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Measles, mumps and rubella vs diphtheria–tetanus–acellular-pertussis–inactivated-polio–*Haemophilus influenzae* type b as the most recent vaccine and risk of early 'childhood asthma'

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Abstract

Background and objective: Live vaccines may have beneficial non-specific effects. We tested whether the live measles, mumps and rubella (MMR) vaccine compared with the non-live diphtheria–tetanus–acellular-pertussis–inactivated-polio–*Haemophilus influenzae* type b (DTaP-IPV-Hib) vaccine as the most recent vaccine was associated with less childhood asthma and fewer acute hospital contacts for childhood asthma among boys and girls.

Methods: This study is a nationwide register-based cohort study of 338 761 Danish children born between 1999 and 2006. We compared (i) the incidence of first-registered childhood asthma based on hospital contacts and drug prescriptions and (ii) the incidence of severe asthma defined as acute hospital contacts for childhood asthma between the ages of 15 and 48 months among children whose last received vaccine was three doses of DTaP-IPV-Hib and then MMR with children whose last received vaccine was three doses of DTaP-IPV-Hib.

Results: For boys, following the recommended vaccine schedule of MMR after DTaP-IPV-Hib3 compared with DTaP-IPV-Hib3 as the last received vaccine, MMR was associated with 8.1 (95% confidence interval 3.9–12.3) fewer childhood asthma cases per 1000 boys, corresponding to 10% (5–15%) reduction in the cumulative incidence of

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childhood asthma. MMR, when given last, was also associated with 16.3 (95% confidence interval 12.7–20.0) fewer acute hospital admissions for childhood asthma per 1000 boys, corresponding to a 27% (22–31%) reduction in the cumulative incidence. No associations were seen for girls.

Conclusion: MMR may have a protective effect against childhood asthma for boys. This calls for an understanding of whether non-specific effects of vaccines can be used to optimize our vaccine programmes.

Key words: Asthma, immunity, heterologous, immunization, measles, mumps and rubella vaccine, non-specific effects of vaccines, infant, asthma, vaccine sequence, trained innate immunity

Key Messages

- The live measles, mumps and rubella (MMR) vaccine as the most recently received vaccine may reduce childhood asthma.
- In a Danish population of children aged 15–48 months, the MMR vaccine compared with the non-live diphtheria–tetanus–acellular-pertussis–inactivated-polio–*Haemophilus influenzae* type b vaccine (DTaP-IPV-Hib) as the most recent vaccine was associated with less childhood asthma and less severe asthma for boys.
- Timely MMR after DTaP-IPV-Hib may protect one in 123 (95% CI 81–256) boys aged between 15 and 48 months from childhood asthma.
- This potential calls for a better understanding of non-specific effects of vaccines.

Introduction

Vaccines may have beneficial non-specific effects (NSEs).[1–4] Live vaccines affect the innate immune system beneficially leading to increased response to unrelated pathogens[2] and are associated with lower morbidity and mortality from non-targeted diseases.[1,3–7] Studies suggest that live vaccines induce a T-helper 1 cell dominant shift, reducing atopic diseases.[4,8,9] In contrast, non-live vaccines can induce tolerance of the innate immune system leading to decreased responses to unrelated pathogens[2] and have been associated with higher morbidity and mortality from non-targeted diseases.[1,3–7] The NSEs of live vaccines are most pronounced as long as a given vaccine is the most recent vaccine and may vary by sex.[4,8,9]

Studies of the live measles, mumps and rubella (MMR) vaccine and childhood asthma have reported preventive effects[10–13], detrimental effects[14] or no effect[15–19]. However, vaccination sequence was not assessed in any of the studies[10–19] and sex-differential effects were only assessed in one study.[11]

The main objective of this study was to test the hypothesis that the live MMR vaccine, as the most recent vaccine, compared with the non-live diphtheria–tetanus–acellular-pertussis–inactivated-polio–*Haemophilus influenzae* type b (DTaP-IPV-Hib) vaccine is associated with a lower incidence of childhood asthma, defined by hospital contacts and drug prescriptions in Danish children aged 15–48 months (hypothesis 1). Our secondary objective was to test whether MMR was associated with a lower incidence of severe childhood asthma defined by acute hospital contacts (hypothesis 2). We examined whether associations differed by sex.

Methods

This study is a register-based cohort study of Danish children followed from the age of 15 months until the age of 48 months for the risk of childhood asthma according to whether their last vaccine received was DTaP-IPV-Hib. Linkage across Danish nation-wide registers is possible using Danish personal identification numbers assigned to all new-borns. We used information from The Danish Civil Registration System, the Danish National Health Service Register, the Danish National Patient Register, the Danish National Prescription Register, the Danish Medical Birth Register, and information from Statistics Denmark (Supplementary Information 1, available as Supplementary data at *IJE* online).

Study base and vaccinations

To reduce interference from vaccines other than MMR and DTaP-IPV-Hib, the study base was children born in Denmark from 1 July 1999 until and including 30

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September 2006 and followed from 15 months of age until 48 months of age (Supplementary Figure 1, available as Supplementary data at *IJE* online). For this study base, the Danish childhood vaccination programme until 48 months of age was three doses of the non-live DTaP-IPV-Hib at 3, 5, and 12 months of age and the first dose of the live MMR at 15 months of age.

In Denmark, vaccines are administered free-of-charge by general practitioners. For the purpose of reimbursement, information about vaccine type, dose and week of vaccination is collected in the Danish National Health Service Register.[20]

Childhood asthma

Asthma in young children may be differentiated by multiple phenotypes[21] and multiple ways of phenotyping.[22] Asthma, asthmatic bronchitis and infection-induced wheezing in young children are difficult to separate using register data, hence we used the term 'childhood asthma' to cover the aforementioned diseases.

Childhood asthma was defined by information from two sources: (i) the Danish National Patient Register[23] holds information on hospital contacts coded with the 10th version of the international classification of diseases (ICD-10); (ii) The Danish National Prescription Register[24] holds information about all redeemed prescriptions in Danish pharmacies.

The main outcome (hypothesis 1) was the incidence of first-registered childhood asthma between 15 and 48 months of age defined as the first registration of a hospital contact (outpatients, inpatients and emergency room) according to ICD-10 codes J45 (*Asthma*) and J46 (*Status asthmaticus*) or the first prescription of inhaled glucocorticoids (R03BA) or montelukast (R03DC03) (at least two prescriptions of either glucocorticoids or montelukast within 12 months). Our second outcome (hypothesis 2) was severe childhood asthma between 15 and 48 months of age defined as the incidence of all acute hospital contacts (inpatients and emergency room visits) with ICD-10 codes J45 or J46. Allowing for recurrent events, adjacent acute hospital contact periods within 5 days of the last hospital discharge counted as one acute hospital contact.

Inclusion and exclusion criteria

To ensure that the study population consisted of children who followed the vaccination schedule before the baseline of our study, only children who had received the first two doses of DTaP-IPV-Hib before the age of 11 months were included. For hypothesis 1, we excluded children who had been registered with childhood asthma before 15 months of age, whereas this restriction did not apply for hypothesis 2, since it focused on repeated events (Figure 1 and Supplementary Figure 2, available as Supplementary data at *IJE* online).

Sequence cohorts

A proportion of Danish children deviate from the recommended schedule of the childhood vaccination programme. This variation allows us to investigate the robustness of the analyses in three partly overlapping vaccine sequence cohorts (Figure 1); recommended sequence (DTaP-IPV-Hib1-3-then-MMR vs DTaP-IPV-Hib1-3 only), early MMR sequence (DTaP-IPV-Hib1-2-then-MMR vs DTaP-IPV-Hib1-2 only) and interrupted sequence (DTaP-IPV-Hib1-2-then-MMR vs DTaP-IPV-Hib1-2-then-MMR-then-DTaP-IPV-Hib3).

Follow-up

For hypothesis 1, all children entered the study at the first Sunday after they turned 15 months of age or when their vaccination sequence qualified them for one of the sequence cohorts described above, whichever occurred last. All children left the study: (a) at the date of a registered childhood asthma event, (b) at 48 months of age, (c) when receiving more than one vaccine in one day or receiving unrelated vaccines, or (d) 12 months before emigrating or dying, to allow two prescriptions to be registered within a year, whichever occurred first. For hypothesis 2, the same entry and exit criteria applied, except that children registered with an acute hospital contact for childhood asthma left the study for 5 days and re-entered the study to make sure that we did not count one episode several times.

Statistical methods

We suspected that hospital admissions due to infectious diseases could affect both vaccination status[25,26] and later childhood asthma[27,28]; furthermore hospital admissions due to infectious diseases have been shown to be reduced by prior MMR vaccination[4,29] (illustrated in Supplementary Figure 3, available as Supplementary data at *IJE* online). This is known as time-varying confounding. We attempted to control for this potential issue using weights, which we updated each week based on 22 covariates (Supplementary Information 1 and 2, available as Supplementary data at *IJE* online). Such an approach is well-established and aims at creating comparable comparison groups at any given time during follow-up.[30,31] We have added a technical description in Supplementary Information 2, available as Supplementary data at *IJE* online.

We calculated the crude and weighted cumulative incidence rates and reported the cumulative incidence rate

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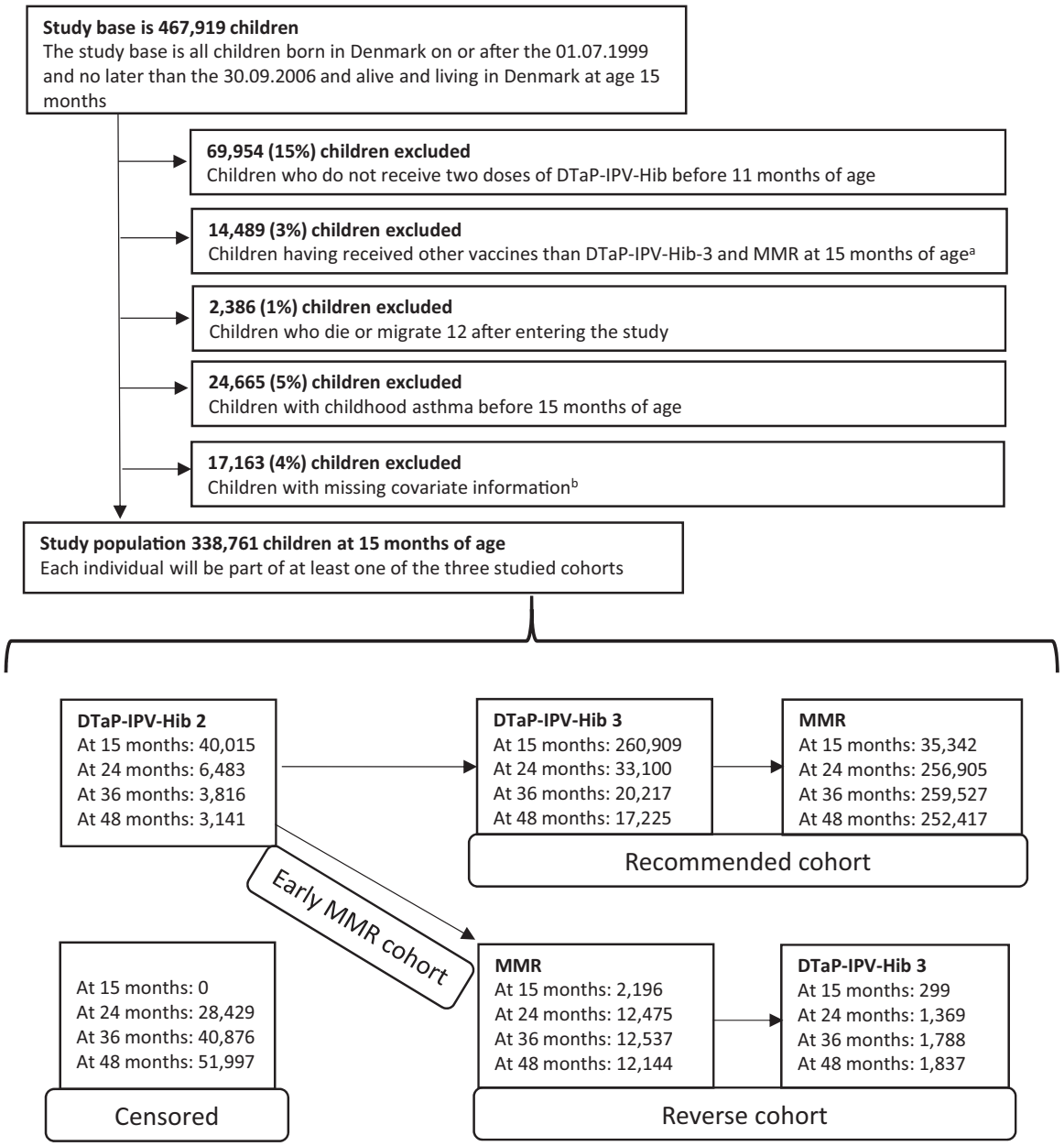

Figure 1. Flow chart of inclusions and vaccine sequence cohorts for hypothesis 1.

