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Early exposure to the combined measles–mumps–rubella vaccine and thimerosal-containing vaccines and risk of autism spectrum disorder

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ABSTRACT

Objective: This case–control study investigated the relationship between the risk of Autism Spectrum Disorder (ASD) onset, and early exposure to the combined Measles–Mumps–Rubella (MMR) vaccine and thimerosal consumption measured from vaccinations in the highly genetically homogenous Japanese population.
Methods: Vaccination histories at 1, 3, 6, 12, 18, 24, and 36 months from birth were investigated in ASD cases (189 samples), and controls (224 samples) matching age and sex in each case. Crude odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated to determine relationship between MMR vaccination and ASD. The differences in mean values of the thimerosal dosage between cases and controls were analyzed using an unpaired *t*-test. MMR vaccination and thimerosal dosage were also investigated using a conditional multiple-regression model.
Results: There were no significant differences in MMR vaccination and thimerosal dosage between cases and controls at any age. Furthermore, the ORs (95% CIs) of MMR vaccination and thimerosal dosage associated with ASD in the conditional multiple regression model were, respectively, 0.875 (0.345–2.222) and 1.205 (0.862–1.683) at age 18 months, 0.724 (0.421–1.243) and 1.343 (0.997–1.808) at 24 months, and 1.040 (0.648–1.668) and 0.844 (0.632–1.128) at 36 months. Thus, there were no significant differences.
Conclusions: No convincing evidence was found in this study that MMR vaccination and increasing thimerosal dose were associated with an increased risk of ASD onset.

1. Introduction

Autism Spectrum Disorder (ASD) is a type of neurodevelopmental disorder that significantly affects patients' social functions for their lifetime. The etiology and pathology of this disorder are still predominantly unknown. It has been indicated that there is a strong association with genetic factors, and the relative risk among siblings is known to be greater than 20 with heritability estimated to be as high as 50–80% [1–4]. In contrast, the concordance rate of identical twins is not 100%, indicating that environmental factors also play an important role in the onset of ASD [1,4,5]. One of the concepts that has been discussed is whether vaccinations increase the risk of ASD onset.

The view that vaccinations and ASD are related dates back to Wakefield et al.'s article [6]; however, the paper was retracted in 2010 because of ethical and methodological problems [7]. Thereafter, other studies suggested a link between the measles–mumps–rubella vaccine (MMR) and ASD [8,9], and concerns emerged that thimerosal (49.6% ethyl mercury by weight) included in other vaccines as a preservative might increase the ASD risk [10–12]. On the other hand, three case–control studies, which

Abbreviations: ASD, Autism Spectrum Disorder; MMR, measles–mumps–rubella; TCV, thimerosal-containing vaccine; YPDC, Yokohama Psycho-Developmental Clinic; MCH handbook, Maternal and Child Health handbook; DPT, diphtheria–pertussis–tetanus.

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used the Metropolitan Atlanta Developmental Disabilities Surveillance Program [13], the UK General Practice Research Database [14], or the UK Doctors' Independent Network Database [15], were conducted in Western countries and demonstrated no link between MMR vaccination and ASD. In addition, another case–control study that utilized the Centers for Disease Control and Prevention's Vaccine Safety Datalink also did not show significant differences in the amount of exposure to thimerosal between ASD and non-ASD groups at various months following birth [16]. Moreover, according to two meta-analytic articles, published in 2014, there were no associations between exposure to MMR vaccine/thimerosal and ASD onset [17,18]. However, most studies have not considered vaccinations timing and the subject's racial heterogeneity even though genetic factors are known to be strongly involved in ASD onset. As an investigation that specified the race of the study participants, we conducted a case–control study from the Japanese population [19]. Japanese people were proven to be highly genetically homogenous according to the genotyping results of 140,387 single nucleotide polymorphisms [20]. In our previous study, there was not any convincing evidence that MMR vaccination was associated with an increased risk of ASD in Japanese people. However, the effects due to the differences in vaccinations timing and the amount of exposure to thimerosal were not accounted for in this study.

