predefined developmental outcome, whereas a HR <1 is

TABLE 1. Numbers With the Various Outcome Conditions for the Term and Preterm Cohorts, the Percentage Male, and the Estimated Median Age in Years at First Mention

Outcome (ICD-9 Codes)	Term Infants			Preterm Infants		
	n	% Male	Median age at First Mention, y	*n*	% Male	Median age at First Mention*, y
General developmental disorders	2035	71.1	3.6	110	66.4	3.6
Unspecified behavioral problem (3129)	816	71.2	4.8	30	70.0	5.3
Enuresis (7883)	1312	53.6	5.6	35	60.0	6.1
Encopresis (7876)	121	66.9	5.5	4	75.0	—
Tics (3072)	70	70.0	5.2	1	100.0	—
ADD (314)	222	77.0	3.7	8	87.5	—
Language/speech (3153)	666	70.4	3.0	33	69.7	3.4
Unspecified delay (3159)	485	67.2	2.4	52	59.6	2.1
Autism (2990)	104	89.4	4.4	2	50.0	—

* Where there are <10 cases, a median age is not calculated

TABLE 2. Distribution in the Term and Preterm Cohorts of the Number of Doses of DTP/DT Received in Total, by 3 and 4 Months of Age

Exposure	Level	Term Cohort		Preterm Cohort	
		n	%	*n*	%
No. of doses of DTP/DT	0	945	0.9	37	1.5
	1	1687	1.7	38	1.5
	2	1090	1.1	60	2.4
	3 (third dose ≤ 1 y)	94730	94.2	2255	91.3
	3 (third dose >1 y)	2120	2.1	81	3.3
Doses by age 3 mo	0	7881	7.8	350	14.2
	1	51309	51.0	1390	56.3
	2	41382	41.1	731	29.6
Doses by age 4 mo	0	3419	3.4	142	5.8
	1	11766	11.7	442	17.9
	2	50349	50.1	1299	52.6
	3	35038	34.8	588	23.8

indicative of a potential protective effect. In all analyses, gender and year of birth were included as potential confounding factors; month of birth was also included when statistically significant at a 5% level. The effect of the number of doses of thimerosal was also examined visually in reverse Kaplan-Meier plots.

The main analysis included all children whether recorded as receiving 0, 1, 2, or 3 doses of DTP/DT at any age. However, it seemed possible that, as a result of socioeconomic or other confounding factors, children who did not complete vaccination in the first year of life would form a biased group. The data therefore also were analyzed after excluding all children who did not receive 3 doses of vaccination by age 366 days.

The median age at first mention of each outcome (Table 1) was estimated by taking the proportion of those who were followed up for 8 years or more with an event by 8 years (eg, 3.33% of 7195 followed up for at least 8 years had a general developmental disorder) and then finding the age by which half of this proportion had had an event (eg, 1.67% of 63 466 followed up for 3.6 years or more). This method of estimating the median age was used to adjust for the effect of censored data but is still conditional on the event occurring by the age of 8.

Validation

Validation of GP notes could be performed only for those GP practices that were still participating in the GPRD and with the case still registered. Validation was performed by sending a questionnaire to the GP asking for confirmation and additional details of the diagnosis and any subsequent related consultations and also the vaccination history, date of birth, and gender. Copies of relevant patient notes were also requested. Validation was sought for all cases of tics for whom validation was possible (36 of the 71 cases) as well as a random subset of 30 with ADD, 40 with language or speech delay, 30 with unspecified developmental delays, and also an additional 30 in the general developmental delay category not covered by the above.

RESULTS

Cohort Selection

Details of the selection of the cohort of 103 043 children are given in Fig 1. The average length of follow-up in the cohort was 4.7 years (range: 2–11). Only 7.3% had a follow-up of longer than 8 years, reflecting that fewer practices contributed to the GPRD from 1988 to 1990.

Exposure

More than 96% of term children eventually received all 3 doses of DTP/DT (Table 2). By 4 months of age, most children had received 2 or 3 doses; however, there was sufficient variability in the number of doses received to enable fairly precise estimates of the trend in the HR per dose for the various outcomes. Preterm children were less vaccinated and received vaccination later than term children.

Figure 2 shows the distribution of HgAll for the term cohort. The median value (interquartile range) of HgAll is 6.5 (4.5–7.0) in the term cohort and 6.1 (4.7–6.8) in the preterm cohort. Although few children received vaccinations early (HgAll >7.5), many got the 3 doses close to the correct time (HgAll: 6.5–7.5). Short delays in receiving the 3 doses were fairly common. However, relatively few children received <3 doses or got the vaccine very late.