MMR = measles, mumps and rubella vaccination. DTaP-IPV-Hib = diphtheria–tetanus–acellular-pertussis–inactivated-polio–*Haemophilus influenzae* type b.

[a] Multiple combinations of other vaccines are received before 15 months of age. The five most frequent vaccines are listed: 5401 children received DTaP-IPV-Hib 4 instead of MMR, 2157 children received DTaP-IPV-Hib 3 with a pneumococcal conjugate vaccine (PCV) instead of DTaP-IPV-Hib 3, 1413 children received PCV instead of MMR, 1405 children received MMR with PCV instead of MMR, 1371 children received DTaP-IPV-Hib 3 with MMR instead of DTaP-IPV-Hib 3.

[b] Children may have missing information for more than one variable. 10 296 'maternal smoking status', 6402 'maternal education level', 1679 missing 'birth weight', 1599 missing 'prematurity (born before the 37th week)', 124 'maternal age', 51 'family income level (quartiles)', 49 'single parenthood', 49 'other children in household', 49 'population density', 3 'parents' place of birth'. See Supplementary Figure 4, available as Supplementary data at *IJE* online, for detailed time-wise proportions of the sequence cohorts.

reduction per 1000 children for each group at 48 months of age (wIRreduction$_{48}$) and cumulative incidence rate ratios at 48 months of age. Standard errors were calculated using robust estimators and confidence intervals (CIs) were estimated with 2.5% and 97.5% quantiles using 100 000 simulations. The analyses assumed independent observations. A spline function of the crude and weighted cumulative incidence rates were plotted for each analysis. We

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investigated whether the $wIRreduction_{48}$ were different for girls and boys. Additionally, to compare with hazards ratios often reported in the medical literature, we used a weighted Cox proportional hazards model to estimate hazard ratios. The weighted Cox proportional hazards model had age as the underlying time scale and was stratified by week (Sunday to Saturday) of birth thereby adjusting for the effect of age and calendar time. We tested the assumption of proportional hazards using Schoenfeld residuals.

Sensitivity analysis

Since infections may affect childhood asthma[27,28] and MMR has been associated with fewer infections in the same cohort,[4] we conducted a sensitivity analysis excluding hospital admissions with childhood asthma co-occurring with hospital admissions for an infectious disease, to ensure we did not partly reproduce earlier results.

If childhood asthma was registered using two prescriptions within 1 year, we used the first date of the two prescriptions. Thus, the registered childhood asthma date was conditioned on a future prescription, which could cause a collider bias, introducing a non-causal association between MMR vaccination and the first prescription for childhood asthma. We conducted a sensitivity analysis using the second date of prescriptions.

Furthermore, we conducted a sensitivity analysis of the effect of DTaP-IPV-Hib 3 vs DTaP-IPV-Hib 2 from 12 to 15 months of age under the hypothesis that the incidence of new-onset childhood asthma and severe asthma would not differ. If DTaP-IPV-Hib 3 is associated with a reduced incidence of asthma compared with DTaP-IPV-Hib 2 in spite of adjustment for potential confounding, this would suggest that we have been unable to fully control for confounding i.e. that the most healthy children receive the next vaccine (residual confounding of a 'healthy vaccinee effect'-bias). Data was analysed using Stata 14.0 and R 3.3.1 with version 1.0–11 for the ipw package. Register-based studies require ethical approval by the Danish Central Scientific Ethics Committee.

Results

From the study base of 467 919 children, 338 761 children were eligible for studying hypothesis 1 (Figure 1) and 364 270 children were eligible for hypothesis 2 (Supplementary Figure 2, available as Supplementary data at *IJE* online). The recommended sequence included the majority of risk time with 773 054 person years of follow up (pyrs), the early MMR sequence had 50 918 pyrs, and the interrupted sequence had 36 788 pyrs.

Most shifts in vaccination sequence cohorts happened between 15 and 20 months of age (Supplementary Figures 4 and 5, available as Supplementary data at *IJE* online). Childhood asthma peaked at 8 months of age, and boys have a higher incidence than girls (Supplementary Figure 6, available as Supplementary data at *IJE* online). Among the recommended sequence for hypothesis 1, 18 776 children were registered with childhood asthma during follow-up (of which 25% were based on hospital contacts, 74% based on glucocorticoids and 1% based on montelukast).

Covariates were approximately similarly distributed between vaccination sequence groups at 16 months of age (Supplementary Table 1, available as Supplementary data at *IJE* online). However, children who had received only DTaP-IPV-Hib 1 + 2 at 16 months of age tended to have a skewed distribution compared with the remaining vaccination sequence groups, especially regarding single parenthood, family income, maternal education, other children in the household, mother smoking during pregnancy, and previous infectious diseases and prescribed antibiotics.

For hypothesis 1, MMR compared with DTaP-IPV-Hib as most recent vaccine was associated with a weighted cumulative incidence reduction of childhood asthma per 1000 children at 48 months of age ($wIRreduction_{48}$) of 4.5 (95% confidence interval [CI] 1.7 to 7.3), 3.7 (95% CI −3.4 to 10.7) and 23.0 (95% CI 3.2 to 42.8) for the recommended, early and interrupted sequences respectively (Table 1). The incidence diverged mostly in the first part of follow-up (Figure 2). The incidence difference tended to be larger among boys than girls (Table 2).

For hypothesis 2, MMR compared with DTaP-IPV-Hib as the last received vaccine, was associated with a $wIRreduction_{48}$ of 8.3 (95% CI 6.1 to 10.5), 13.4 (95% CI 7.3 to 19.4), and 1.7 (95% CI –11.8 to 15.2) for the rate of acute hospital contacts for childhood asthma in the recommended, early and interrupted sequences (Table 3 and Figure 3). Again, the association was stronger among boys compared with girls in the recommended sequence (Table 4).

When analysing the hypotheses using hazard ratios, the assumption of proportional hazards was not met for hypothesis 1 (Supplementary Table 2, available as Supplementary data at *IJE* online) and was more stable for hypothesis 2 (Supplementary Table 3, available as Supplementary data at *IJE* online).

Excluding concurrent hospital contacts for infectious diseases and using the date of the second prescription provided similar estimates (Supplementary Tables 4–6, available as Supplementary data at *IJE* online).

The weighted cumulative incidence difference from 12 to 15 months of age per 1000 children for DTaP-IPV-Hib 3 compared with DTaP-IPV-Hib 2 for the hypothesis 1 and 2

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Table 1. MMR vs DTaP-IPV-Hib and the risk of childhood asthma (hypothesis 1)

Prior vaccination	Last vaccination	Events and person years	Unweighted cumulative incidence per 1000 children at 48 months of age (95% CI)	Weighted cumulative incidence per 1000 children at 48 months of age (95% CI)	Weighted cumulative incidence reduction per 1000 children at 48 months of age (95% CI)	Ratio of weighted cumulative incidence at 48 months of age (95% CI)
Recommended sequence						
DTaP-IPV-Hib 1 + 2	DTaP-IPV-Hib 3	4085/99 108	70.1 (67.4–72.8)	66.2 (63.6–68.8)	0 (ref)	1 (ref)
DTaP-IPV-Hib 1 + 2+3	MMR	14 670/673 946	60.7 (59.7–61.7)	61.7 (60.7–62.7)	4.5 (1.7 to 7.3)	0.93 (0.89–0.97)
Early MMR sequence						
DTaP-IPV-Hib 1	DTaP-IPV-Hib 2	779/18 339	67.7 (61.8–73.5)	67.5 (62.5–72.6)	0 (ref)	1 (ref)
DTaP-IPV-Hib 1 + 2	MMR	725/32 579	61.5 (57.0–65.9)	63.9 (58.9–68.8)	3.7 (−3.4 to −10.7)	0.95 (0.85–1.05)
Interrupted sequence						
DTaP-IPV-Hib 1 + 2	MMR	725/32 579	61.5 (57.0–65.9)	61.3 (56.8–65.8)	23.0 (3.2 to 42.8)	0.73 (0.58–0.95)
DTaP-IPV-Hib1 + 2 +MMR	DTaP-IPV-Hib 3	98/4209	81.5 (62.6–99.9)	84.3 (64.8–103.4)	0 (ref)	1 (ref)

Individuals are weighted with stabilized inverse probability of treatment and censoring weights in order to handle potential time variant confounding. The inverse probability of vaccination was modelled based on a Cox proportional hazards model with population density, parents' place of birth, single parenthood, family income level (quartiles), maternal education level, singleton, other children in household, sex, caesarean section, premature (born before the 37th week), birth weight, maternal age, mother smoking during pregnancy, time-varying chronic diseases, history of any registered hospital admission due to infectious diseases before 15 months of age, history of any registered prescribed antibiotics before 15 months of age, family members with asthma at 15 months of age, family members with atopic dermatitis or allergic rhinoconjunctivitis at 15 months of age, birth month, birth year plus time-dependent accumulations of hospital admissions due to infectious diseases as well as antibiotic prescriptions from 15 months of age and onwards. The inverse probability of not being censored was modelled based on Cox proportional hazards model with the aforementioned covariates plus the time-dependent vaccination status.

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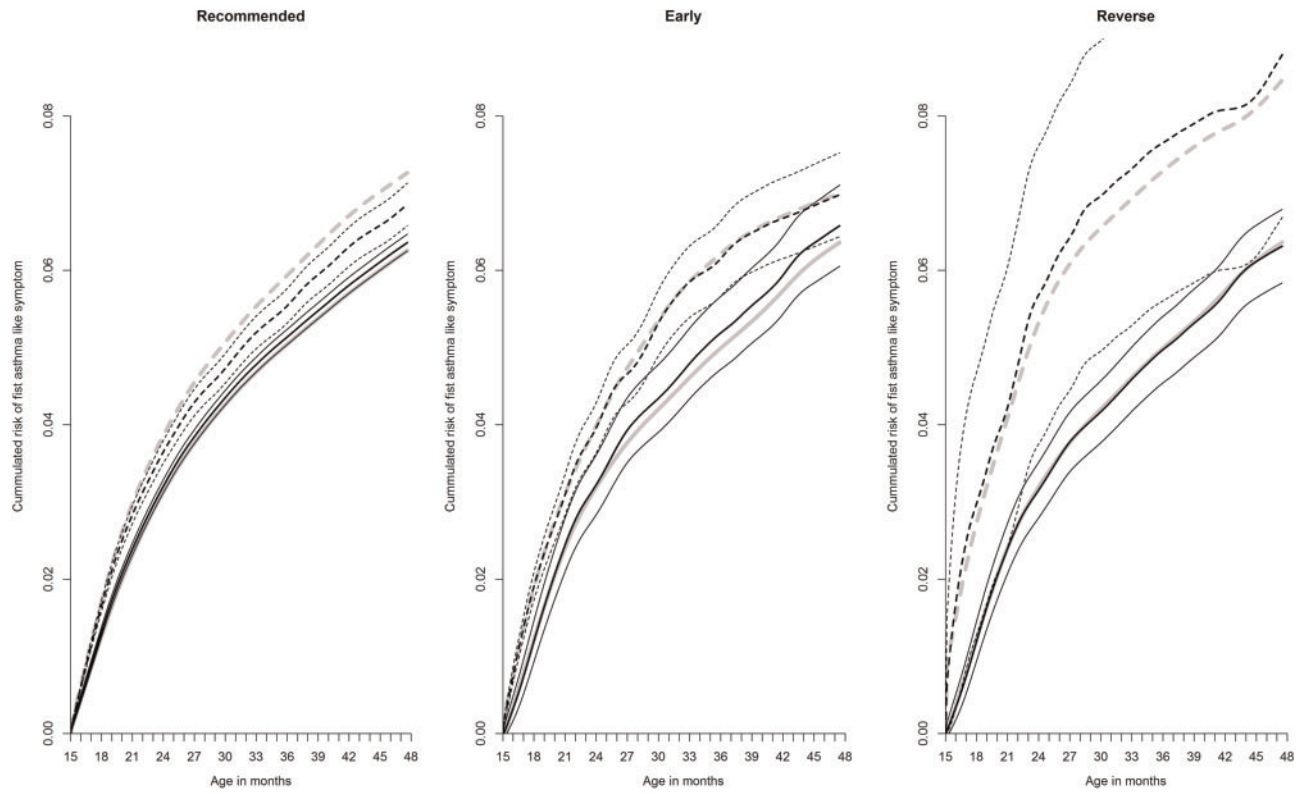

Figure 2. Weighted cumulated incidence plots for hypothesis 1.

Approximated with a spline fit with 20 degrees of freedom. Solid lines indicate MMR as the latest vaccine (the above and below solid lines indicate the 95% confidence interval). Dashed lines indicate either DTaP-IPV-Hib 2 (early) or DTaP-IPV-Hib 3 (recommended and interrupted) as the latest vaccine (the above and below dashed lines indicate the 95% confidence interval). The bold and transparent solid and dashed lines represent the unweighted cumulative incidences.

outcomes were respectively 2.7 (95% CI 1.6 to 3.8) and 0.6 (95% CI –0.1 to 1.3). The association tended to be stronger among boys than girls (Supplementary Tables 7 and 8, available as Supplementary data at IJE online).