The risks related to ASD onset and vaccinations are still debated [21] and many parents and guardians avoid vaccinations due to fear of their children developing ASD [22–27], despite the existence of these studies. Therefore, we conducted a case–control study with Japanese subjects, who are highly genetically homogenous, to further investigate whether exposure to MMR vaccine/thimerosal is related to ASD onset in greater detail. We also accounted for temporal factors from birth to vaccinations. The present study involves the same study population as our previous study [19], and consists of a more in-depth investigation of the vaccine data.

2. Materials and methods

2.1. Study population

2.1.1. Cases (Fig. 1)

Case data from patients of the Yokohama Psycho-Developmental Clinic (YPDC) were used in this study. The YPDC opened in April 1997 and is located in the Kanto area of Japan. It only accepts patients with suspected neurodevelopmental disorders. Of the patients who initially consulted the YPDC from April 1997 until March 2011, eligible case subjects: (1) were diagnosed with ASD, and (2) had been born between April 1, 1986 and April 30, 1992, the possible time period for MMR vaccination.

2.1.2. Diagnosis of ASD

To consider diagnoses, the developmental history and the present illness of patients were obtained through the use of the Diagnostic Interview for Social and Communication Disorder, version 10 (DISCO). This diagnostic interview, the DISCO is a semi-structured interview form for diagnosing ASD. It is recognized as one of the best ways to obtain a reliable and valid diagnosis of ASD [28–30]. Patients were diagnosed based on the application of the ASD algorithm of the Diagnostic and Statistical Manual, 5th edition, using the DISCO data.

2.1.3. Period of birth

MMR vaccination in Japan was conducted under specific circumstances and for only a short period of time. A combined MMR vaccination program commenced from April 1989, and only one vaccination using MMR was included in the immunization schedule. The monovalent mumps, measles, and rubella vaccines remained the optimal choice of vaccine for those who did not participate in the MMR program. However, soon after the immunization program had started, there were several cases of aseptic meningitis, which may have been caused by the mumps vaccine [31]. As a result, in April 1993, the Government ceased extensive inoculation with MMR. Therefore, children who were born from April 1984 to April 1992 could receive MMR vaccination. However, children who were born between April 1984 and March 1986 were able to receive it after the age of three. Therefore, they were excluded from the samples, because autism features always appear before the age of three. As a result, children who were born from April 1986 to April 1992 were included in the present study.

2.1.4. Controls (Fig. 1)

Control subjects were recruited as volunteers from general schools in the Kanto area which is the same area where YPDC patients reside. There were 450 students who were born from April 1986 to April 1992 in these schools. Students who had previously been recognized as having developmental problems and were already receiving care were excluded. We obtained informed consent from 252 students (56.0%).

2.2. MCH handbook and source of data

The vaccination records, such as the type of vaccine, dose, manufacturer, lot number, medical institution, and date of prior vaccinations were obtained from the Maternal and Child Health (MCH) handbook, which is a record provided to all mothers by the relevant Japanese health system institution. It is a highly reliable data record of early development, health, and immunization, and the data are record by health professionals (e.g., public health nurses, obstetricians, and pediatricians) [32,33].

From this handbook, we assessed the type of vaccine, frequency, dose, timing, manufacturer, and lot number of vaccinations that were given by 36 months of age when ASD features become apparent. The targeted vaccines were the MMR and the thimerosal-containing vaccines (TCVs) such as the diphtheria–pertussis–tetanus vaccine (DPT); the polio vaccine; the Japanese B encephalitis vaccine; the flu vaccine; and the hepatitis B vaccine. Case and control subjects whose records in the MCH handbook were missing or illegible and those who were vaccinated outside Japan were excluded.

2.3. Selection of case children and matched control children

Among the patients who initially consulted the clinic between April 1997 and March 2011, 1875 cases of ASD were identified. Of these, 89 cases were excluded because the MCH handbook was missing or the vaccination record in the handbook could not be read, and three were excluded because they had received vaccinations outside Japan. Of the remaining 1783 cases, 354 cases (males: $n = 286$, 80.8%) were born between April 1986 and April 1992, the time period when MMR vaccinations were administered to children less than 3 years old.

For the control group, 252 subjects from the general school population were recruited into the present study. Of these, 28 cases were subsequently excluded because the MCH handbook was missing or the vaccination record could not be read. The goal was to have a matched control for each case. However, since there were not enough controls to match to all cases, 189 subjects were chosen randomly from the ASD group as the case group. The controls were individually matched to cases by age and sex. There were 189 cases, mean age 22.6 years (SD 2.2), and 224 controls, mean age 22.6 years (SD 2.2), with case-to-control ratios ranging from 1:1 to 1:2 (Fig. 1).