Outcomes

All of the neurodevelopmental disorders investigated were more common in boys than in girls (Table 1). They also occurred more often in preterm children, with general developmental disorders occurring in 4.5% of preterm children and 2.0% of term children. The estimated median age of first mention of the disorders in term children varied from 2.4 years for unspecified delays to 5.6 years for enuresis. The age at first mention was similar for the term and preterm cohorts. Other than the general developmental disorders category, the most common disorders were enuresis, behavioral problems, and language/speech delays.

Risk Estimates

Table 3 shows the adjusted HRs per DTP/DT dose or HgAll unit for the various disorders. There were apparent protective effects from DTP/DT exposure for general developmental disorders, ADD, and unspecified developmental delay. The only evidence of a greater hazard with increasing thimerosal exposure was for tics, and this was significant only in the analysis that excluded children who did not receive 3 doses by 1 year of age. For the other disorders, exclusion of children who did not receive 3 doses by age 1 did not substantially affect the HRs; for example, the HR per dose at age 4 months was 0.86 (95% CI: 0.81–0.92) for general developmental disorders.

In the preterm cohort, none of the HRs was significantly different from 1 (data not shown). This cohort was not large enough to have the power to identify small effects; however, the direction of the effects was similar to the term cohort. For example, for

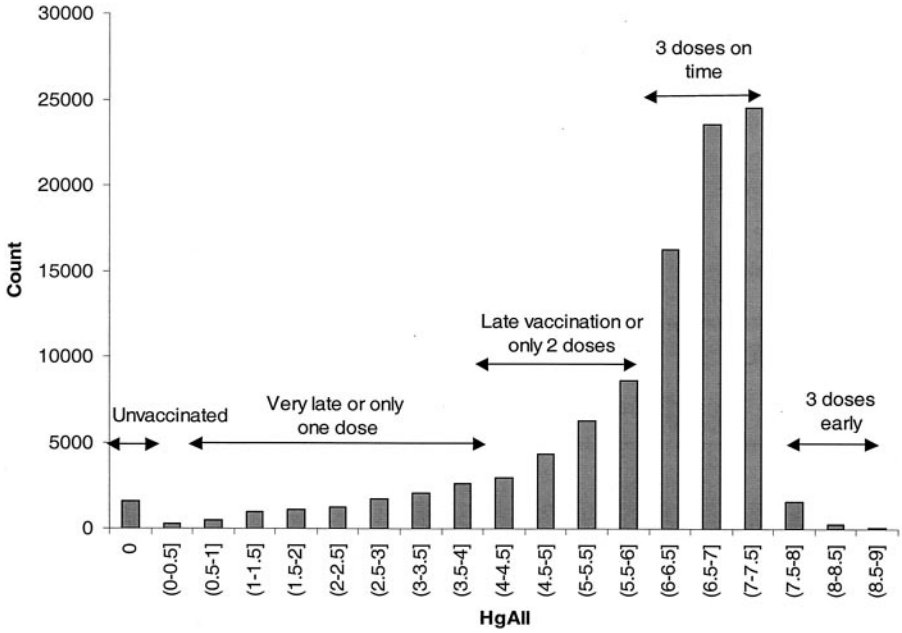

Fig 2. Distribution of the HgAll variable in the term cohort.

TABLE 3. HR for Various Neurodevelopmental Disorders According to the Number of Doses of DTP/DT Received by 3 and 4 Months of Age and the Age-Specific Cumulative Exposure HgAll in the Term Cohort

Outcome	Doses by 3 Months			Doses by 4 Months			HgAll		
	HR* Per Dose	95% CI	*P* Value	HR Per Dose	95% CI	*P* Value	HR Per Unit	95% CI	*P* Value
General developmental disorders	0.87	0.81–0.93	<.001	0.89	0.84–0.94	<.001	0.95	0.92–0.97	<.001
Behavioral problem	0.97	0.87–1.08	.55	0.98	0.90–1.07	.68	0.98	0.94–1.02	.36
Enuresis	1.07	0.98–1.17	.13	1.04	0.97–1.12	.25	1.02	0.98–1.05	.29
Encopresis	0.81	0.61–1.07	.13	0.82	0.65–1.02	.074	0.92	0.84–1.02	.11
Tics	1.45	0.99–2.15	.059	1.34	0.96–1.85	.082	1.14	0.97–1.35	.11
Tics†	1.62	1.05–2.50	.031	1.50	1.02–2.20	.035	1.33	1.06–1.69	.015
ADD	0.79	0.64–0.98	.033	0.82	0.70–0.97	.022	0.90	0.84–0.97	.004
Language or speech delay	0.89	0.79–1.01	.070	0.96	0.87–1.06	.38	0.99	0.94–1.03	.56
Unspecified developmental delay	0.80	0.69–0.92	.002	0.84	0.75–0.94	.002	0.91	0.86–0.95	<.001
Autism	0.89	0.65–1.21	.46	0.94	0.73–1.21	.66	0.99	0.88–1.12	.89

