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

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ABSTRACT. *Objective.* **There is an established link between exposure to mercury and impaired childhood cognitive development and early motor skills. Thimerosal (also known as thiomersal), a preservative used in a number of children's vaccines, contains ethylmercury (an organic compound of mercury), and there has been concern that this exposure to mercury may be of some detriment to young children. The aim of this research was to test in a large United Kingdom population–based cohort whether there is any evidence to justify such concerns.**

Methods. **We used population data from a longitudinal study on childhood health and development. The study has been monitoring >14 000 children who are from the geographic area formerly known as Avon, United Kingdom, and were delivered in 1991–1992. The age at which doses of thimerosal-containing vaccines were administered was recorded, and measures of mercury exposure by 3, 4, and 6 months of age were calculated and compared with a number of measures of childhood cognitive and behavioral development covering the period from 6 to 91 months of age.**

Results. **Contrary to expectation, it was common for the unadjusted results to suggest a beneficial effect of thimerosal exposure. For example, exposure at 3 months was inversely associated with hyperactivity and conduct problems at 47 months; motor development at 6 months and at 30 months; difficulties with sounds at 81 months; and speech therapy, special needs, and "statementing" at 91 months. After adjustment for birth weight, gestation, gender, maternal education, parity, housing tenure, maternal smoking, breastfeeding, and ethnic origins, we found 1 result of 69 to be in the direction hypothesized—poor prosocial behavior at 47 months was associated with exposure by 3 months of age (odds ratio: 1.12; 95% confidence interval: 1.01-1.23) compared with 8 results that still supported a beneficial effect.**

Conclusions. **We could find no convincing evidence that early exposure to thimerosal had any deleterious effect on neurologic or psychological outcome.** *Pediatrics* **2004;114:577–583;** ***ALSPAC, cohort study, neurodevelopment, safety, thimerosal, thiomersal, mercury, vaccines.***

ABBREVIATIONS. wDTP, whole-cell diphtheria/tetanus/pertussis; DT, diphtheria/tetanus; ALSPAC, Avon Longitudinal Study of Parents and Children; DTP, diphtheria/tetanus/pertussis; SDQ, Strengths and Difficulties Questionnaire; OR, odds ratio; CI, confidence interval.

Thiomersal (thimerosal in the United States) is a preservative that is used in a range of children's vaccines and contains ethylmercury, an organic compound that is metabolized into mercury. High doses of a related organic mercury-containing compound methylmercury (MeHg) are toxic as shown after manmade disasters such as Minimata and Iraq.[1] However, there is also evidence that lower doses of MeHg can have adverse effects on childhood development if exposed in utero or in the early months of life. This stems from work-focused communities such as the Faroes,[2] who consume large quantities of fish and whale meat, although these findings have not been replicated in studies in the Seychelles among communities also dependent on fish.[1]

It has been suggested that low doses of ethylmercury might have a similar effect on childhood cognitive development as methylmercury; however, there is little evidence to support this claim.[3] Moreover, ethylmercury is more quickly metabolized and evacuated from the body than methylmercury.[4]

Current guidelines on safe exposure to thimerosal have been extrapolated from data on methylmercury and are varied, from 0.1 μg/kg/day of the Environ-

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mental Protection Agency in the United States to 0.47 μg/kg/day of the World Health Organization.[5] Before the change to thimerosal-free vaccines, US children could have been exposed to levels as high as 187.5 μg by the time they were 6 months of age, exceeding the Environmental Protection Agency guidelines. In the United Kingdom, the only vaccines that contain thimerosal and have been routinely used in the past 2 decades are whole-cell diphtheria/tetanus/pertussis (wDTP) vaccine or diphtheria-tetanus (DT) vaccine and any combination vaccine containing wDTP or DT. Although the United Kingdom exposure is lower by 6 months, the accelerated United Kingdom primary immunization schedule of 2/3/4 months means that a maximum exposure of 75 μg may be received by 4 months of age.

A recent US study[6] searched a large database of conditions linked to immunization history in young children and demonstrated a mild relationship between exposure to thimerosal and neurologic problems, including unspecified developmental delay, tics, attention-deficit disorder, and language and speech delay. The Institute of Medicine has stated that, although the hypothesis is biologically plausible, there is currently insufficient evidence to support a causal relationship and that more studies should be conducted to investigate this.[7] The current study was 1 of 2 British studies that were commissioned to provide additional information.