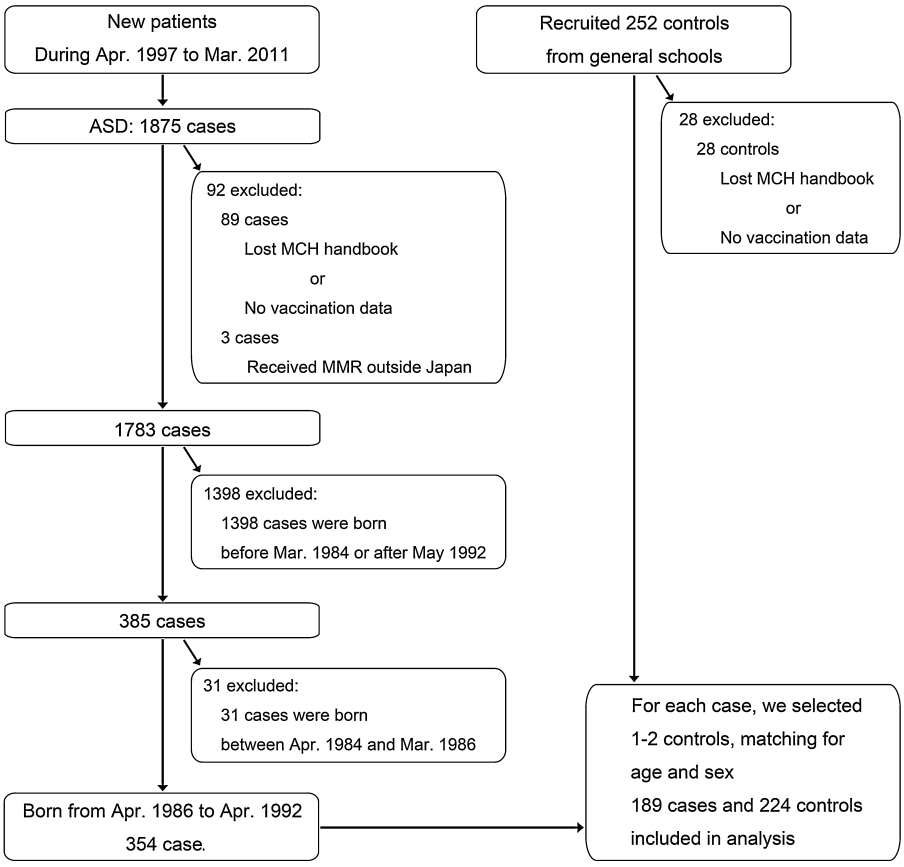

Fig. 1. Flow chart of cases and controls identified, excluded, and included in the analysis.

2.4. Statistical analysis

2.4.1. MMR

The number of individuals who received MMR vaccination by 1, 3, 6, 12, 18, 24, and 36 months of age were determined in both case and control groups, and the differences of whether or not an individual received the vaccinations at each age were investigated with χ^2 test. In addition, the crude odds ratios (ORs) and 95% confidence intervals (CIs) of MMR vaccination-induced ASD were calculated.

2.4.2. TCVs

The thimerosal content in each vaccine was calculated from the manufacturer, lot number, and vaccination dose of the vaccine recorded in the MCH handbook. The amount of exposure to thimerosal was determined in both case and control groups at 1, 3, 6, 12, 18, 24, and 36 months of age. In addition, the differences in thimerosal exposure at each age were investigated in the case and control groups with F-test and unpaired *t*-test. According to the results of the F-test, Student's *t*-test or Welch's *t*-test was chosen.

2.4.3. Conditional multiple logistic model

The effects of both MMR vaccination and thimerosal dosage on ASD onset were investigated by calculating the odds ratios and their 95% CIs using a conditional multiple logistic model with MMR vaccination and thimerosal dosage as explanatory variables.