Discussion

Among boys but not girls, MMR vaccination compared with DTaP-IPV-Hib as the last received vaccine across cohorts was associated with a lower incidence of childhood asthma and fewer acute hospital contacts for childhood asthma.

Strengths and weaknesses

This was a large nationwide study and we applied state-of-the-art statistical methods, the weighted approach, to handle potential time-varying confounding.[32] The weights were not extreme so no single individual affected the results disproportionally (Supplementary Figure 7, available as Supplementary data at *IJE* online). The 95% confidence interval for the incidence rate difference was calculated assuming independent observations, which is a limitation as children have contributed risk time to both vaccination groups.

By ensuring that children had followed the vaccination programme (received DTaP-IPV-Hib 1 and 2 before 11 months of age) we increased the homogeneity of the study population,[33] and by including many potential confounders we may to some extent have controlled for unmeasured confounding, though it cannot be ruled out. Potential time-varying confounding due to children's health status was modelled by previous chronic diseases as well as hospital admissions and antibiotic use for infectious diseases. The comparison between DTaP-IPV-Hib 3 and DTaP-IPV-Hib 2 for hypothesis 1 and to some degree hypotheses 2 suggests that there may be confounding not fully adjusted for (residual confounding of a 'healthy vaccinee effect'-bias). However, in the interrupted sequence cohort, children who received the next vaccine (DTaP-IPV-Hib 3 after MMR) had a higher risk for childhood asthma compared with those who had only received MMR, which indicates that a 'healthy vaccinee effect'-bias does not fully

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Table 2. MMR vs DTaP-IPV-Hib and the risk of childhood asthma by sex (hypothesis 1)

	Prior vaccination	Last vaccination	Events and person years	Unweighted cumulative incidence per 1000 children at 48 months of age (95% CI)	Weighted cumulative incidence per 1000 children at 48 months of age (95% CI)	Weighted cumulative incidence reduction per 1000 children at 48 months of age (95% CI)	Additive sex differential effect, *P*-value	Ratio of weighted cumulative incidence at 48 months of age (95% CI)	Multiplicative sex differential effect, *P*-value
Recommended sequence									
Boys	DTaP-IPV-Hib 1 + 2	DTaP-IPV-Hib 3	2475/49 812	82.1 (78.0–86.1)	77.7 (73.8–81.6)	0 (ref)	0.01	1 (ref)	0.04
	DTaP-IPV-Hib 1 + 2+3	MMR	8224/334 111	68.6 (67.1–70.2)	69.6 (68.1–71.2)	8.1 (3.9 to 12.3)		0.90 (0.85–0.95)	
Girls	DTaP-IPV-Hib 1 + 2	DTaP-IPV-Hib 3	1610/49 296	57.9 (54.3–61.4)	54.7 (51.4–58.1)	0 (ref)		1 (ref)	
	DTaP-IPV-Hib 1 + 2+3	MMR	6446/339 835	52.8 (51.5–54.1)	53.7 (52.4–55.1)	1.0 (−2.6 to 4.6)		0.98 (0.92–1.05)	
Early MMR sequence									
Boys	DTaP-IPV-Hib 1	DTaP-IPV-Hib 2	459/9381	79.4 (70.3–88.4)	78.6 (70.8–86.3)	0 (ref)	0.31	1 (ref)	0.38
	DTaP-IPV-Hib 1 + 2	MMR	414/16 410	70.1 (63.3–76.9)	71.3 (64–78.6)	7.3 (−3.4 to 18.0)		0.91 (0.79–1.05)	
Girls	DTaP-IPV-Hib 1	DTaP-IPV-Hib 2	320/8958	55.3 (47.9–62.6)	56.1 (49.6–62.6)	0 (ref)		1 (ref)	
	DTaP-IPV-Hib 1 + 2	MMR	311/16 169	52.6 (46.8–58.4)	56.1 (49.5–62.6)	0.0 (−9.2 to 9.2)		1.00 (0.85–1.18)	
Interrupted sequence									
Boys	DTaP-IPV-Hib 1 + 2	MMR	414/16 410	70.1 (63.3–76.9)	70 (63.2–76.8)	28.5 (−0.9 to 57.9)	0.60	0.71 (0.54–1.01)	0.85
	DTaP-IPV-Hib1 + 2+MMR	DTaP-IPV-Hib 3	60/2065	100.3 (71.5–128.2)	98.6 (69.5–126.7)	0 (ref)		1 (ref)	
Girls	DTaP-IPV-Hib 1 + 2	MMR	311/16 169	52.6 (46.8–58.4)	52.4 (46.6–58.1)	17.8 (−9.2 to 44.7)		0.75 (0.53–1.21)	
	DTaP-IPV-Hib1 + 2+MMR	DTaP-IPV-Hib 3	38/2144	62.5 (37.8–86.6)	70.1 (43.5–96.1)	0 (ref)		1 (ref)	

Individuals are weighted with stabilized inverse probability of treatment and censoring weights in order to handle potential time variant confounding. The inverse probability of vaccination was modelled based on a Cox proportional hazards model with population density, parents' place of birth, single parenthood, family income level (quartiles), maternal education level, singleton, other children in household, sex, caesarean section, premature (born before the 37th week), birth weight, maternal age, mother smoking during pregnancy, time-varying chronic diseases, history of any registered hospital admission due to infectious diseases before 15 months of age, history of any registered prescribed antibiotics before 15 months of age, family members with asthma at 15 months of age, family members with atopic dermatitis or allergic rhinoconjunctivitis at 15 months of age, birth month, birth year plus time-dependent accumulations of hospital admissions due to infectious diseases as well as antibiotic prescriptions from 15 months of age and onwards. The inverse probability of not being censored was modelled based on Cox proportional hazards model with the aforementioned covariates plus the time-dependent vaccination status.

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Table 3. MMR vs DTaP-IPV-Hib and risk of hospital admissions and emergency room visits due to childhood asthma (hypothesis 2)

Prior vaccination	Last vaccination	Events and person years	Unweighted cumulative incidence per 1000 children at 48 months of age (95% CI)	Weighted cumulative incidence per 1000 children at 48 months of age (95% CI)	Weighted cumulative incidence reduction per 1000 children at 48 months of age (95% CI)	Ratio of weighted cumulative incidence at 48 months of age (95% CI)
Recommended sequence						
DTaP-IPV-Hib 1 + 2	DTaP-IPV-Hib 3	2597/111 106	49.0 (46.7–51.3)	43.5 (41.4–45.6)	0 (ref)	1 (ref)
DTaP-IPV-Hib 1 + 2+3	MMR	9244/754 021	34.2 (33.5–34.9)	35.2 (34.5–36.0)	8.3 (6.1 to 10.5)	0.81 (0.77–0.85)
Early MMR Sequence						
DTaP-IPV-Hib 1	DTaP-IPV-Hib 2	624/20 840	61.4 (55.7–67.1)	57.3 (52.6–62.0)	0 (ref)	1 (ref)
DTaP-IPV-Hib 1 + 2	MMR	490/36 983	37.0 (33.7–40.3)	43.9 (40.0–47.8)	13.4 (7.3 to 19.5)	0.77 (0.68–0.86)
Interrupted sequence						
DTaP-IPV-Hib 1 + 2	MMR	490/36 983	37.0 (33.7–40.3)	37.5 (34.2–40.8)	1.7 (−11.8 to 15.2)	0.96 (0.71–1.45)
DTaP-IPV-Hib1 + 2+MMR	DTaP-IPV-Hib 3	60/4840	41.1 (28.6–53.3)	39.2 (26.0–52.2)	0 (ref)	1 (ref)

Individuals are weighted with stabilized inverse probability of treatment and censoring weights in order to handle potential time variant confounding. The inverse probability of vaccination was modelled based on a Cox proportional hazards model with population density, parents' place of birth, single parenthood, family income level (quartiles), maternal education level, singleton, other children in household, sex, caesarean section, premature (born before the 37th week), birth weight, maternal age, mother smoking during pregnancy, time-varying chronic diseases, history of any registered hospital admission due to infectious diseases before 15 months of age, history of any registered prescribed antibiotics before 15 months of age, family members with asthma at 15 months of age, family members with atopic dermatitis or allergic rhinoconjunctivitis at 15 months of age, birth month, birth year plus time-dependent accumulations of hospital admissions due to infectious diseases as well as antibiotic prescriptions from 15 months of age and onwards. The inverse probability of not being censored was modelled based on Cox proportional hazards model with the aforementioned covariates plus the time-dependent vaccination status.

explain our results. Receiving the MMR vaccine as the last vaccine was associated with approximately similar cumulative incidence rates across sequences, whereas DTaP-IPV-Hib in contrast was associated with greater cumulative incidence rates. As this pattern was independent of which sequence children followed, it suggests that both vaccines affect the risk of childhood asthma beneficially and detrimentally, respectively.

MMR vaccination coverage in Denmark may be under-reported,[34] which would increase proportionally with time if MMR vaccinated children stay categorized as DTaP-IPV-Hib 3 vaccinated, thus biasing the estimate towards null over time — a pattern we also observed. The inclusion criteria DTaP-IPV-Hib 1 and 2 before 11 months of age decreased the misclassification of the reference groups in the recommended sequence and early MMR sequence. Unsystematic under-reporting would also cause conservative estimates. Simultaneous administration of vaccines was outside the scope of our analysis.

Neither of our sensitivity analyses indicated that we should have reached other conclusions. Further analyses indicated that it was the first childhood asthma prescription rather than the criteria of two prescriptions within 1 year that captured the effect of MMR on childhood asthma (analysis not shown).

Studies on MMR and childhood asthma

No randomized trial has studied the effect of MMR on the risk of childhood asthma; ten diverse observational studies on the effect of MMR or measles vaccines on childhood asthma show conflicting results (Supplementary Table 9, available as Supplementary data at *IJE* online).[10–19] The ten studies vary from large prospective cohort studies to small cross-sectional studies and represent children from 11 countries (two sets of studies partly overlap in study populations[16–19] and one study partly overlaps with the study population of our study[11]). The studies were further heterogeneous with regards to outcome definition, age group and sequence of vaccines. Specifically, our study indicated that the effect of vaccine status on the incidence of childhood asthma decreased with age, making comparisons for unlike age groups problematic. Our study is the first study to strictly investigate the effect of having MMR as the most recent vaccine on the risk of childhood asthma. Not differentiating the vaccine sequence mixes effects of multiple vaccine combinations,[35] a problem that was highlighted in a recent WHO review of NSEs of vaccines[3] and also supported by this study. Furthermore, applying the inclusion criteria where all children had received the first two doses of DTaP-IPV-Hib before 11 months of age increased the exchangeability of the

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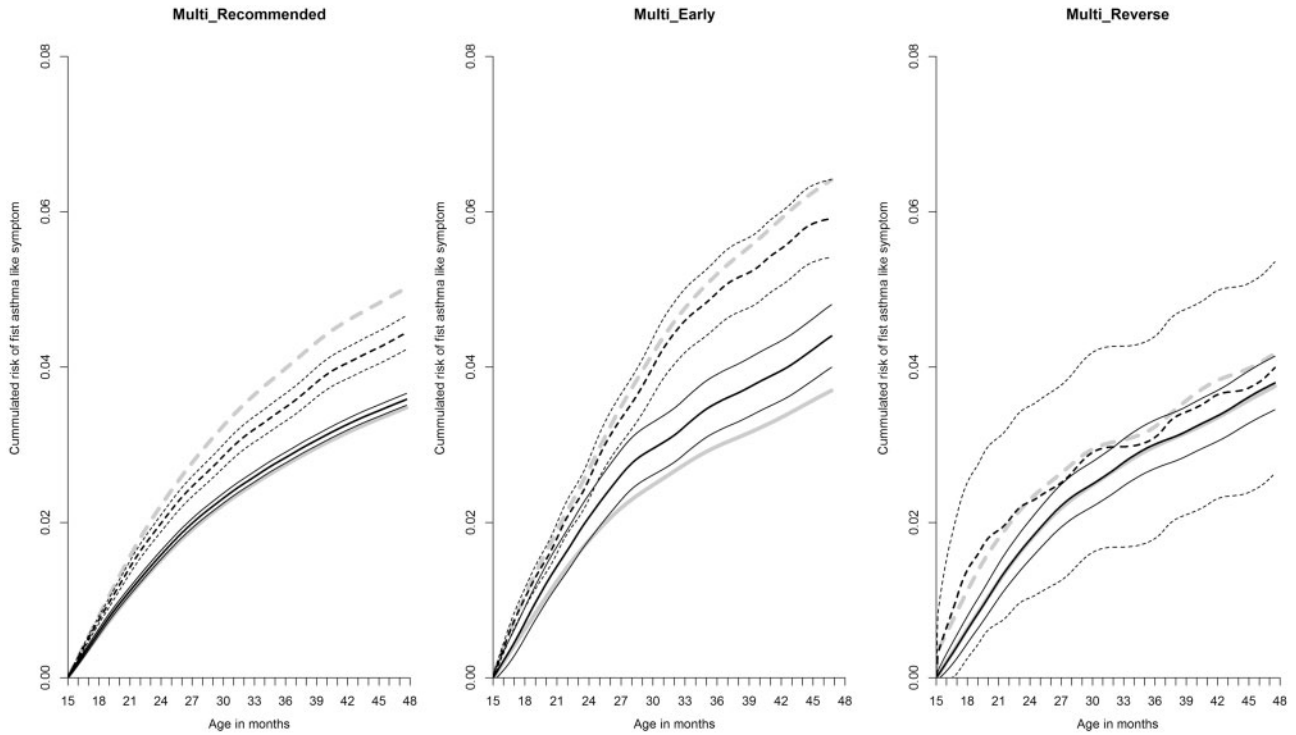

Figure 3. Weighted cumulated incidence plots for hypothesis 2.