METHODS

Study Design

The Avon Longitudinal Study of Parents and Children (ALSPAC) enrolled women who resided in Avon in the southwest of England and had an expected date of delivery between April 1, 1991, and December 31, 1992. A total of 14 541 women were recruited; of these, 13 617 had singleton offspring surviving to 12 months of age. Additional details of the study aims and design are available (www.alspac.bris.ac.uk/).[8] Ethical approval was obtained from the study's own ethics committee and local research ethics committees.

Information on childhood behavior and development was collected in questionnaires administered regularly after the birth of the study child. Data presented here are derived from questions asked at 6, 18, 30, 47, 81, and 91 months of age. Information on potential confounders comes from questionnaires given to the mother during both pregnancy and the period that followed.

The information on immunizations was taken from the Bristol-based Child Health Surveillance Database (NHS Public Health Network). Preschool immunizations and examinations were recorded and monitored for all children who resided in the Avon area, and information available consists of date and type of immunization given.

Measures of Exposure

Mercury exposure for each child was defined according to the number of diphtheria/tetanus/pertussis (DTP) or DT doses received by 3 months (93 days) and by 4 months (124 days) of age. A continuous variable (HgAll) was also created from the age in days at DTP/DT doses 1, 2, and 3 in an attempt to calculate the age-specific DTP mercury exposure up to 6 months of age (see below).

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

When a dose was given later than 183 days (6 months), this age was truncated to 183; hence, the contribution to the numerator from this immunization would be 0. The higher the value of HgAll, the earlier the 3 doses of DTP/DT were given and hence the greater the exposure to mercury at a young age. The denominator of 40 was chosen to achieve a score of between 0 and 10 solely to make the parameter estimates more sensibly scaled; however, before this scaling, 1 unit of the variable HgAll corresponded to a 1-day difference in the age at which DTP/DT was given. This measure is the same as that used by Andrews et al.[9]

Outcome Variables

Behavior Ratings

We used the Strengths and Difficulties Questionnaire (SDQ),[10] completed by the mother when the children were 47 and 81 months of age. The SDQ is a behavior scale that is used extensively in Europe and has been shown to have a good correlation with the Child Behavior Checklist.[11] The scale comprises 25 questions that are used to construct 5 subscales (prosocial, hyperactivity, emotional symptoms, conduct problems, and peer problems) and a total difficulties score (the total of all but the prosocial subscale that measures positive aspects of behavior). These scores have been prorated as instructed by their author[10]: no more than 2 missing items are permitted within each of the subscales, and no more than 8 missing items are permitted for the total difficulties score. Those children with a permitted number of missing values have their part-missing scores scaled up to make them comparable to the completely observed scores. The prosocial score differed from the others in that it was measuring positive behaviors. Hence, for this score, we use the low tail of the distribution as our binary outcome to indicate an adverse behavioral outcome.

Speech Problems and the Mother's Worries About Her Child's Speech

A number of questions have been examined regarding the child's speech as well as worries that the mother might have about speech from the 81-month questionnaire. 1) Does he or she stumble or get stuck on words or repeat them many times? (eg, I I I I want a sweet). 2) Does your child have difficulty in pronouncing certain sounds (eg, th, sss, t)? 3) Which aspects of your child's growth and development are you worried about—his/her speech? At 91 months, the mother was asked whether the child had ever had speech therapy.

Fine Motor Development

Fine motor skills were assessed using a scale based on the revised Denver Scale.[12] The items used were those from Denver II and were adapted for parental report with the study population after piloting and discussion with focus groups. These scores are administered when the children are ~6, 18, and 30 months of age and have been corrected for gestation and age of child when the questionnaire was completed; the age range has been restricted to an 8-week window around the 3 intended age points. The lower ~10% of the tail was taken to be the adverse developmental outcome.

Tics

At 18, 30, and 42 months, we asked how often the child has a tic or twitch (weekly or more, less than weekly, or never). Because of the small number of cases, a variable was created showing whether any report of tics had been made over the 3 time points, giving a total of 171 cases. The question was asked again at 91 months; however, of the 167 children with tics at 91 months, only 11 had been reported as having tics in the period up to 42 months.