2.4.4. Power analysis

To calculate power levels of the present study, we conducted power analyses in accordance to a general power calculation model for the χ^2 test, *t*-test, and the conditional multiple regression model. In brief, calculations of the power level were based on an alpha level of 0.05, two tails, and a medium effect size ($w = 0.30$ for the χ^2 test, $d = 0.50$ for the *t*-test, and $f^2 = 0.15$ for the conditional multiple regression model, in accordance with Cohen's criteria), which we consider to be clinically meaningful.

ORs were considered significant when the lower 95% CI exceeded 1.0. The *t*-tests were two-sided, and significance was defined as $p < 0.05$. For power calculation, G*power v3.1 was used.

2.5. Ethical considerations

The protocol of this study was approved by the Ethics Committees of the Nagoya University Graduate School of Medicine, and the study itself was conducted in conformity with the established ethical standards of all institutions. The study was explained to the participants both verbally and in writing, and written consent was obtained from all participants.

3. Results

3.1. MMR

None of the individuals in the case group received MMR vaccinations by 12 months of age. Subsequently, the MMR vaccination rate gradually began to increase. For the control group, one individual (0.4%) received the MMR vaccination by 6 months of age. However, there was no subject who received the MMR vaccination from 6 months to 12 months. The rate gradually began to increase after 12 months. Eventually, the rates of cases and controls at 36 months were 24.9% and 24.1%, respectively. The OR of MMR vaccination causing ASD at 36 months was 1.04 (0.65–1.68). Furthermore, regarding each timing by 36 months, the ORs were: 0.81 (95% CI: 0.31–2.09) at 18 months and 0.93 (0.55–1.57) at 24 months. These results demonstrated that statistical differences in

Table 1
Case and control children who received MMR vaccinations.

Age (months)	*n* (%)		*p*-value	ORs (95% CIs)
	Cases (*n* = 189)	Controls (*n* = 224)		
1	0 (0)	0 (0)	1	–
3	0 (0)	0 (0)	1	–
6	0 (0)	1 (0.4)	0.36	0 (0–∞)
12	0 (0)	1 (0.4)	0.36	0 (0–∞)
18	9 (4.8)	13 (5.8)	0.64	0.81 (0.31–2.09)
24	35 (18.5)	44 (19.6)	0.77	0.93 (0.55–1.57)
36	47 (24.9)	54 (24.1)	0.86	1.04 (0.65–1.68)

OR, odds ratios; CI, confidence interval. The case group involved 189 samples, and the control group involved 224 samples at each months from birth.

Table 2
Cumulative exposure to thimerosal according to exposure period.

Age (months)	Cumulative exposure amount, μg				*p*-value
	Cases (*n* = 189)		Controls (*n* = 224)		
	Mean (SD)	Min–Max	Mean (SD)	Min–Max	
1	1.3 (18.2)	0–250	0 (0)	0–0	0.28[a]
3	1.3 (18.2)	0–250	2.2 (33.4)	0–500	0.73[b]
6	10.6 (84.9)	0–750	16.7 (120.7)	0–1500	0.54[b]
12	172.0 (457.1)	0–2250	112.1 (372.8)	0–1600	0.15[b]
18	412.7 (627.1)	0–2250	348.7 (605.2)	0–2100	0.29[a]
24	804.2 (741.6)	0–2250	676.8 (719.5)	0–2250	0.08[a]
36	1314.8 (796.5)	0–2750	1389.3 (583.5)	0–2750	0.29[b]

SD, standard deviation; Min–Max, the minimum and maximum amounts of thimerosal cumulative exposure. The case group involved 189 samples, and the control group involved 224 samples at each month from birth.
There is 495.5 μg of mercury for every 1000 μg of thimerosal.
[a] Student's *t*-test,
[b] Welch's *t*-test.
According to the results of the F-test, Student's *t*-test or Welch's *t*-test was chosen.
The article has been modified following feedback and the data in Table 2 updated.

the rate of vaccinations could not be detected between the two groups at each age (Table 1).