Approximated with a spline fit with 20 degrees of freedom. Solid lines indicate MMR as the latest vaccine (the above and below solid lines indicate the 95% confidence interval). Dashed lines indicate either DTaP-IPV-Hib 2 (early) or DTaP-IPV-Hib 3 (recommended and interrupted) as the latest vaccine (the above and below dashed lines indicate the 95% confidence interval). The bold and transparent solid and dashed lines represent the unweighted cumulative incidences.

comparison groups in our study compared with the previous studies. Despite differences in design and definition of anti-asthma medication, the study overlapping with the study population of our study found similar effects of MMR on the use of medication and for hospital admissions due to asthma.[11] However, they did not find similar sex differential effects, which may have been masked by the effects of other vaccines.

Biological mechanisms

Successful immunisation by live vaccines, like natural infections, has been shown to induce a shift from a predominant T-helper 2 cell immune response to a T-helper 1 cell predominant response. This may allow an accelerated clearance of infections,[1] and thus a potentially reduced risk of childhood asthma.

MMR compared with DTaP-IPV-Hib as the most recent vaccine has been associated with fewer admissions for infectious diseases.[4] Since persistent respiratory infections may destroy epithelial cells of the respiratory tract, making children with childhood asthma more prone to severe episodes,[36] and as respiratory infections can function as irritants exaggerating wheeze attacks,[9] then a reduction in infectious diseases could lead to a lower risk of childhood asthma.

Recent cutting-edge immunological research shows that live vaccines can train the innate immune system for swifter clearance of non-related pathogens possibly through epigenetic reprogramming.[2] In accordance with our results indicating that males benefited more from the MMR vaccine, a new immunological study of Gambian children showed that measles vaccine was associated with enhanced proinflammatory innate responses for males but not for females, possibly by modifying signalling via Toll-like receptor 4 (TLR4).[37] The duration of trained immunity is yet unknown, but according to our data the absolute risk difference was proportionally largest the first 10–15 months after vaccination and waned thereafter (Figures 2 and 3).

Conclusion

Our study indicated that boys experience less childhood asthma and fewer acute hospital contacts for childhood asthma when the live MMR vaccine compared with the

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Table 4. MMR vs DTaP-IPV-Hib and risk of hospital admissions and emergency room visits due to childhood asthma by sex (hypothesis 2)

	Prior vaccination	Last vaccination	Events and person years	Unweighted cumulative incidence per 1000 children at 48 months of age (95% CI)	Weighted cumulative incidence per 1000 children at 48 months of age (95% CI)	Weighted cumulative incidence reduction per 1000 children at 48 months of age (95% CI)	Additive sex differential effect, *P*-value	Ratio of weighted cumulative incidence at 48 months of age (95% CI)	Multiplicative sex differential effect, *P*-value
Recommended sequence									
Boys	DTaP-IPV-Hib 1 + 2	DTaP-IPV-Hib 3	1797/57 414	66.8 (63.1–70.5)	60.4 (56.9–63.8)	0 (ref)	<0.01	1 (ref)	<0.01
	DTaP-IPV-Hib 1 + 2+3	MMR	5930/383 299	42.9 (41.7–44.0)	44.0 (42.9–45.2)	16.3 (12.7 to 20.0)		0.73 (0.69–0.78)	
Girls	DTaP-IPV-Hib 1 + 2	DTaP-IPV-Hib 3	800/53 692	29.6 (27.1–32.1)	25.9 (23.7–28.2)	0 (ref)		1 (ref)	
	DTaP-IPV-Hib 1 + 2+3	MMR	3314/370 722	25.2 (24.3–26.1)	26.0 (25.1–26.9)	−0.1 (−2.5 to 2.4)		1.00 (0.92–1.10)	
Early MMR sequence									
Boys	DTaP-IPV-Hib 1	DTaP-IPV-Hib 2	407/10 970	75.8 (67.0–84.4)	70.8 (63.6–77.9)	0 (ref)	0.42	1 (ref)	0.76
	DTaP-IPV-Hib 1 + 2	MMR	343/19 113	49.5 (44.3–54.7)	54.9 (49.0–60.8)	15.8 (6.6 to 25.1)		0.78 (0.67–0.90)	
Girls	DTaP-IPV-Hib 1	DTaP-IPV-Hib 2	217/9870	45.3 (38.0–52.5)	42.5 (36.6–48.3)	0 (ref)		1 (ref)	
	DTaP-IPV-Hib 1 + 2	MMR	147/17 870	23.5 (19.6–27.4)	31.6 (26.6–36.5)	10.9 (3.2 to 18.6)		0.74 (0.60–0.92)	
Interrupted sequence									
Boys	DTaP-IPV-Hib 1 + 2	MMR	343/19 113	49.5 (44.3–54.7)	49.9 (44.7–55.1)	−5.2 (−22.1 to 11.6)	0.29	1.12 (0.80–1.76)	0.26
	DTaP-IPV-Hib1 + 2+MMR	DTaP-IPV-Hib 3	43/2479	53.3 (36.2–70.1)	44.7 (28.5–60.6)	0 (ref)		1 (ref)	
Girls	DTaP-IPV-Hib 1 + 2	MMR	147/17 870	23.5 (19.6–27.4)	24.1 (20.1–28.0)	9.8 (−12.1 to 31.7)[a]		0.71 (0.42–1.97)[a]	
	DTaP-IPV-Hib1 + 2+MMR	DTaP-IPV-Hib 3	17/2361	28.4 (9.4–47.0)	33.9 (12.1–55.2)	0 (ref)		1 (ref)	

Individuals are weighted with stabilized inverse probability of treatment and censoring weights in order to handle potential time variant confounding. The inverse probability of vaccination was modelled based on a Cox proportional hazards model with population density, parents' place of birth, single parenthood, family income level (quartiles), maternal education level, singleton, other children in household, sex, caesarean section, premature (born before the 37th week), birth weight, maternal age, mother smoking during pregnancy, time-varying chronic diseases, history of any registered hospital admission due to infectious diseases before 15 months of age, history of any registered prescribed antibiotics before 15 months of age, family members with asthma at 15 months of age, family members with atopic dermatitis or allergic rhinoconjunctivitis at 15 months of age, birth month, birth year plus time-dependent accumulations of hospital admissions due to infectious diseases as well as antibiotic prescriptions from 15 months of age and onwards. The inverse probability of not being censored was modelled based on Cox proportional hazards model with the aforementioned covariates plus the time-dependent vaccination status.

[a]109 out of 100 000 simulations were negative and removed.

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non-live DTaP-IPV-Hib vaccine was the most recent vaccine. Data did not convincingly suggest an effect for girls. For now, these results are only indications, thus we hope other research groups will test our findings that MMR compared with DTaP-IPV-Hib as most recent vaccine reduces the risk of childhood asthma among boys and investigate why girls may not experience the same benefit. If supported, the question of whether a beneficial effect of MMR would persist or be countered by a subsequent non-live vaccine should be addressed.

If our estimates are correct then for 1000 boys following the recommended vaccine schedule and receiving MMR after DTaP-IPV-Hib, MMR prevents 8.1 (95% CI 3.9 to 12.3) childhood asthma cases between 15 months and 48 months. Thus, one childhood asthma case is prevented for each 123 (95% CI 81–256) MMR vaccinations administrated. Though most childhood asthma cases occurred before 15 months of age in this study, potential immune modulation via MMR or other approaches for preventing childhood asthma calls for a better understanding of NSEs of vaccines.[38]

Supplementary data

Supplementary data are available at *IJE* online.

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Supplementary material

Supplementary information 1. Sources of covariates 2

Supplementary information 2. Stabilised inverse probability of treatment and censoring weights 3

Supplementary figure 1. The Danish vaccination programme and the study base 4

Supplementary figure 2. Flow chart of inclusions and vaccine sequence cohorts for hypothesis 2. 5

Supplementary figure 3. Directed acyclic graph showing assumed exposure dependent confounding 6

Supplementary figure 4. Relative size of groups according to vaccination history and censoring from 15 to 48 months of age (Hypothesis 1) 7

Supplementary figure 5. Relative size of groups according to vaccination history and censoring from 15 to 48 months of age (Hypothesis 2) 8

Supplementary figure 6. Monthly incidence rate of new-onset childhood asthma cases per 1000 children 9

Supplementary figure 7. Time-varying stabilized inverse probability for treatment and censoring weights for hypothesis 1: 10

Supplementary table 1. Distribution of covariates among children, 16 months of age, with no history of childhood asthma before 15 months of age by sequence 11

Supplementary table 2. Weighted hazard ratios for hypothesis 1 15

Supplementary table 3. Weighted hazard ratios for hypothesis 2 16

Supplementary table 4. Sensitivity analysis. Exclusion of overlap with hospital contacts due to infectious diseases for hypothesis 1 17

Supplementary table 5. Sensitivity analysis. Exclusion of overlap with hospital contacts due to infectious diseases for hypothesis 2 18

Supplementary table 6. Sensitivity analysis. MMR vs DTaP-IPV-Hib and the risk of childhood asthma using the second prescription as event date for criteria 2 of the algorithm (hypothesis 1) 19

Supplementary table 7. Sensitivity analysis. DTaP-IPV-Hib 3 vs DTaP-IPV-Hib 2 and the risk of childhood asthma by sex (outcome related to hypothesis 1) 20

Supplementary table 8. Sensitivity analysis. DTaP-IPV-Hib 3 vs DTaP-IPV-Hib 2 and the risk of childhood asthma by sex (outcome related to hypothesis 2) 21

Supplementary table 9. Overview of previously published papers on MMR or measles vaccine and childhood asthma 22

Supplementary information 1. Sources of covariates

The Danish Civil Registration System[S1] includes information on births, deaths, migration, family, and household composition, population density, and parent' s place of birth. From the Danish National Patient Register we obtained information of previous admissions due to childhood asthma and infectious diseases as well as chronic diseases coded according to Kristensen et al.[S2] From the Danish National Prescription Register we obtained redeemed prescriptions for systemic antibiotics.[S3] We obtained this information from Statistics Denmark along with information on family income[S4] and maternal education[S5]. Using family linkage we defined family (parent or sibling) asthma, atopic dermatitis and allergic rhinoconjunctivitis according to Henriksen et al.[S6] We obtained information on birth weight, caesarean section, and maternal smoking during pregnancy from the Danish Medical Birth Register.[S7]

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Supplementary information 2. Stabilised inverse probability of treatment and censoring weights