Special Needs

At 91 months, the mother was asked whether she had been informed, by the school or education authority, that her child had been designated as having special educational needs. She was also asked whether the child had been "statemented" (children are "statemented" when they have a learning difficulty or disability that affects their ability to function at school without the provision of extra resources; this category would include children, eg, with autism).

Confounders Used

The 9 confounders were as follows: birth weight (<2500 g, 2500 g+), gestation (<37 weeks, 37 weeks+), highest maternal educational attainment (3 groups created from a 5-point scale), gender, parity (first born, second born, third or more), housing tenure

(mortgaged, public housing, other-rented), midpregnancy maternal smoking (no, yes), child's ethnicity (white, nonwhite), and breastfeeding for 3 months or more. These are variously associated with childhood behavior and development. In addition, they all were related to the exposure variables at the 5% level of significance. Information was available on maternal fish consumption during pregnancy as a potential alternative source of mercury. It has previously been shown[13] that these measures are not positively associated with reduced child development; hence, these data were not used in the main analysis. The potential for a compounding of effects of thimerosal exposure and fish consumption was considered subsequently.

Statistical Methods

Distributions of outcome variables that comprised continuous data were heavily skewed and so were dichotomized because a transformation could not normalize the data. Each distribution was split such that the reference category contained ~80% to 90% of the data, with the upper tail (or lower for prosocial SDQ and Denver fine motor) constituting the adverse developmental outcome.

Unadjusted associations were assessed using a χ^2 test for trend with the continuous exposure measure being grouped in equal quartiles and the other 3 exposure variables treated as ordinal. After this, multivariable logistic regression models were derived with HgAll used in its continuous form and the other 2 exposures as ordinal variables.

RESULTS

Exposure Variables

Of the 13 617 eligible children, dates of immunization were available on all 3 doses for a total of 12 810. An additional 146 children who had a record of <3 doses but were known still to be living in Avon by the time they were 6 months of age (70 had no doses, 25 had 1 dose, and 51 had 2 doses) were included. As a result, exposure was known for a total of 12 956 subjects (see Fig 1 for a more detailed breakdown of the exclusions). None of the children in our sample of 12 956 had received influenza or hepatitis B vaccine (thimerosal-containing vaccines given to children in high-risk groups).

Doses by 3 Months

The distribution of number of doses obtained by 93 days was as follows: no doses, 527 (4.1%); 1 dose, 6586 (50.8%); and 2 or more doses, 5843 (45.1%).

Doses by 4 Months

For doses by 124 days, the distribution was as follows: no doses, 198 (1.5%); 1 dose, 1254 (9.7%); 2 doses 6675 (51.5%), and 3 doses; 4829 (37.3%). Thus, only 37% had achieved the third immunization by exactly 4 months of age. However, of those 6675 children with 2 doses by that time, 2118 received the third in the following week and another 1332 in the week after that. In fact, 5155 (77%) of them were fully immunized by the end of their fifth month.

Cumulative Dose

HgAll has a negatively skewed distribution with a median of ~6.5 units and a range of 0 to 10 units.

Outcome Variables and Unadjusted Results

The prevalence of each outcome along with the amount of data available (for which we also have exposure information) can be seen in the first 2 columns of Table 1. The reduction in sample size on adjustment shown in the final column was attributable mainly to the following confounders: breastfeeding (19.9% of 12 956 cases missing), maternal education level (16.6%), and child's ethnicity (13.5%). Other confounders suffered from up to 5% missing data.

Table 2 shows the unadjusted odds ratios for the 3 exposure variables and each of the outcomes. Confidence intervals are not shown. The following were significantly inversely associated at the 5% level with exposure by 93 days: hyperactivity at 47 months (P = .012), conduct problems at 47 months (P = .007), motor development at 6 months (P = .001) and at 30