* Adjusted for gender, year of birth, month of birth (general developmental disorders only).
† Results from the analysis that excluded those who did not receive 3 doses of DTP/DT by 366 days.

general developmental disorders, the HR per doses at 4 months was 0.80 (95% CI: 0.63–1.00). There was no evidence that the higher exposure by body mass in preterm children gave an increased risk of neurodevelopmental problems.

Table 4 shows the HRs of 1, 2, and 3 doses by 4 months of age compared with the baseline of 0 doses for variables with a significant trend by dose. The results show that for general developmental disorders, ADD, and unspecified delay, there is a decreasing trend by dose. For tics, the effect is less clear, with the main difference being the lower hazard at 1 dose. Reverse Kaplan-Meier plots show these results in more detail (Fig 3).

The 4109 children who were dropped as a result of the initial exclusion criteria were examined in a separate analysis. As with the premature children, they had a lower DTP/DT exposure than the main cohort and also a greater risk of outcome events. As with the term cohort, this group showed a protective DTP/DT effect for general developmental disorders with a HR for the trend in doses by 4 months of age of 0.84 (95% CI: 0.72–0.97).

Validation

From the validation exercise, responses were received from 162 of 166 general practices. Of these, 10 could not provide any information. Of the remaining 152, 122 (80%) confirmed that the child presented with the given condition, 11 (7%) stated that the diagnosis reflected only parental concern, 11 (7%) had the diagnosis incorrectly coded, and in 8 (5%) no record of the diagnosis or subsequent episodes could be found in the notes. Of the 122 with a confirmed diagnosis, 48 were transient problems, 31 were long term, and for 43, the duration could not be determined. For tics, responses were received for all 36, of whom the duration of symptoms could be determined in 27. In 24 (89%) of 27, the tic was only a transient problem. In 3 cases, tics was recorded when in fact the individual presented with a parasitic tick. The validation confirmed that the dates of vaccina-

TABLE 4. Effect of Number of DTP/DT Doses Received by 4 Months of Age on Outcomes With Significant Associations in the Trend Analysis for the Term Cohort

Outcome	DTP/DT Doses by Age 4 Months	No. With Outcome	HR*	95% CI
General developmental disorders	0	86	1.00	Reference
	1	302	0.99	0.78–1.25
	2	1028	0.85	0.68–1.06
	3	619	0.75	0.60–0.94
Tics	0	3	1.00	Reference
	1	2	0.17	0.03–1.04
	2	40	1.14	0.35–3.73
	3	25	1.12	0.34–3.77
Tics†	0	0	0.00	Not estimable
	1	2	0.18	0.04–0.76
	2	38	0.98	0.58–1.62
	3	25	1.00	Reference
ADD	0	15	1.00	Reference
	1	34	0.62	0.34–1.14
	2	105	0.49	0.29–0.85
	3	68	0.47	0.27–0.83
Unspecified developmental delay	0	20	1.00	Reference
	1	85	1.20	0.74–1.96
	2	234	0.80	0.51–1.26
	3	146	0.73	0.46–1.16

* Adjusted for gender, year of birth, and month of birth (general developmental disorders only).
† Results from the analysis that excluded those who did not receive 3 doses of DTP/DT by 366 days.