The stabilised inverse probability of treatment and censoring weights (sIPTCW) allow us to interpret each analysis as a mimic of a randomised controlled trial where children are randomised to be vaccinated at 15 months of age and receiving no other vaccines until end of follow up at 48 months of age while the control arm was not vaccinated during this interval. The sIPTCW weighting creates pseudo populations among vaccinated and unvaccinated children that share the same population characteristics as the combined population compensated for individuals who are censored during follow-up. All children are followed from the first Sunday after they become eligible and all time-dependent covariates as vaccination status, chronic diseases, hospital contacts due to infectious diseases and antibiotic prescriptions are updated every week at Sundays. The stabilised inverse probability of treatment weights (sIPTW), the stabilised inverse probability of no censoring (sIPCW), and the sIPTCW are defined in formula 1-3 adapted from.[S1]

$$sIPTW_i(t) = \prod_{k=0}^{t} \frac{pr(A_{i,k} = a_{i,k} | \bar{A}_{i,k-1} = \bar{a}_{i,k-1})}{pr(A_{i,k} = a_{i,k} | \bar{A}_{i,k-1} = \bar{a}_{i,k-1}, \bar{L}_{i,k} = \bar{l}_{i,k})} \quad [1]$$

$$sIPCW_i(t) = \prod_{k=0}^{t} \frac{pr(C_{i,k} = 0 | \bar{C}_{i,k-1} = 0, \bar{A}_{i,k-1} = \bar{a}_{i.k-1})}{pr(C_{i,k} = 0 | \bar{C}_{i,k-1} = 0, \bar{A}_{i,k-1} = \bar{a}_{i,k-1}, \bar{L}_{i,k} = \bar{l}_{i,k})} \quad [2]$$

$$sIPTCW_i(t) = sIPTW_i(t) \times sIPCW_i(t) \quad [3]$$

Where *i* indicates every individual. *t* is the maximum follow up time in weeks. *k* is end of every follow up week, $A_k = a_{i,k}$ is ones actual vaccination status at end of week *k* (value can only change from unvaccinated to vaccinated). $\bar{A}_{k-1} = \bar{a}_{i,k-1}$ is ones vaccination status at week *k*-1. $\bar{L}_k = \bar{l}_{i,k}$ is all time-variant and baseline covariates potentially causing confounding; population density, parents' place of birth, single parenthood, family income level (quartiles), maternal education level, singleton, other children in household, sex, caesarean section, prematurity (born before the 37th week), birth weight, maternal age, mother smoking during pregnancy, time-varying chronic diseases, history of any registered hospital admission due to infectious diseases before 15 months of age, history of any registered prescribed antibiotics before 15 months of age, family members with asthma at 15 months of age, family members with atopic dermatitis or allergic rhinoconjunctivitis at 15 months of age, birth month, birth year plus time-dependent accumulations of hospital admissions due to infectious diseases from 15 months of age until end of week k, as well as accumulations of antibiotic prescriptions from 15 months of age until end of week *k*. $C_k = 0$ is not being censored at end of week k. $\bar{C}_{k-1} = 0$ is not being censored at end of week *k*-1. The term $V_{i,k} = v_{i,k}$described in the formulas in [S1,S2] is here ignored as all the defined covariates in $\bar{L}_{i,k} = \bar{l}_{i,k}$ could potentially cause confounding in our analyses.[S3]

We used the R package "ipw" [S4] to calculate sIPTCW utilizing a Cox proportional hazards model for estimating the probabilities of one's vaccination status $pr(A_k = a_{i,k} | \ldots)$ and the probability of not being censored $pr(C_k = 0 | \ldots)$ at week k. We visualised the distribution of weights by week to check for extreme weights (Supplementary figure 7).

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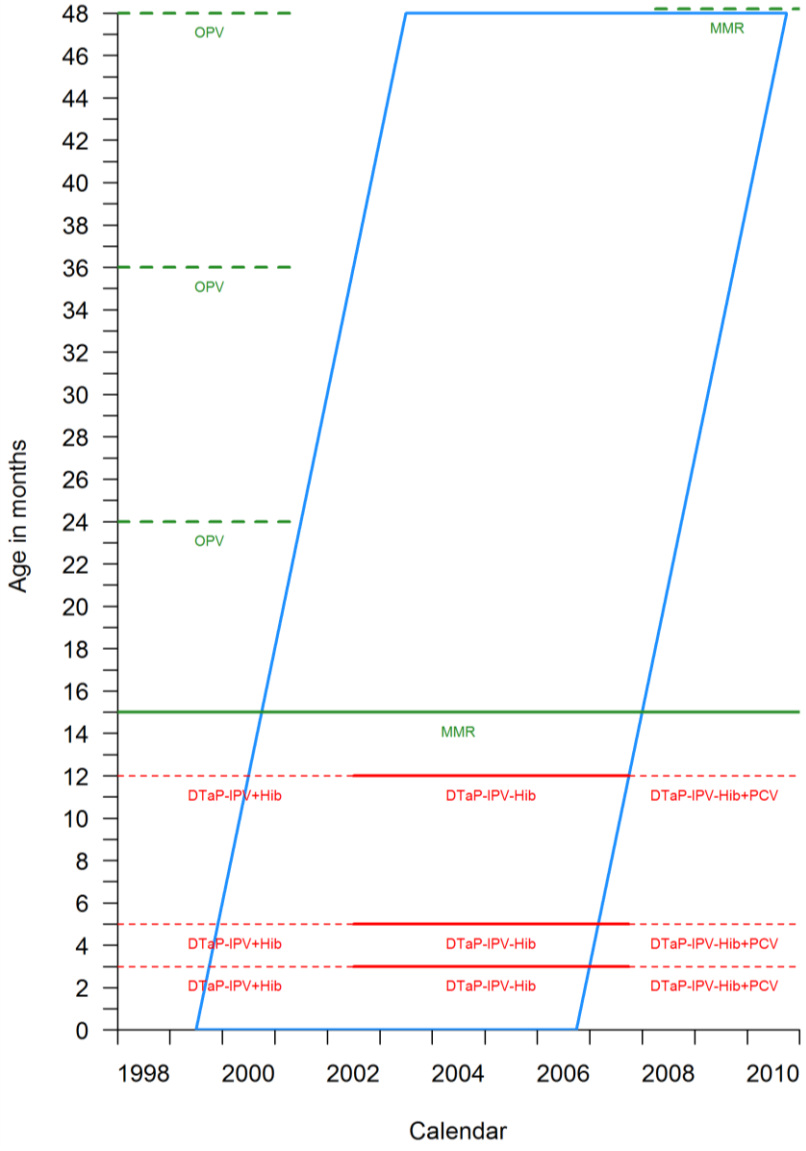
Supplementary figure 1. The Danish vaccination programme and the study base

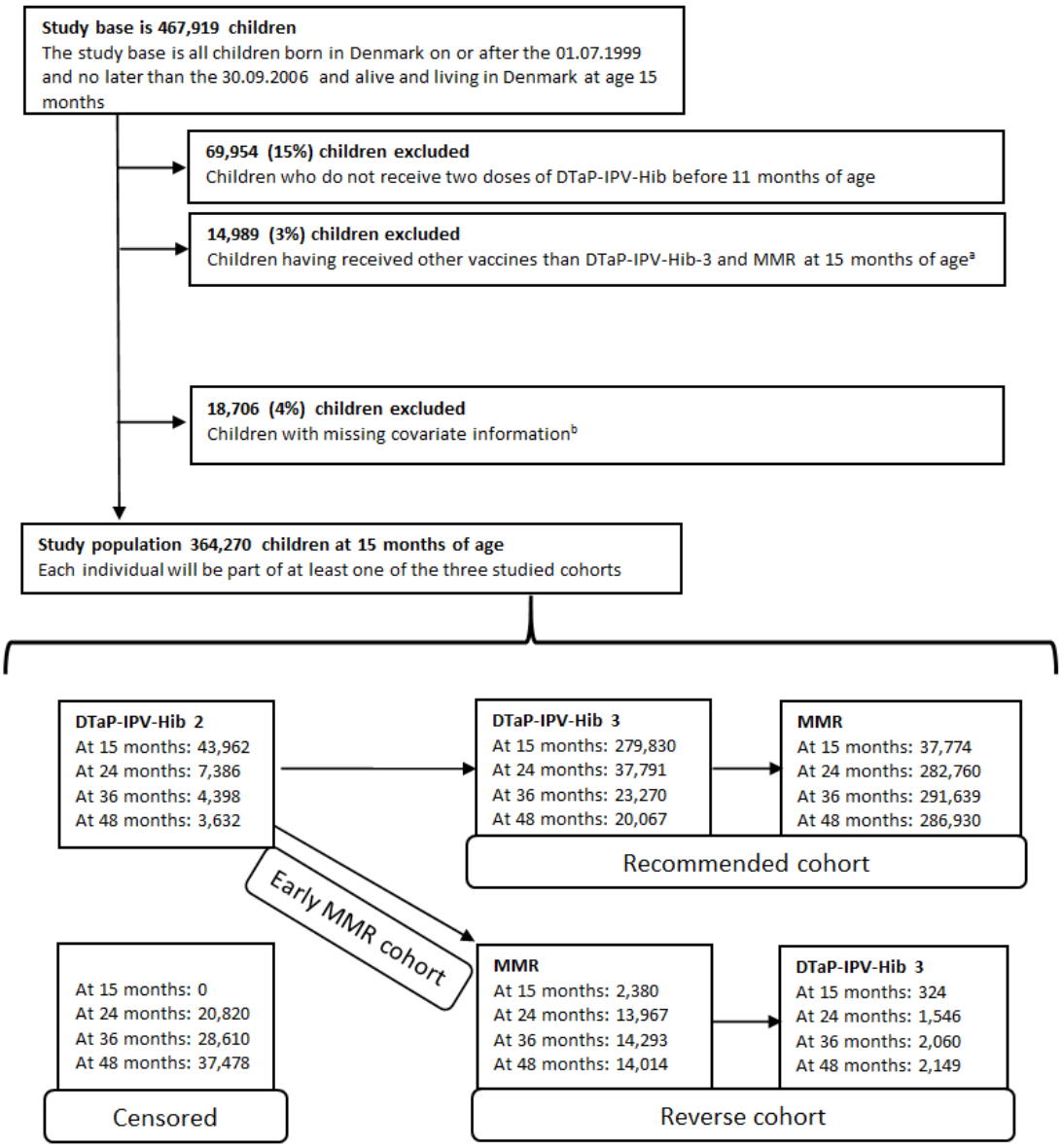


Children studied follow the vaccination schedule within the blue box.

OPV = oral polio vaccine, MMR = measles, mumps and rubella vaccine, DTaP-IPV+Hib = diphtheria-tetanus-acellular-pertussis-inactivated polio vaccine as one injection and *Haemophilus influenzae* type b vaccine as a separate injection, DTaP-IPV-Hib = diphtheria-tetanus-acellular-pertussis-inactivated polio and *Haemophilus influenzae* type b vaccine in one injection, DTaP-IPV-Hib+PCV = diphtheria-tetanus-acellular-pertussis-inactivated polio and *Haemophilus influenzae* type b vaccine in one injection and pneumococcal conjugate vaccine in a separate injection.

The phase out of oral polio vaccine (OPV) administrated at 2, 3 and 4 years was 1st of July 2001. The introduction of the seven-valent PCV at 3, 5 and 12 month was 1st of April 2008 for children born after 1st of October 2007; in April 2010, the 13 valent PCV replaced PCV7. End of follow up at 48 months is due to the introduction of a booster MMR at 4 years of age the 1st of April 2008.

Supplementary figure 2. Flow chart of inclusions and vaccine sequence cohorts for hypothesis 2.



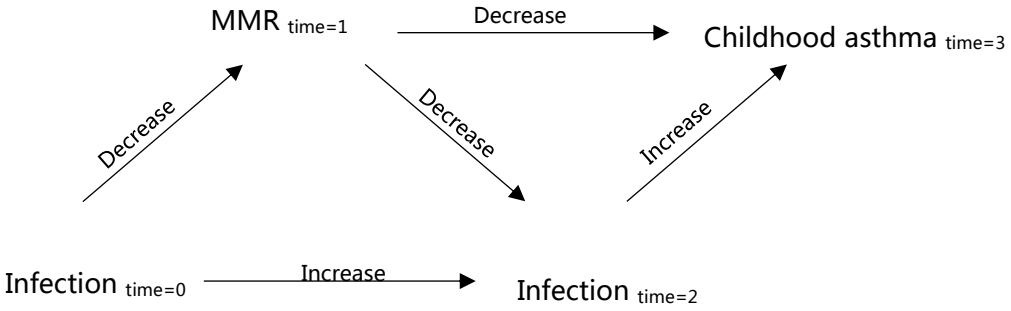
MMR = measles, mumps and rubella vaccination
DTaP-IPV-Hib = diphtheria-tetanus-acellular pertussis-polio-*Haemophilus Influenzae* type b

a) Multiple combinations of other vaccines are received before 15 months of age. The 5 most frequent vaccines are listed: 5,401 children received DTaP-IPV-Hib 4 instead of MMR, 2,157 children received DTaP-IPV-Hib 3 with a pneumococcal conjugate vaccine (PCV) instead of DTaP-IPV-Hib 3, 1,413 children received PCV instead of MMR, 1,405 children received MMR with PCV instead of MMR, 1,375 children received DTaP-IPV-Hib 3 with MMR instead of DTaP-IPV-Hib 3.