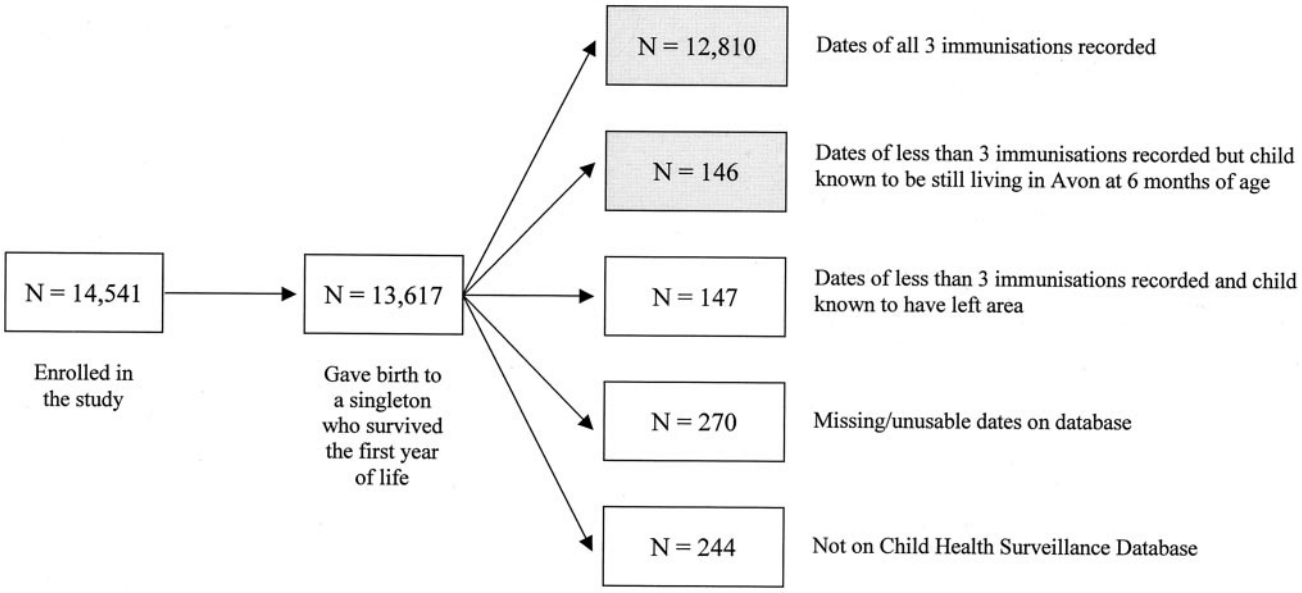

Fig 1. How the starting sample for the analysis was reached. The groups indicated by the 2 shaded boxes were believed to have valid thimerosal exposure data.

TABLE 1. Outcome Measures Used in Study of Effect of Exposure to Ethylmercury Measured in Children Delivered in Avon, UK, between 1991 and 1992

	% of Cases	*N* Unadjusted Sample	*N* Adjusted Sample
Behavior (47 mo)			
Prosocial	23.6	8858	7282
Hyperactivity	14.3	8862	7288
Emotional symptoms	10.5	8872	7290
Conduct problems	13.3	8857	7282
Peer problems	11.0	8871	7290
Total difficulties	15.4	8838	7268
Behavior (81 mo)			
Prosocial	19.2	7878	6610
Hyperactivity	11.0	7854	6602
Emotional symptoms	13.0	7871	6608
Conduct problems	10.6	7880	6612
Peer problems	14.6	7874	6608
Total difficulties	14.0	7851	6600
Fine motor skills			
6 mo	9.3	9788	8153
18 mo	11.0	9882	7969
30 mo	13.3	8522	6975
Speech			
Stumbles on words (81 mo)	17.8	7869	6597
Difficulty with sounds (81 mo)	13.6	7841	6573
Speech worries (81 mo)	3.3	7948	6654
Speech therapy (91 mo)	11.2	7346	6170
Tics			
Any tics (18–42 mo)	2.0	8256	6970
Tics (91 mo)	2.0	7495	6295
Special needs			
Child has special needs (91 mo)	8.4	7519	6310
LEA statement (91 mo)	2.9	7698	6441

LEA indicates Local Education Authority.

months ($P < .001$), difficulties with sounds at 81 months ($P = .014$), speech therapy at 91 months ($P = .024$), and special needs ($P = .038$) and statementing ($P = .013$) also at 91 months. All but speech therapy was found to be significant with both the 124-day exposure and HgAll with the inclusion of an additional association with conduct problems at 81 months ($P = .004$) for 124-day ($P = .016$) and for HgAll.