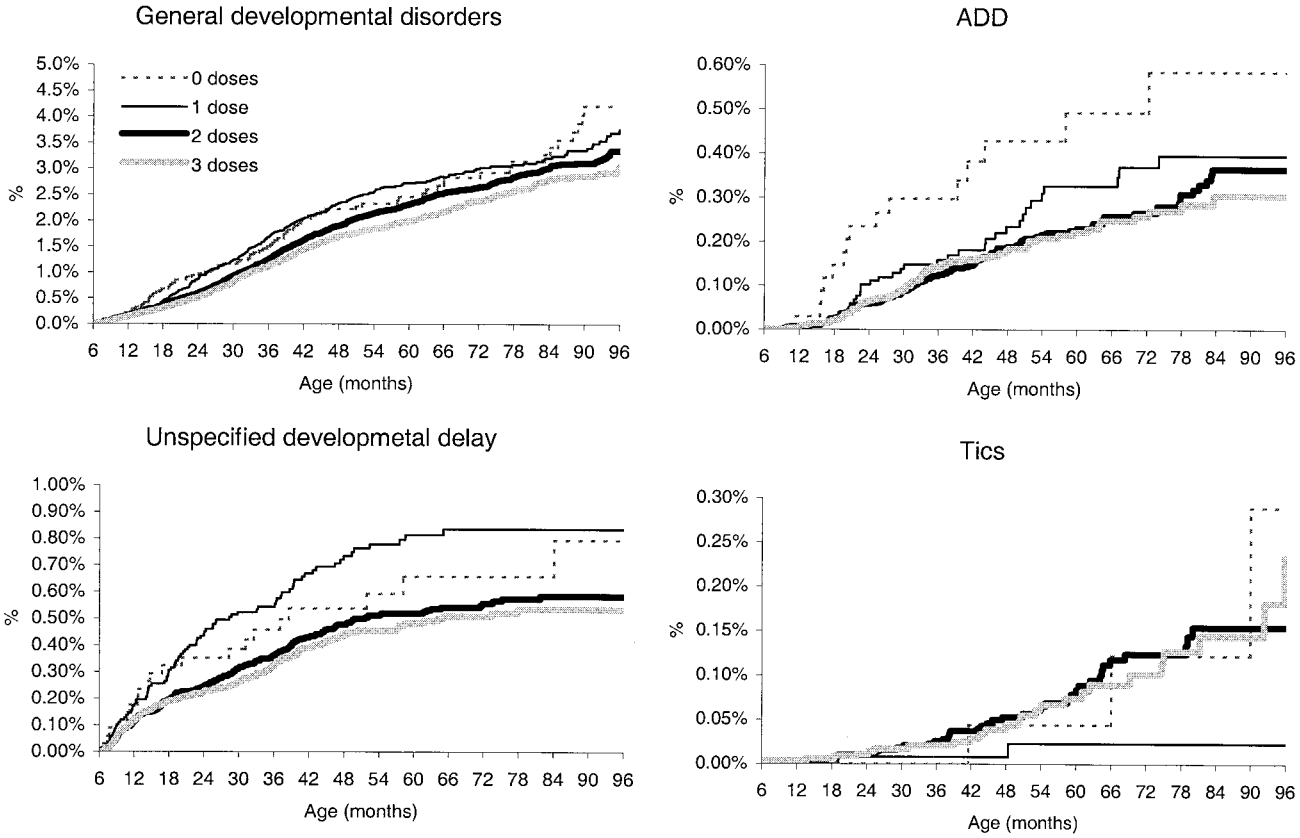

Fig 3. Cumulative percentage of children with general developmental disorders, ADD, unspecified developmental delays, and tics from 6 months to 96 months of age, stratified according to DTP/DT doses received by 4 months of age. Plots are derived from the inverse of the Kaplan-Meier survival curves and take account of variable follow-up times in individuals.

tion were accurate and that the dates of the events recorded in the GPRD were correct or close to the date noted in the GP record.

DISCUSSION

With the possible exception of tics, there was no evidence of an increased risk of various neurodevelopmental disorders with increasing thimerosal exposure at a young age via DTP/DT vaccination in the United Kingdom. For general developmental disorders, unspecified developmental delay, and ADD, there was an apparent protective effect from increasing thimerosal exposure. These outcomes all had a median age at first mention at a relatively young age

and therefore were more likely to be affected by confounding factors that are also associated with delayed or incomplete vaccination. Outcome conditions first mentioned when the child was older did not show any evidence of an association with DTP/DT dosage, with the exception of the apparent higher risk of tics in 1 analysis.

Although we were able to make some exclusions on the basis of medical events in the first 6 months of life, a limitation of our study was the inability to adjust for many potential confounding factors, such as unrecorded medical conditions and socioeconomic factors. The longitudinal United Kingdom study, published with this article,[11] did have information available on potential confounding variables. In that study, early thimerosal exposure generally showed no association or was protective. The size of the protective effects reduced when controlling for confounding variables, although the changes were small. This suggests that additional adjustment for confounding in the GPRD study would have a relatively small effect.