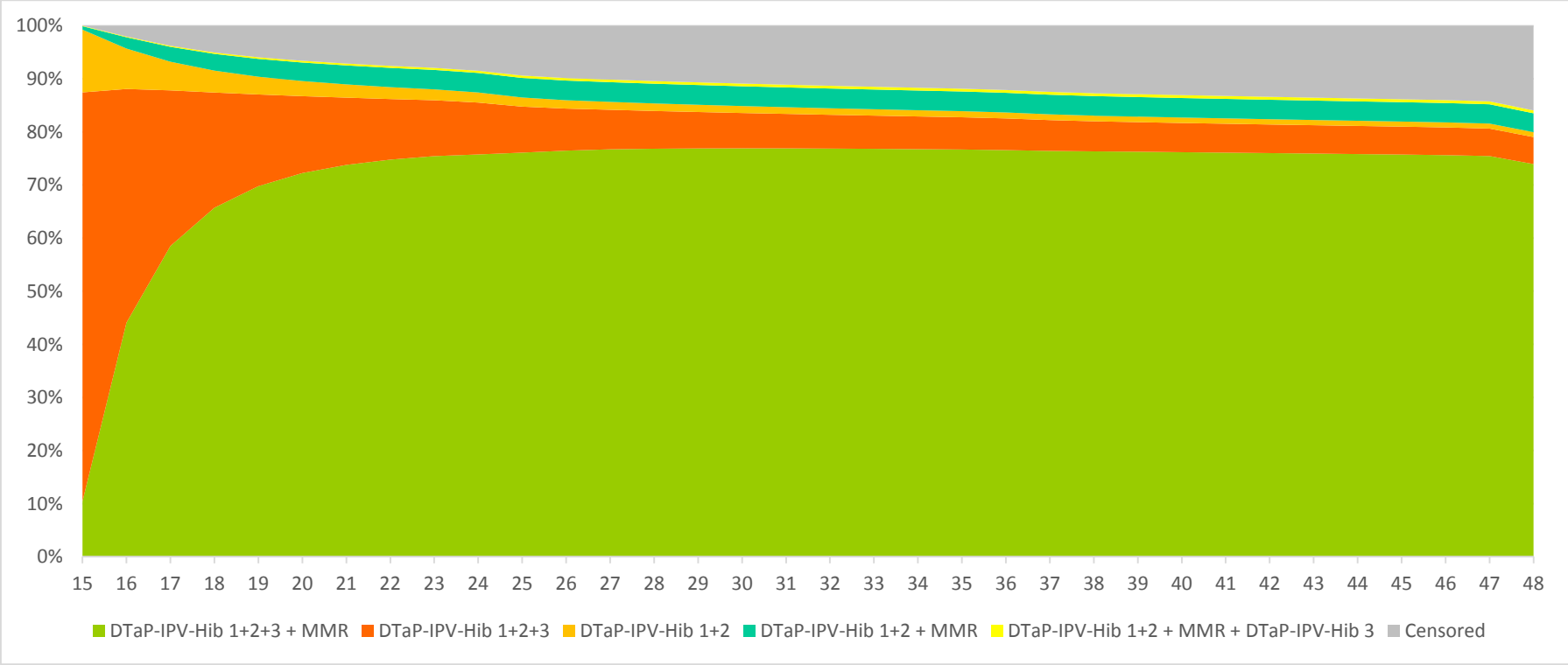
b) Children may have missing information for more than one covariate. 11,101 missing maternal smoking status, 7,108 missing maternal education level, 1,794 missing birth weight, 1,691 missing premature (born before the 37th week), 126 missing maternal age, 54 missing family income level (quartiles), 52 missing single parenthood, 52 missing other children in household, 52 missing population density, 4 missing parents' place of birth.

See supplementary figure 5 for detailed time-wise proportions of the sequence cohorts.

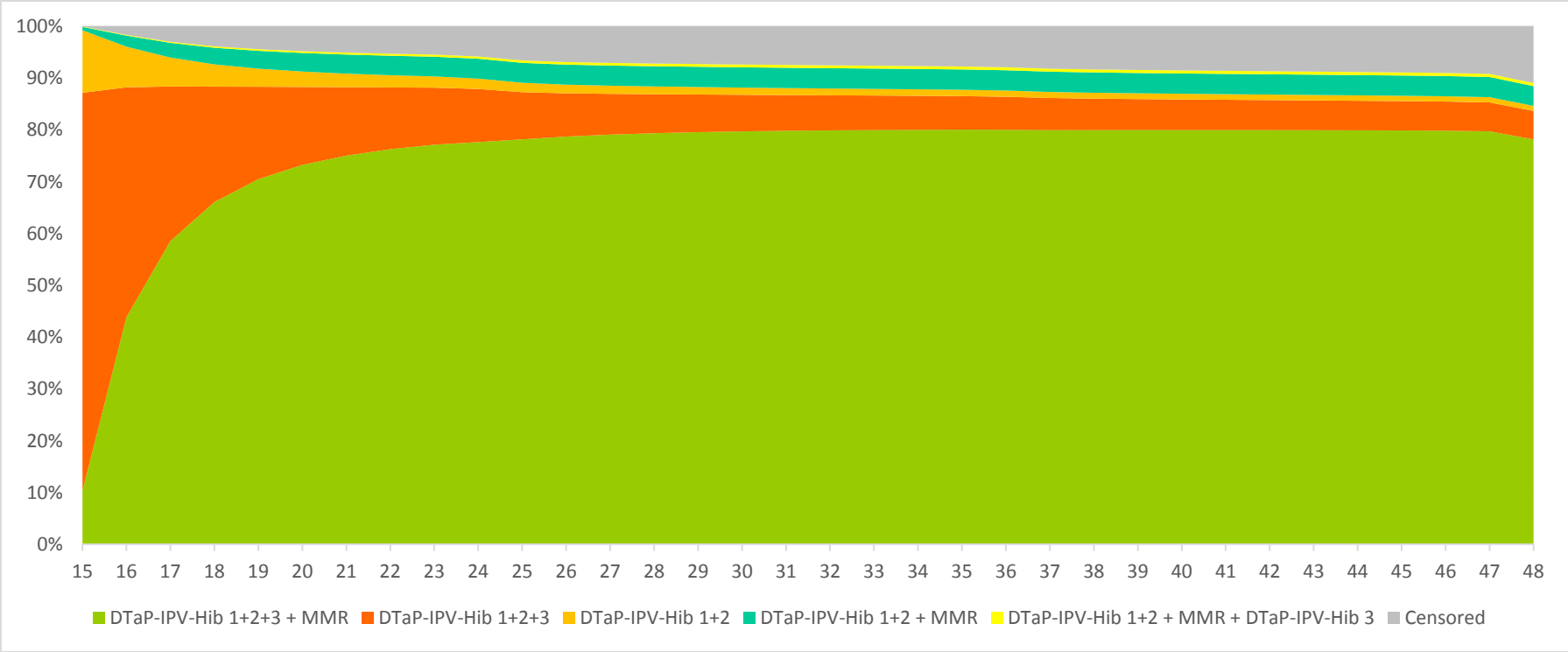
Supplementary figure 3. Directed acyclic graph showing assumed exposure dependent confounding



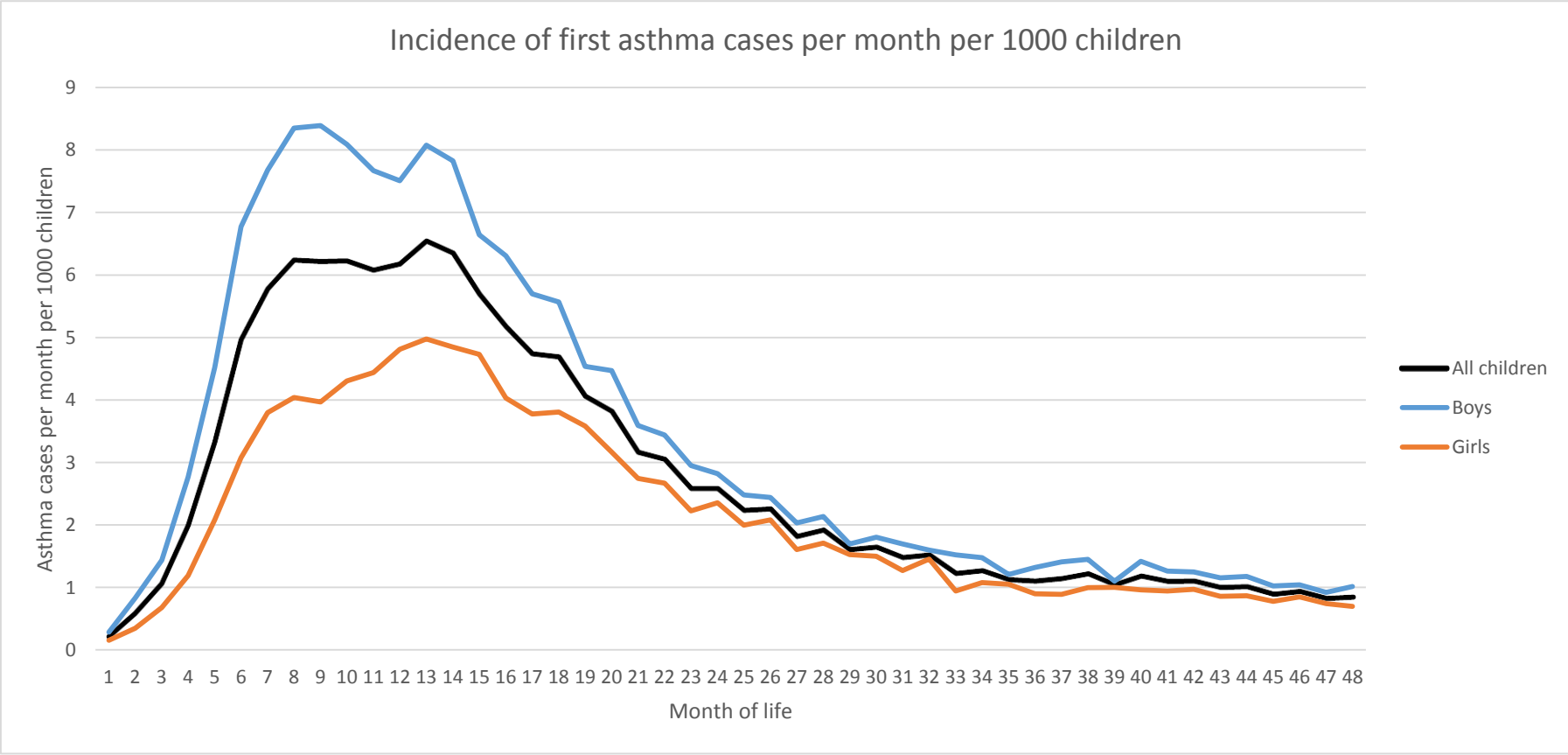
Supplementary figure 4. Relative size of groups according to vaccination history and censoring from 15 to 48 months of age (Hypothesis 1)



Supplementary figure 5. Relative size of groups according to vaccination history and censoring from 15 to 48 months of age (Hypothesis 2)

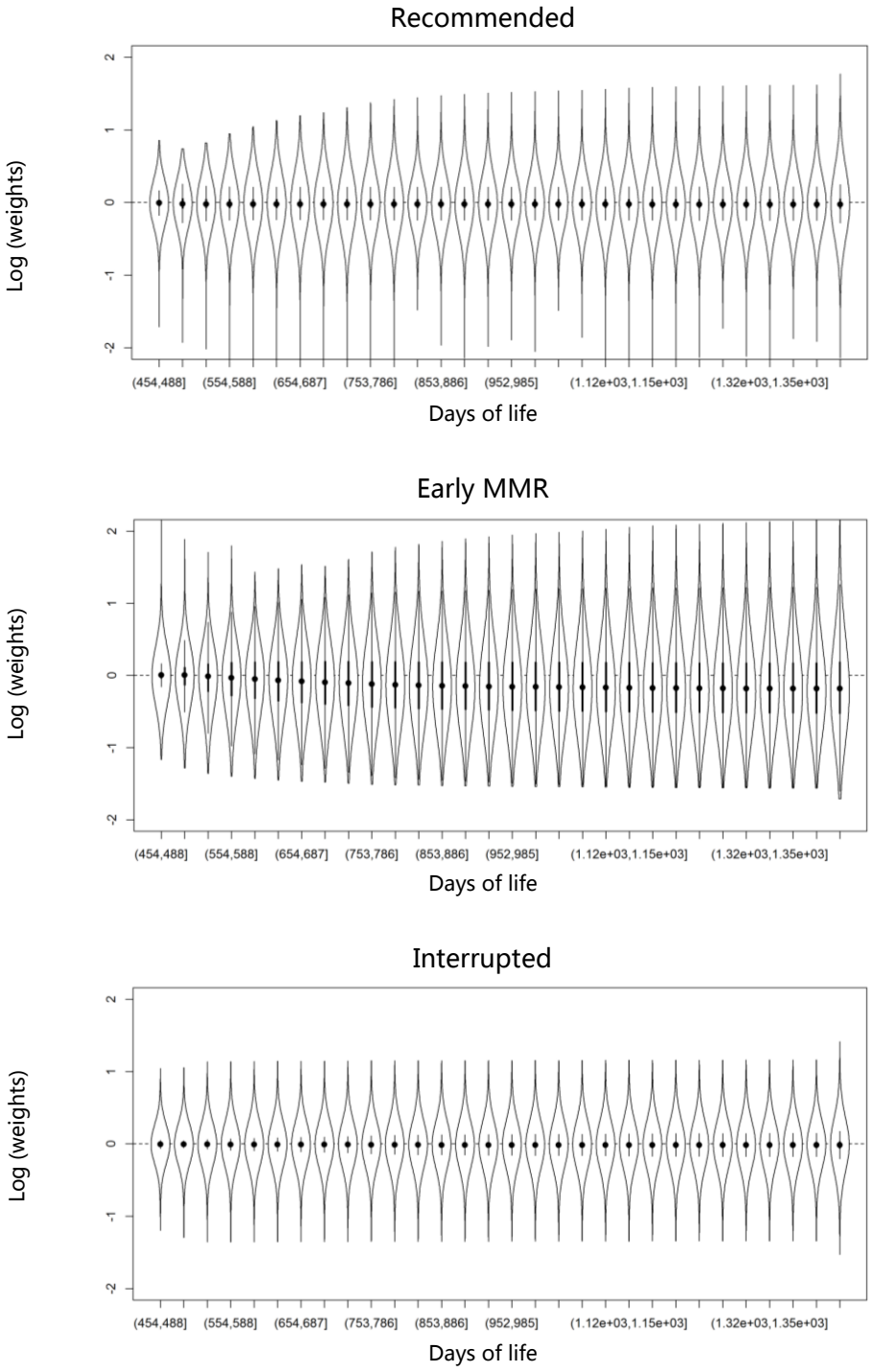


Supplementary figure 6. Monthly incidence rate of new-onset childhood asthma cases per 1000 children



Monthly incidence rate of new-onset childhood asthma per 1000 children among the full background population.