Multivariable Model

The results of the multivariable model are shown in Table 2. The combined effect of controlling for the 9 confounders was to remove a number of the significant negative associations found in the unadjusted analyses. However, this has proved insufficient to reverse the effect to the direction originally hypothesized.

There was only 1 (marginally) significant finding in the direction hypothesized: between poor prosocial behavior at 47 months of age and exposure by 3 months ($P = .031$); however, a single finding is to be expected given the 69 statistical tests performed. In 8 other analyses, the results were statistically significant but in the reverse direction, ie, the more exposed the infant, the more beneficial the outcome. These were doses by 3 months and conduct problems at 47 months ($P = .035$) and fine motor development at 30 months ($P = .021$); doses by 4 months and reported tics at 91 months ($P = .027$) and child with special educational needs ($P = .010$); and cumulative exposure and fine motor development at 30 months ($P = .003$), tics at 91 months ($P = .025$), special educational needs ($P < .001$), and child statemented by Local Education Authority ($P = .006$).

The size of the effects of each of the 9 potential confounding variables (birth weight, gestation, maternal education, gender, parity, housing tenure, midpregnancy smoking, child's ethnicity, and breastfeeding) on the relationship between exposure and outcome was examined. As an example, we studied the relationship between parity and exposure by 3 months of age. There was a strong inverse relationship with 54% of "only children" having had 2 or more doses by this time, 42% of those with 1 sibling and 34% of those with 2 or more siblings have the same exposure (χ^2 statistic for trend = 319.3, $P < .001$). Conversely, parity had the opposite relationship with fine motor development at 30 months. Ten percent of those with no siblings were in the lower tail, compared with 17% of those with 2 or more siblings (χ^2 statistic = 64.0, $P < .001$).

As a result, when controlling for parity in a model that examined the relationship between thimerosal exposure and fine motor development at 30 months, the odds ratio (OR) changed from 0.82 (confidence interval [CI]: 0.73–0.92; $P < .001$) to 0.87 (CI: 0.78–0.98; $P = .018$), thus reducing the apparent protective effect of thimerosal.

To investigate further, we chose 3 of the strongest unadjusted associations between the exposure and an adverse outcome in which to study the amount of confounding attributable to each of the 9 confounders. The pairs chosen were 1) conduct problems at 81 months and HgAll, 2) Denver development at 30

TABLE 2. Results of Regression Models With Exposure to Ethylmercury Defined by Dosage by 3 and 4 Months and a Cumulative Measure up to 6 Months and Measured in Children Delivered in Avon, UK, between 1991 and 1992