Our study has many similarities to the US VSD study and, with the exception of tics, does not confirm the hypotheses raised by the preliminary analysis of that study. Both studies were cohort studies with limited adjustment for confounding. The main difference was the lower total thimerosal exposure in the United Kingdom. It should be noted, however, that the exposure in the United Kingdom by 4 months of age was similar to the United States by the same age; however, in the United States, exposure increased further from 4 to 7 months. If the increased risk in the US study were attributable only to the additional thimerosal exposure after 4 months of age, then it is possible that our study may not have been able to detect the risks found in the US study. In the final analysis of the US cohort study,[13] which had a longer follow-up time and separate analyses for each of the 2 HMOs and also controlled for other variables including health care–seeking behavior, the only variables that remained significant were tics in 1 HMO and language delay in the other. Therefore, many of the preliminary results from the US study were probably attributable to confounding or chance.

The validation exercise confirmed most diagnoses with only 7% of the sample validated deemed incorrectly coded. An additional 13% were questionable because they reflected only parental concern or could not be located in the notes. This lack of specificity is a limitation of the study because it biases against finding an association. If we assume that a conservative 20% of cases have a false diagnosis and that there is a true HR per dose of 1.20, then this bias will result in a slightly lower observed HR of 1.15. Other validation exercises undertaken using the GPRD have found clinical diagnoses to be accurate.[14–16] The predominance of boys as well as the median age at first mention was as expected for the various conditions[17] and provides a degree of validation.

The question remaining is whether there could be a true effect of thimerosal exposure on tics. Evidence supporting a true effect is that it was significant in the US study and in a secondary analysis in the GPRD study; however, there are many reasons to doubt that there is a true effect. First, the US study was a screening study that looked at many outcomes; the borderline significance in 1 HMO of tics merely raised the question. Second, although the GPRD study gave a borderline significant association, the Avon longitudinal United Kingdom study showed no evidence of a relationship between thimerosal exposure and tics or twitches despite that this outcome was reported for ~150 children. Third, the validation exercise revealed that the vast majority of tics were minor transient events. Finally, no other developmental outcomes were found to be associated with thimerosal exposure, contrary to what would be expected if there were a true effect on tics. Although the possibility of a true effect of thimerosal on minor transient tics cannot be ruled out, it is more plausible that the association found is a chance effect or the result of confounding.

Other than the US VSD study, the only other published cohort study that has assessed exposure to thimerosal-containing vaccines and any of the outcomes that we looked at is a study in Denmark that looked at autism.[18] The thimerosal exposure in this study was 25 μg of Hg at 5 weeks, then 50 μg of Hg at 9 weeks and 10 months. As with our study, the authors found no evidence of an association.

A recent study that measured Hg levels in blood and excretion via the stools and urine in term infants who received vaccines that contained thimerosal[2] found no evidence of a rise in blood concentrations above "safe values" and showed that Hg in ethylmercury is eliminated rapidly via the stools. This provides additional evidence that 3 doses of DTP given at monthly intervals does not present an Hg-related risk for neurodevelopmental disorders.

The results of the 2 United Kingdom studies were presented to the WHO Global Advisory Committee on Vaccine Safety in June 2002.[8] These studies contributed to the conclusion that there is currently no evidence of mercury toxicity in infants, children, or adults who are exposed to thimerosal in vaccines and that there is no reason to change current immunization practices with thimerosal-containing vaccines on grounds of safety. This conclusion is particularly important for developing countries that administer thimerosal-containing DTP vaccines according to the expanded immunization schedule.

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TWO MINORITIES SPUR RAPID U.S. GROWTH

"Explosive growth among Hispanic and Asian-Americans propelled a surge in the United States population from 2000 to 2003 to nearly 300 million people, the Census Bureau reported on Monday. The number of people of Hispanic descent, the nation's largest minority group, rose to 39.9 million, a 13 percent increase from April 2000 to July 2003, the agency said. That far outpaced the 3 percent increase in the American population during the same time, to 290.8 million. Asian-Americans were the next fastest growing among the large minority groups, up 12.6 percent, to 11.9 million, while the black population rose nearly 4 percent, to 37 million. About 4.3 million people listed themselves as of more than one race, up 10.5 percent from 2000."

Associated Press. *New York Times*. June 15, 2004

Noted by JFL, MD

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