Supplementary figure 7. Time-varying stabilized inverse probability for treatment and censoring weights for hypothesis 1:



The plots illustrate how weights are used to balance the vaccinated group and the unvaccinated group by up- and down-weighting individuals for hypothesis 1. The stabilised inverse probability of treatment and censoring weights are on the y-axis while follow up time is on the x-axis for 30 days at a time. Extreme weights are a concern in weighted marginal structural models, but the plots indicates range limits around 0.2 ($e^{-1.6}$) to 5 ($e^{1.6}$).

Supplementary table 1. Distribution of covariates among children, 16 months of age, with no history of childhood asthma before 15 months of age by sequence

	Recommended sequence		Early MMR sequence		Interrupted sequence
At 16 months of age	DTaP-IPV-Hib 1 DTaP-IPV-Hib 2 DTaP-IPV-Hib 3	DTaP-IPV-Hib 1 DTaP-IPV-Hib 2 DTaP-IPV-Hib 3 MMR	DTaP-IPV-Hib 1 DTaP-IPV-Hib 2	DTaP-IPV-Hib 1 DTaP-IPV-Hib 2 MMR	DTaP-IPV-Hib 1 DTaP-IPV-Hib 2 MMR DTaP-IPV-Hib 3
	100% (n = 149077)	100% (n = 149346)	100% (n = 25788)	100% (n = 7198)	100% (n = 460)
Population density					
< 50k	7% (10870)	6% (9089)	7% (1825)	6% (451)	4% (20)
50-500k	56% (83418)	57% (84972)	56% (14556)	59% (4248)	50% (230)
500-200k	19% (28768)	20% (30060)	18% (4761)	19% (1379)	22% (101)
200-500k	5% (6811)	4% (6672)	5% (1313)	4% (309)	7% (34)
>500k	13% (19210)	12% (18553)	13% (3333)	11% (811)	16% (75)
Parents' place of birth					
Denmark	82% (122185)	83% (124133)	80% (20574)	82% (5902)	82% (377)
Danmark and foreign	10% (14506)	9% (13814)	11% (2823)	9% (674)	11% (51)
Foreign	8% (12386)	8% (11399)	9% (2391)	9% (622)	7% (32)
Single parenthood					
Two adults	93% (139170)	95% (141386)	89% (23067)	94% (6734)	93% (429)
Single parent	7% (9907)	5% (7960)	11% (2721)	6% (464)	7% (31)
Family income level (quartiles)					

First (lowest)	23% (34950)	20% (29315)	31% (8083)	22% (1619)	23% (106)
Second	23% (34859)	22% (33060)	25% (6362)	23% (1661)	20% (92)
Third	22% (32761)	23% (34302)	19% (5014)	21% (1536)	18% (81)
Fourth	18% (26301)	20% (29585)	14% (3584)	18% (1304)	20% (93)
Fifth (highest)	14% (20206)	15% (23084)	11% (2745)	15% (1078)	19% (88)
Maternal education level					
Primary	19% (27628)	16% (24338)	26% (6634)	18% (1298)	17% (77)
High school exam	10% (15579)	10% (15627)	10% (2598)	10% (732)	11% (49)
Vocational training	33% (48594)	35% (52086)	30% (7855)	34% (2437)	34% (157)
Bachelor / academic	29% (43799)	29% (43615)	26% (6653)	28% (2041)	26% (120)
Master or higher	9% (13477)	9% (13680)	8% (2048)	10% (690)	12% (57)
Singleton					
Singleton	96% (142696)	96% (143442)	96% (24814)	97% (6987)	99% (454)
Twin	4% (6249)	4% (5790)	4% (951)	3% (208)	1% (6)
Triplet or more	0% (132)	0% (114)	0% (23)	0% (3)	0% (0)
Other children in household					
0	37% (55416)	51% (75989)	27% (6988)	49% (3522)	48% (220)
1	41% (61091)	34% (51354)	44% (11398)	35% (2497)	34% (156)
2	17% (24941)	12% (17484)	21% (5355)	13% (941)	15% (67)
3+	5% (7629)	3% (4519)	8% (2047)	3% (238)	4% (17)
Sex					
Boy	50% (75156)	49% (73814)	51% (13260)	51% (3670)	49% (227)
Girl	50% (73921)	51% (75532)	49% (12528)	49% (3528)	51% (233)
Caesarean section					
No	81% (121128)	81% (121112)	81% (20999)	81% (5814)	83% (380)
Yes	19% (27949)	19% (28234)	19% (4789)	19% (1384)	17% (80)
Premature (born before the 37th week)					
No	94% (139465)	94% (140508)	93% (24099)	95% (6808)	94% (432)
Yes	6% (9612)	6% (8838)	7% (1689)	5% (390)	6% (28)

Birth weight					
< 2kg	2% (2708)	1% (2112)	2% (525)	1% (94)	1% (4)
2kg-2500g	3% (4852)	3% (4743)	3% (853)	3% (202)	3% (13)
2500g-3kg	12% (17456)	12% (18330)	12% (3023)	13% (904)	9% (42)
3kg-3500g	31% (46461)	32% (47834)	31% (7996)	32% (2277)	32% (146)
3500g-4kg	34% (50285)	34% (50214)	33% (8632)	34% (2434)	35% (162)
4kg-4500g	15% (22097)	14% (21154)	15% (3823)	14% (1041)	17% (77)
>4500g	4% (5218)	3% (4959)	4% (936)	3% (246)	3% (16)
Maternal age					
<20	1% (1805)	1% (1591)	2% (483)	2% (111)	2% (10)
20-24	10% (15373)	11% (16753)	12% (3162)	12% (846)	9% (43)
25-29	34% (50117)	37% (55683)	32% (8150)	36% (2583)	34% (158)
30-34	37% (55233)	35% (52457)	35% (9067)	35% (2537)	35% (163)
30-39	15% (23106)	13% (19829)	16% (4226)	14% (985)	17% (77)
>40 years	2% (3443)	2% (3033)	3% (700)	2% (136)	2% (9)
Mother smoking during pregnancy					
No	81% (120845)	83% (124291)	74% (19182)	82% (5937)	83% (384)
Yes	19% (28232)	17% (25055)	26% (6606)	18% (1261)	17% (76)
Chronic diseases at 16 months[a]					
No	96% (143425)	97% (144436)	96% (24669)	96% (6927)	97% (444)
Yes	4% (5652)	3% (4910)	4% (1119)	4% (271)	3% (16)
History of any registered hospital admission due to infectious diseases before 15 months of age[b]					
None	88% (131397)	90% (134545)	85% (21956)	89% (6391)	87% (402)
One	10% (15400)	9% (13164)	12% (3206)	10% (725)	12% (53)
Two or more	2% (2280)	1% (1637)	2% (626)	1% (82)	1% (5)
History of any registered prescribed antibiotics before 15 months of age[c]					
None	45% (67181)	50% (74292)	40% (10283)	47% (3378)	46% (213)
One	27% (40451)	27% (40396)	27% (6985)	27% (1953)	25% (115)
Two	15% (21786)	13% (19484)	16% (4165)	14% (996)	15% (69)
Three or more	13% (19659)	10% (15174)	17% (4355)	12% (871)	14% (63)

Family members with asthma					
No	84% (125287)	86% (128699)	81% (20957)	85% (6114)	85% (390)
Yes	16% (23790)	14% (20647)	19% (4831)	15% (1084)	15% (70)
Family members with atopic dermatitis or allergic rhinoconjunctivitis					
No	45% (67654)	46% (68671)	46% (11846)	45% (3246)	46% (212)
Yes	55% (81423)	54% (80675)	54% (13942)	55% (3952)	54% (248)

a) Chronic diseases [yes / no] defined according to Kristensen K, Hjuler T, Ravn H, Simoes EAF, Stensballe LG. Chronic diseases, chromosomal abnormalities, and congenital malformations as risk factors for respiratory syncytial virus hospitalization: a population-based cohort study. Clin Infect Dis. 2012 Mar;54(6):810–7.

b) Hospital contacts, ambulatory visits and emergency visits defined according to Sorup S, Benn CS, Poulsen A, Krause TG, Aaby P, Ravn H. Live vaccine against measles, mumps, and rubella and the risk of hospital admissions for nontargeted infections. JAMA. 2014 Feb 26;311(8):826–35.

c) Systemic antibiotics, ATC-codes J01 and sub-groups.

d) Family member is a parent or sibling. Asthma, atopic dermatitis and allergic rhinoconjunctivitis defined according to Henriksen L, Simonsen J, Hærskjjold A, Linder M, Kieler H, Thomsen SF, et al. Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in Danish and Swedish children. J Allergy Clin Immunol. 2015 Aug;136(2):360–2.

Supplementary table 2. Weighted hazard ratios for hypothesis 1

Prior vaccination	Last vaccination	Events and person years	weighted hazard ratio (95% CI)	Proportional hazards test, p-value	weighted hazard ratio, 15-23 months of age (95% CI)	weighted hazard ratio, 24-35 months of age (95% CI)	weighted hazard ratio, 36-48 months of age (95% CI)
Recommended Sequence							
DTaP-IPV-Hib 1+2	DTaP-IPV-Hib 3	4,085/99,108	1 (ref)	<0.001	1 (ref)	1 (ref)	1 (ref)
DTaP-IPV-Hib 1+2+3	MMR	14,670/673,946	0.90 (0.87-0.94)		0.87 (0.83-0.91)	1.04 (0.94-1.14)	94.0 (0.81-1.08)
Early MMR Sequence							
DTaP-IPV-Hib 1	DTaP-IPV-Hib 2	779/18,339	1 (ref)	<0.01	1 (ref)	1 (ref)	1 (ref)
DTaP-IPV-Hib 1+2	MMR	725/32,579	0.94 (0.84-1.06)		0.86 (0.74-0.99)	0.91 (0.71-1.17)	1.62 (1.07-2.46)
Interrupted Sequence							
DTaP-IPV-Hib 1+2	MMR	725/32,579	0.82 (0.66-1.03)	0.06	0.64 (0.46-0.90)	0.85 (0.57-1.26)	1.15 (0.73-1.82)
DTaP-IPV-Hib1+2+MMR	DTaP-IPV-Hib 3	98/4,209	1 (ref)		1 (ref)	1 (ref)	1 (ref)

Individuals are weighted with stabilised inverse probability of treatment and censoring weights in order to handle potential time variant confounding. The inverse probability of vaccination was modelled based on a Cox proportional hazards model with population density, parents' place of birth, single parenthood, family income level (quartiles), maternal education level, singleton, other children in household, sex, caesarean section, premature (born before the 37th week), birth weight, maternal age, mother smoking during pregnancy, time-varying chronic diseases, history of any registered hospital admission due to infectious diseases before 15 months of age, history of any registered prescribed antibiotics before 15 months of age, family members with asthma at 15 months of age, family members with atopic dermatitis or allergic rhinoconjunctivitis at 15 months of age, birth month, birth year plus time-dependent accumulations of hospital admissions due to infectious diseases as well as antibiotic prescriptions from 15 months of age and onwards. The inverse probability of not being censored was modelled based on Cox proportional hazards model with the aforementioned covariates plus the time-dependent vaccination status.