	Doses by 93 Days			Doses by 124 Days			HgAll		
	UOR	Adjusted Model		UOR	Adjusted Model		UOR	Adjusted Model	
		AOR	CI		AOR	CI		AOR	CI
Behavior (47 mo)									
Prosocial	1.02	1.12*	1.01–1.23	0.98	1.05	0.97–1.15	0.99	1.03	0.98–1.08
Hyperactivity	0.87*	0.91	0.81–1.03	0.88†	0.95	0.85–1.05	0.94*	0.98	0.93–1.04
Emotional symptoms	1.04	1.03	0.89–1.18	1.01	0.99	0.88–1.11	1.04	1.03	0.96–1.10
Conduct problems	0.86†	0.87*	0.77–0.99	0.90*	0.94	0.85–1.05	0.93†	0.96	0.90–1.01
Peer problems	1.06	1.06	0.93–1.22	1.04	1.07	0.95–1.21	1.02	1.02	0.96–1.09
Total difficulties	0.94	1.01	0.90–1.14	0.93	1.01	0.91–1.12	0.95*	0.96	0.94–1.05
Behavior (81 mo)									
Prosocial	0.98	0.97	0.87–1.09	0.95	0.97	0.88–1.07	0.98	0.99	0.94–1.04
Hyperactivity	0.97	0.98	0.85–1.13	0.97	1.01	0.89–1.15	0.97	1.00	0.93–1.07
Emotional symptoms	0.93	0.90	0.79–1.03	0.99	0.97	0.86–1.08	0.97	0.97	0.91–1.03
Conduct problems	0.92	0.93	0.80–1.07	0.86†	0.93	0.82–1.05	0.92†	0.95	0.90–1.02
Peer problems	1.03	1.04	0.92–1.18	1.01	1.03	0.92–1.15	0.99	1.01	0.95–1.07
Total difficulties	0.94	0.94	0.83–1.08	0.94	0.98	0.88–1.10	0.95	0.98	0.92–1.04
Fine motor skills									
6 mo	0.82†	0.97	0.84–1.11	0.88*	1.00	0.89–1.13	0.92†	0.99	0.93–1.05
18 mo	0.97	1.01	0.89–1.15	0.94	1.01	0.90–1.13	0.96	0.99	0.93–1.05
30 mo	0.82‡	0.86*	0.76–0.98	0.86†	0.92	0.82–1.02	0.90‡	0.92†	0.87–0.97
Speech									
Stumbles on words (81 mo)	0.95	0.93	0.83–1.05	0.96	0.99	0.90–1.10	0.97	0.99	0.94–1.05
Difficulty with sounds (81 mo)	0.87*	0.93	0.82–1.06	0.86†	0.91	0.82–1.01	0.93†	0.95	0.90–1.01
Speech worries (81 mo)	0.85	0.93	0.73–1.18	0.91	1.00	0.82–1.23	0.93	0.98	0.88–1.09
Speech therapy (91 mo)	0.86*	0.93	0.81–1.08	0.94	0.99	0.87–1.12	0.96	0.98	0.92–1.05
Tics									
Any tics (18–42 mo)	0.92	0.89	0.62–1.26	0.83	0.82	0.61–1.11	0.90	0.90	0.77–1.04
Tics (91 mo)	0.82	0.73	0.53–1.01	0.81	0.74*	0.57–0.97	0.90	0.87*	0.76–0.98
Special needs									
Child has special needs (91 mo)	0.86*	0.90	0.76–1.06	0.81†	0.84*	0.73–0.96	0.87‡	0.89‡	0.83–0.95
LEA statement (91 mo)	0.74*	0.78	0.60–1.02	0.81*	0.83	0.67–1.04	0.86†	0.87†	0.78–0.96

UOR indicates unadjusted odds ratio; AOR, adjusted odds ratio; LEA, Local Education Authority.
* $P < .05$.
† $P < .01$.
‡ $P < .001$.

months, and dosage by 3 months and 3) difficulty with sounds at 81 months and dosage by 4 months.

The unadjusted associations were recalculated for the complete-case sample for which we had all confounders. The effect size for 1 remained unchanged and for both 2 and 3 strengthened. Each confounder was then entered individually into a model that contained only the exposure variable, and the effect on the exposure's effect size was observed. The percentage change in the size of this effect was then studied to assess the amount of confounding that was taking place. We found that the only variable with a consistently high confounding effect was parity, with up to one third of the apparent effect of the exposure variable accounted for by this variable. Other than that, housing tenure and smoking accounted for 18% and 9.2% of the effect size, respectively, for example 1 and all other variables accounted for <5% each.

Missing Data

Outcome data were not available for all subjects. We compared the response to the 81-month questionnaire with the variable describing thimerosal exposure at 124 days of age. For our sample of 12 956, the response rate was 61.3%; however, this was strongly related to thimerosal exposure. Response rates ranged from 48% for those with no exposure by 124 days to 65.4% for those with full exposure (3 doses; χ^2 test for trend $P < .001$). A similar pattern was observed both for the other 2 exposure variables and for completion of other questionnaires used in this study.

A substantial number of cases were removed through inclusion of the 9 confounding factors. Additional investigation showed no evidence of a different unadjusted relationship for those cases for which only some of the confounders were observed.

To determine whether the 146 children with fewer than 3 doses of vaccine recorded were an atypical group, we refitted the multivariable models without these cases. The results were essentially the same.

Combined Effect of Fish Consumption and Thimerosal

Daniels et al[13] did not find an adverse association between maternal fish consumption during the third trimester of pregnancy and later neurodevelopment. In some cases, they actually observed a beneficial effect of increased fish in the diet, concluding that the nutritional contribution of fish might outweigh potentially harmful effects of methylmercury at the low levels present.