3.2. TCVs

In the case group, there was one individual who received a hepatitis B vaccinations immediately after birth due to maternal hepatitis B, and thus the mean amount of exposure to thimerosal at 1 month of age was 1.3 μg (SD: ±18.2). Subsequently, the amount of exposure to thimerosal gradually began to increase in this group at 6 months in accordance with DPT and other vaccinations, and was 1314.8 μg (±796.5) by 36 months. In the control group, while there were no individuals who were vaccinated with TCVs by 1 month, one individual received a DPT vaccination by 3 months and the mean amount of exposure to thimerosal was therefore 2.2 μg (±33.4). As a result, the amount of exposure to thimerosal gradually began to increase from 6 months, and was 1389.3 μg (±583.5) by 36 months. The mean amount of exposure to thimerosal was compared between the case and control groups at 36 months using an unpaired *t*-test, but statistically significant difference was not observed. Moreover, the mean amount of exposure of thimerosal at 1, 3, 6, 12, 18, and 24 months were also compared, but there were no statistically significant differences between the cases and controls at any age (Table 2).

3.3. Conditional multiple logistic model

In the conditional multiple logistic model, the ORs of 1 μg thimerosal exposure and MMR vaccination causing ASD were 1.205 (95% CI: 0.862–1.683) and 0.875 (0.345–2.222) at 18 months, 1.343 (0.997–1.808) and 0.724 (0.421–1.243) at 24 months, and 0.844 (0.632–1.128) and 1.040 (0.648–1.668), at 36 months, respectively. There were no significant differences between cases and controls in MMR vaccination and thimerosal exposure at any age (Table 3).

3.4. Power analysis

We conducted χ^2 tests considering MMR vaccinations, *t*-tests for thimerosal exposure, and a conditional multiple regression model for both MMR vaccinations and thimerosal exposure. Each test had almost 100% power to detect medium size differences in Cohen's criteria, which we consider to be clinically meaningful.

4. Discussion

In this study, we conducted a case–control study to assess the rate of MMR vaccination and amount of exposure to thimerosal at 1, 3, 6, 12, 18, 24, and 36 months of age with the objective to determine the risk of ASD onset due to early exposure to MMR vaccine/

Table 3
Odds ratios and 95% confidence intervals of cumulative exposure amount of thimerosal and MMR vaccination.

Age (months)	Factors	ORs	95% CIs
18	MMR (−)	1	
	MMR (+)	0.875	0.345–2.222
	Thimerosal	1.205	0.862–1.683
24	MMR (−)	1	
	MMR (+)	0.724	0.421–1.243
	Thimerosal	1.343	0.997–1.808
36	MMR (−)	1	
	MMR (+)	1.040	0.648–1.668
	Thimerosal	0.844	0.632–1.128

OR, odds ratios; CIs, confidence intervals; MMR, measles, mumps, rubella vaccine. The case group involved 189 samples, and the control group involved 224 samples at each month from birth.
Odds ratios and 95% confidence intervals of thimerosal and MMR vaccinations cumulative exposure in each month from birth were analyzed with a conditional multiple logistic model. Odds ratio for thimerosal is for a 1 μg increase in thimerosal exposure. There is 495.5 μg of mercury for every 1000 μg of thimerosal.

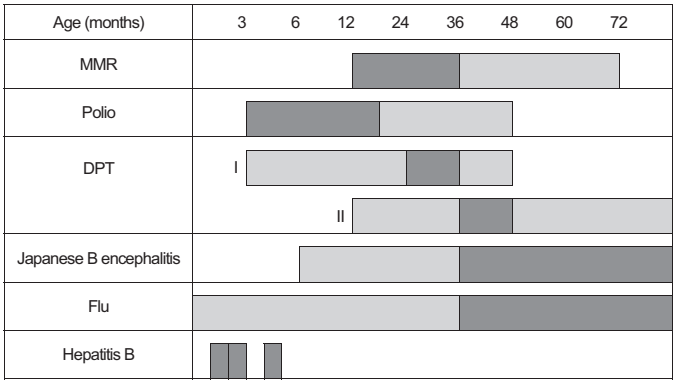

Fig. 2. The MMR and TCVs vaccinations schedule for Japan during the duration of the study. The recommended ages of the vaccinations are illustrated by the darker-shaded areas. The lighter-shaded areas show ages that they could receive the vaccinations. "I" represents the first DPT vaccination, and "II" represents the second DPT vaccination.