These findings are not dissimilar from our own results for thimerosal. This is all the more surprising when one considers that there is a negligible correlation between the 2 variables. For instance, 35.1% of those in the lowest quartile of the cumulative dose of

thimerosal by 6 months were in the top group of the fish variable (a composite measure of white and oily fish) used by Daniels et al, compared with 34.8% of those in the top quartile of cumulative dose.

We found in a bivariable analysis that it was not uncommon for both fish consumption and thimerosal to provide an independent beneficial effect. For instance, for conduct problems at 81 months of age, we found HgAll to give an OR of 0.92 (95% CI: 0.87–0.98) and fish to give an OR of 0.86 (95% CI: 0.80–0.92)—both exposures being used as 4-level ordinal variables with P values of .005 and $<.001$, respectively. In this particular example, fish remained marginally significant (OR: 0.92; 95% CI: 0.85–0.99; $P = .033$), whereas HgAll was not longer so (OR: 0.96; 95% CI: 0.89–1.02) once an adjustment for confounders had been made.

On the basis of the literature, one would expect that high levels of fish in pregnancy together with a high cumulative dose of thimerosal in early life would give an increased risk of neurodevelopmental delay compared with either factor in isolation. To investigate this, we created a 3-level variable. Group 1 was below the median of HgAll and scored low on fish intake, group 3 was above the median of HgAll and scored high on fish intake, and group 2 consisted of the middle ground. Table 3 shows the odds of each adverse outcome for groups 2 and 3 compared with that of group 1. We find that the odds are generally lower for group 3 than for group 2; furthermore, the odds for both groups are seldom >1. Hence, these 2 variables confer a combined benefit rather than a detriment.

DISCUSSION

This study, based on a large United Kingdom–based prospective cohort, shows no evidence of any harmful effect of an accelerated immunization schedule with thimerosal-containing vaccines. We are in agreement with the other British study[9] in showing little or no risk associated with the administering of thimerosal-containing vaccines to children younger than 6 months. Their 1 positive finding was a higher rate of tics; however, we showed no evidence of increased tics by 42 months and actually a reduction in reported tics at 91 months.

A reported limitation in the study by Andrews et al[9] was the lack of information on potential confounding variables. We have now shown that, with the variables we have considered at least, there is surprisingly little effect giving weight to their findings.

One explanation for the lack of a significant finding in our study is that the size of the effect of a confounder that has not been considered overwhelms any possible detrimental effect of thimerosal that one would expect to be acting in the opposite direction. This seems unlikely because many of the variables that we had expected to be strong confounders made very little difference to the results.

The analysis of the children with missing outcome data showed that these tended to be immunized later

TABLE 3. Combined Effect of Exposure to Methylmercury From Maternal Fish Consumption During Pregnancy and Exposure to Ethylmercury From Thiomersal During the First 6 Months of Life, Measured in Children Delivered in Avon, UK, between 1991 and 1992