TCVs. We also conducted conditional multiple logistic model analyses to comprehensively investigate these findings. Our results showed that the rate of MMR vaccination and amount of exposure to thimerosal were not statistically significantly different between the ASD and non-ASD groups. These results therefore indicated that MMR vaccination and increased amount of exposure to thimerosal do not elevate the risk for ASD onset. Our results are consistent with the findings from previous case–control studies [13–16] that investigated the rate of MMR vaccination or the amount of exposure to thimerosal during the prenatal and infant periods. One of the significant findings of this study is that there were no differences between the case and control groups in receiving MMR vaccination or the amount of exposure to thimerosal at 1, 3, 6, 12, 18, 24, and 36 months, and ASD features become apparent by 36 months so these data indicate that early vaccinations do not become risks for ASD onset.

The strengths of our study were: the study population consisted of individuals other than Caucasians; the study included Japanese people, considered to be highly homogenous on the genetic level, which gave us the opportunity to minimize the effect of population-specific risk factors that might interact with environmental exposures (i.e., immunization); the study used the MCH handbook, a highly reliable data source; and the study was carried out using ASD diagnoses that were made with high reliability and validity.

In Japan, the prevalence of ASD has not decreased even after MMR vaccine were discontinued [34,35]. Internationally, the prevalence of ASD remains high in spite of the increased usage of thimerosal-free vaccines [36–38]. Our results also corroborate these current epidemiological situations.

Nonetheless, the present study does not guarantee the safety of the vaccines. There are numerous potential side effects that can occur as a result of being vaccinated, and because the actual circumstance differs depending on the individual, it is clearly essential to assess and consider advantages and disadvantages for each individual. Moreover, the development of vaccines with reduced risks or potential risks other than ASD onset are also desired.

MMR vaccinations prior to 12 months of age and TCV vaccinations prior to 6 months of age are rare in Japan compared to other countries. This tendency might be because of the vaccination schedule in Japan (Fig. 2). MMR vaccinations were recommended for children over 12 months of age, and certain TCVs were recommended for those over 36 months, in the past. Additionally, there was no data of body weight when samples received TCV vaccinations. We could not calculate dosages of thimerosal exposure per kilogram. These factors hampered the study of the effects of vaccinations in infants immediately after birth, using a retrospective study design. It is unclear whether early vaccinations are more harmful or not. It may be necessary to conduct a prospective study that follows subjects who were vaccinated very early in life.

Moreover, various genetic and environmental factors have been elucidated as potential risks involved in the onset of ASD [1]. In particular, several studies have been discussed that address whether ASD cases who are apparently associated with vaccinations have had their own health problems prior to vaccinations or have a family history of autoimmune diseases [39]. While the present study investigated MMR and TCVs as environmental factors, it did not include a variety of other factors, such as maternal psychiatric state and medications during pregnancy, infections, air pollution, or metals, which may be related to the onset of ASD and infant neurodevelopment [40–48]. Future studies should be conducted including these other factors. Nonetheless, it is presumable that multiple factors affecting the onset of ASD exist and that the size of their effects may not be large [49]. Thus, it is essential to further increase the sample size to compositely investigate these factors.

Furthermore, we could utilize highly reliable data in the present study by using vaccine records from the MCH handbook. On the other hand, this study did not account for the reasons why vaccines were not given to certain individuals. ASD is known to exhibit various comorbidities such as epilepsy and malformations as well as hyperkinesia and temper tantrums. These may be the reasons why parents and guardians avoid vaccinations, and may have potentially affected their decisions in consenting to the vaccinations. Therefore, it may be desirable to investigate the reasons for avoiding the vaccinations. A prospective study that follows women from their pre-pregnancy or prenatal stages in the general population in order to study other environmental factors affecting their children may also be desirable in the future.

We believe it is necessary to explore genetic factors as well as conduct research that accounts for environmental factors in order elucidate the pathology of ASD. These may lead to early diagnosis of ASD or the development of a biomarker to identify high-risk groups, which may, in turn, contribute to improved quality of life for ASD patients and their families.

MMR vaccination and increased thimerosal exposure did not elevate the risk for ASD onset in this Japanese population. Therefore, there is no need to avoid these vaccinations due to concern of inducing ASD. Nonetheless, many facts regarding the pathology of ASD remain unknown, and further elucidation in the future is anticipated.

Conflict of interest

The authors have no conflicts of interest to declare.

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