	Unadjusted Effect		Adjusted Effect	
	Group 2, OR (95% CI)	Group 3, OR (95% CI)	Group 2, OR (95% CI)	Group 3, OR (95% CI)
Behavior (47 mo)				
Prosocial	0.87 (0.75–1.01)	0.86 (0.74–1.00)	0.86 (0.73–1.02)	0.94 (0.79–1.11)
Hyperactivity	0.96 (0.81–1.14)	0.70 (0.58–0.85)	1.08 (0.89–1.32)	0.90 (0.73–1.12)
Emotional symptoms	0.83 (0.68–1.01)	0.83 (0.67–1.01)	0.80 (0.65–1.00)	0.78 (0.62–0.99)
Conduct problems	0.77 (0.65–0.92)	0.63 (0.53–0.76)	0.83 (0.68–1.01)	0.76 (0.61–0.94)
Peer problems	0.88 (0.72–1.06)	0.82 (0.67–1.01)	0.92 (0.74–1.15)	0.94 (0.74–1.19)
Total difficulties	0.78 (0.67–0.93)	0.64 (0.54–0.76)	0.89 (0.73–1.07)	0.82 (0.67–1.00)
Behavior (81 mo)				
Prosocial	0.88 (0.74–1.04)	0.83 (0.70–0.99)	0.87 (0.72–1.05)	0.83 (0.68–1.01)
Hyperactivity	0.89 (0.73–1.10)	0.78 (0.63–0.97)	0.88 (0.69–1.11)	0.82 (0.64–1.06)
Emotional symptoms	0.81 (0.67–0.98)	0.83 (0.68–1.01)	0.78 (0.63–0.97)	0.80 (0.64–1.00)
Conduct problems	0.80 (0.65–0.99)	0.63 (0.51–0.79)	0.85 (0.67–1.07)	0.74 (0.58–0.95)
Peer problems	0.67 (0.56–0.81)	0.69 (0.58–0.84)	0.68 (0.56–0.84)	0.71 (0.58–0.88)
Total difficulties	0.76 (0.63–0.91)	0.66 (0.54–0.80)	0.80 (0.65–0.98)	0.74 (0.59–0.92)
Fine motor skills				
6 mo	0.89 (0.73–1.09)	0.82 (0.67–1.02)	0.93 (0.75–1.17)	0.98 (0.77–1.25)
18 mo	0.81 (0.68–0.97)	0.69 (0.57–0.84)	0.81 (0.66–0.99)	0.75 (0.60–0.94)
30 mo	0.88 (0.73–1.05)	0.73 (0.60–0.88)	0.88 (0.72–1.08)	0.77 (0.62–0.96)
Speech				
Stumbles on words (81 mo)	0.84 (0.71–1.00)	0.85 (0.71–1.01)	0.85 (0.70–1.04)	0.89 (0.72–1.08)
Difficulty with sounds (81 mo)	1.10 (0.90–1.34)	1.04 (0.84–1.28)	0.95 (0.76–1.19)	0.94 (0.75–1.19)
Speech worries (81 mo)	0.95 (0.65–1.38)	1.08 (0.73–1.58)	0.80 (0.53–1.20)	1.05 (0.69–1.60)
Speech therapy (91 mo)	0.80 (0.65–0.99)	0.74 (0.59–0.92)	0.73 (0.57–0.90)	0.73 (0.57–0.93)
Tics				
Any tics (18–42 mo)	0.70 (0.46–1.06)	0.41 (0.25–0.66)	0.98 (0.57–1.69)	0.55 (0.29–1.02)
Tics (91 mo)	0.97 (0.61–1.56)	0.77 (0.46–1.27)	1.01 (0.60–1.70)	0.70 (0.40–1.24)
Special needs				
Child has special needs (91 mo)	0.86 (0.68–1.10)	0.82 (0.64–1.05)	0.80 (0.61–1.05)	0.81 (0.62–1.08)
LEA statement (91 mo)	0.75 (0.52–1.10)	0.59 (0.40–0.89)	0.77 (0.52–1.16)	0.64 (0.41–1.00)

LEA indicates Local Education Authority.

and hence have a lower thimerosal exposure at any given age. We also found that for the nonmissing data, those who were immunized later tended to have the kind of sociodemographic status that was associated with the poor developmental outcomes. This means that the children with missing outcome data are likely to have lower thimerosal exposure but more adverse outcomes. Therefore, any bias introduced as a result of not having the missing data is likely to be in the direction of the hypothesis (higher exposure associated with adverse outcomes). Although this bias would be expected to effect the unadjusted analysis, it should have much less effect on the adjusted analysis that controls for sociodemographic factors. Although it could be argued that scores based on maternal reported behavior/development are not sensitive enough to detect the subtle differences that we might expect in a population with no other major sources of mercury, we have shown that there is also no detrimental effect with the less subjective measure of a child's having special educational needs.

One limitation of this study is the uniformity in the exposure variable. As stated earlier, 77% of those who had had only 2 doses by 4 months of age had received their third vaccine by the end of the fifth month. We would expect this to reduce our power to detect a harmful effect of the thimerosal preservative; however, this does not explain why 5 of the 6 significant results and 39 of the 57 nonsignificant results are in the direction contrary to that hypothesized.

CONCLUSION

We could find no convincing evidence that early exposure to thimerosal had any deleterious effect on neurologic or psychological outcome when given according to an accelerated schedule. This is reassuring for developing countries that receive DTP vaccines according to the Expanded Program of Immunization schedule and where multidose vials that contain the thimerosal preservative are often the only option. In the face of the current evidence from this study and the growing literature, the dangers posed by contaminated multidose vaccine vials far outweigh any potential risk posed by thimerosal.

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