Supplementary table 3. Weighted hazard ratios for hypothesis 2

Prior vaccination	Last vaccination	Events and person years	Adjusted hazard ratio (95% CI)	Proportional hazards test, p-value	Adjusted hazard ratio, 15-24 months of age (95% CI)	Adjusted hazard ratio, 24-36 months of age (95% CI)	Adjusted hazard ratio, 36-48 months of age (95% CI)
Recommended Sequence							
DTaP-IPV-Hib 1+2	DTaP-IPV-Hib 3	2,597/111,106	1 (ref)	<0.01	1 (ref)	1 (ref)	1 (ref)
DTaP-IPV-Hib 1+2+3	MMR	9,244/754,021	0.81 (0.75-0.87)		0.80 (0.74-0.87)	0.84 (0.73-0.96)	0.79 (0.65-0.96)
Early MMR Sequence							
DTaP-IPV-Hib 1	DTaP-IPV-Hib 2	624/20,840	1 (ref)	<0.01	1 (ref)	1 (ref)	1 (ref)
DTaP-IPV-Hib 1+2	MMR	490/36,983	0.77 (0.62-0.95)		0.84 (0.67-1.07)	0.63 (0.46-0.87)	0.96 (0.56-1.64)
Interrupted Sequence							
DTaP-IPV-Hib 1+2	MMR	490/36,983	1.07 (0.69-1.67)	0.86	1.03 (0.55-1.92)	1.38 (0.71-2.71)	0.84 (0.47-1.49)
DTaP-IPV-Hib1+2+MMR	DTaP-IPV-Hib 3	60/4,840	1 (ref)		1 (ref)	1 (ref)	1 (ref)

Individuals are weighted with stabilised inverse probability of treatment and censoring weights in order to handle potential time variant confounding. The inverse probability of vaccination was modelled based on a Cox proportional hazards model with population density, parents' place of birth, single parenthood, family income level (quartiles), maternal education level, singleton, other children in household, sex, caesarean section, premature (born before the 37th week), birth weight, maternal age, mother smoking during pregnancy, time-varying chronic diseases, history of any registered hospital admission due to infectious diseases before 15 months of age, history of any registered prescribed antibiotics before 15 months of age, family members with asthma at 15 months of age, family members with atopic dermatitis or allergic rhinoconjunctivitis at 15 months of age, birth month, birth year plus time-dependent accumulations of hospital admissions due to infectious diseases as well as antibiotic prescriptions from 15 months of age and onwards. The inverse probability of not being censored was modelled based on Cox proportional hazards model with the aforementioned covariates plus the time-dependent vaccination status.

Supplementary table 4. Sensitivity analysis. Exclusion of overlap with hospital contacts due to infectious diseases for hypothesis 1

Prior vaccination	Last vaccination	Events and person years	Unweighted cumulative incidence per 1,000 children at 48 months of age (95% CI)	weighted cumulative incidence per 1,000 children at 48 months of age (95% CI)	weighted cumulative incidence reduction per 1,000 children at 48 months of age (95% CI)	Ratio of weighted cumulative incidence at 48 months of age (95% CI)
Recommended Sequence						
DTaP-IPV-Hib 1+2	DTaP-IPV-Hib 3	3,845/99,310	67.9 (65.2-70.6)	64.0 (61.5-66.6)	0 (ref)	1 (ref)
DTaP-IPV-Hib 1+2+3	MMR	14,274/675,185	58.8 (57.8-59.8)	59.7 (58.7-60.7)	4.4 (1.6 to 7.1)	0.93 (0.89-0.97)
Early MMR Sequence						
DTaP-IPV-Hib 1	DTaP-IPV-Hib 2	731/18,381	65.7 (59.8-71.5)	65.8 (60.7-70.9)	0 (ref)	1 (ref)
DTaP-IPV-Hib 1+2	MMR	704/32,640	59.5 (55.1-63.9)	61.9 (57.1-66.8)	3.9 (-3.1 to 10.9)	0.94 (0.84-1.05)
Interrupted Sequence						
DTaP-IPV-Hib 1+2	MMR	704/32,640	59.5 (55.1-63.9)	59.4 (55.0-63.8)	23.6 (3.9 to 43.3)	0.72 (0.57-0.94)
DTaP-IPV-Hib1+2+MMR	DTaP-IPV-Hib 3	96/4,217	79.9 (61.2-98.3)	83.0 (63.6-102.1)	0 (ref)	1 (ref)

Individuals are weighted with stabilised inverse probability of treatment and censoring weights in order to handle potential time variant confounding. The inverse probability of vaccination was modelled based on a Cox proportional hazards model with population density, parents' place of birth, single parenthood, family income level (quartiles), maternal education level, singleton, other children in household, sex, caesarean section, premature (born before the 37th week), birth weight, maternal age, mother smoking during pregnancy, time-varying chronic diseases, history of any registered hospital admission due to infectious diseases before 15 months of age, history of any registered prescribed antibiotics before 15 months of age, family members with asthma at 15 months of age, family members with atopic dermatitis or allergic rhinoconjunctivitis at 15 months of age, birth month, birth year plus time-dependent accumulations of hospital admissions due to infectious diseases as well as antibiotic prescriptions from 15 months of age and onwards. The inverse probability of not being censored was modelled based on Cox proportional hazards model with the aforementioned covariates plus the time-dependent vaccination status.

Supplementary table 5. Sensitivity analysis. Exclusion of overlap with hospital contacts due to infectious diseases for hypothesis 2

Prior vaccination	Last vaccination	Events and person years	Unweighted cumulative incidence per 1,000 children at 48 months of age (95% CI)	weighted cumulative incidence per 1,000 children at 48 months of age (95% CI)	weighted cumulative incidence reduction per 1,000 children at 48 months of age (95% CI)	Ratio of weighted cumulative incidence at 48 months of age (95% CI)
Recommended Sequence						
DTaP-IPV-Hib 1+2	DTaP-IPV-Hib 3	1,832/111,108	35.9 (33.9-37.9)	31.8 (30.0-33.6)	0 (ref)	1 (ref)
DTaP-IPV-Hib 1+2+3	MMR	6,659/754,017	24.7 (24.1-25.3)	25.4 (24.7-26.0)	6.4 (4.5 to 8.4)	0.80 (0.75-0.85)
Early MMR Sequence						
DTaP-IPV-Hib 1	DTaP-IPV-Hib 2	411/20,841	42.9 (37.9-47.8)	39.7 (35.7-43.7)	0 (ref)	1 (ref)
DTaP-IPV-Hib 1+2	MMR	346/36,983	26.3 (23.4-29.1)	31.3 (28.0-34.6)	8.4 (3.2 to 13.6)	0.79 (0.68-0.91)
Interrupted Sequence						
DTaP-IPV-Hib 1+2	MMR	346/36,983	26.3 (23.4-29.1)	26.6 (23.7-29.4)	-2.4 (-14.0 to 9.1)*	1.10 (0.74-2.06)*
DTaP-IPV-Hib1+2+MMR	DTaP-IPV-Hib 3	37/4,840	24.6 (14.5-34.7)	24.1 (12.9-35.2)	0 (ref)	1 (ref)

Individuals are weighted with stabilised inverse probability of treatment and censoring weights in order to handle potential time variant confounding. The inverse probability of vaccination was modelled based on a Cox proportional hazards model with population density, parents' place of birth, single parenthood, family income level (quartiles), maternal education level, singleton, other children in household, sex, caesarean section, premature (born before the 37th week), birth weight, maternal age, mother smoking during pregnancy, time-varying chronic diseases, history of any registered hospital admission due to infectious diseases before 15 months of age, history of any registered prescribed antibiotics before 15 months of age, family members with asthma at 15 months of age, family members with atopic dermatitis or allergic rhinoconjunctivitis at 15 months of age, birth month, birth year plus time-dependent accumulations of hospital admissions due to infectious diseases as well as antibiotic prescriptions from 15 months of age and onwards. The inverse probability of not being censored was modelled based on Cox proportional hazards model with the aforementioned covariates plus the time-dependent vaccination status.

* 1 out of 100,000 simulations was negative and removed.

Supplementary table 6. Sensitivity analysis. MMR vs DTaP-IPV-Hib and the risk of childhood asthma using the second prescription as event date for criteria 2 of the algorithm (hypothesis 1)

Prior vaccination	Last vaccination	Events and person years	Unweighted cumulative incidence per 1,000 children at 48 months of age (95% CI)	weighted cumulative incidence per 1,000 children at 48 months of age (95% CI)	weighted cumulative incidence reduction per 1,000 children at 48 months of age (95% CI)	Ratio of weighted cumulative incidence at 48 months of age (95% CI)
Recommended Sequence						
DTaP-IPV-Hib 1+2	DTaP-IPV-Hib 3	3,074/99,621	68.6 (65.8-71.5)	64.1 (61.4-66.7)	0 (ref)	1 (ref)
DTaP-IPV-Hib 1+2+3	MMR	14,927/676,925	58.8 (57.8-59.7)	59.6 (58.6-60.5)	4.5 (1.7 to 7.3)	0.93 (0.89-0.97)
Early MMR Sequence						
DTaP-IPV-Hib 1	DTaP-IPV-Hib 2	592/18,442	65.6 (59.5-71.7)	65.6 (60.3-70.8)	0 (ref)	1 (ref)
DTaP-IPV-Hib 1+2	MMR	726/32,728	59.0 (54.8-63.2)	61.2 (56.5-65.9)	4.4 (-2.7 to 11.4)	0.93 (0.84-1.04)
Interrupted Sequence						
DTaP-IPV-Hib 1+2	MMR	726/32,728	59.0 (54.8-63.2)	58.8 (54.6-63.0)	20.7 (3.6 to 37.8)	0.74 (0.60-0.94)
DTaP-IPV-Hib1+2+MMR	DTaP-IPV-Hib 3	106/4,228	75.9 (60.1-91.5)	79.5 (62.8-95.9)	0 (ref)	1 (ref)

Individuals are weighted with stabilised inverse probability of treatment and censoring weights in order to handle potential time variant confounding. The inverse probability of vaccination was modelled based on a Cox proportional hazards model with population density, parents' place of birth, single parenthood, family income level (quartiles), maternal education level, singleton, other children in household, sex, caesarean section, premature (born before the 37th week), birth weight, maternal age, mother smoking during pregnancy, time-varying chronic diseases, history of any registered hospital admission due to infectious diseases before 15 months of age, history of any registered prescribed antibiotics before 15 months of age, family members with asthma at 15 months of age, family members with atopic dermatitis or allergic rhinoconjunctivitis at 15 months of age, birth month, birth year plus time-dependent accumulations of hospital admissions due to infectious diseases as well as antibiotic prescriptions from 15 months of age and onwards. The inverse probability of not being censored was modelled based on Cox proportional hazards model with the aforementioned covariates plus the time-dependent vaccination status.

Supplementary table 7. Sensitivity analysis. DTaP-IPV-Hib 3 vs DTaP-IPV-Hib 2 and the risk of childhood asthma by sex (outcome related to hypothesis 1)

	Prior vaccination	Last vaccination	Events and person years	Unweighted cumulative incidence per 1,000 children at 15 months of age (95% CI)	weighted cumulative incidence per 1,000 children at 15 months of age (95% CI)	weighted cumulative incidence reduction per 1,000 children at 15 months of age (95% CI)	Additive sex differential effect, p-value	Ratio of weighted cumulative incidence at 15 months of age (95% CI)	Multiplicative sex differential effect, p-value
Overall									
	DTaP-IPV-Hib 1	DTaP-IPV-Hib 2	2,102/23,120	20.6 (19.6-21.6)	19.4 (18.4-20.3)	0 (ref)		1 (ref)	
	DTaP-IPV-Hib 1+2	DTaP-IPV-Hib 3	3,762/54,489	15.6 (15.1-16.1)	16.6 (16.1-17.2)	2.7 (1.6 to 3.8)		0.86 (0.81-0.91)	
By sex									
Boys	DTaP-IPV-Hib 1	DTaP-IPV-Hib 2	1,318/11,770	25.0 (23.5-26.6)	24.0 (22.4-25.5)	0 (ref)		1 (ref)	
	DTaP-IPV-Hib 1+2	DTaP-IPV-Hib 3	2,251/27,224	18.8 (18.0-19.6)	19.8 (19.0-20.7)	4.1 (2.4 to 5.9)		0.83 (0.77-0.89)	
Girls	DTaP-IPV-Hib 1	DTaP-IPV-Hib 2	784/11,351	16.0 (14.7-17.3)	14.7 (13.5-15.9)	0 (ref)	0.01	1 (ref)	0.12
	DTaP-IPV-Hib 1+2	DTaP-IPV-Hib 3	1,511/27,365	12.4 (11.8-13.0)	13.4 (12.7-14.1)	1.3 (-0.1 to 2.7)		0.91 (0.83-1.01)	

This cohort consisted of the same background cohort as for the analyses for hypothesis 1, however defined to individuals who had had their first two doses of DTP before the age of 12 months, had not been registered with childhood asthma before 12 months of age and had no missing information on covariates.

Individuals are weighted with stabilised inverse probability of treatment and censoring weights in order to handle potential time variant confounding. The inverse probability of vaccination was modelled based on a Cox proportional hazards model with population density, parents' place of birth, single parenthood, family income level (quartiles), maternal education level, singleton, other children in household, sex, caesarean section, premature (born before the 37th week), birth weight, maternal age, mother smoking during pregnancy, time-varying chronic diseases, history of any registered hospital admission due to infectious diseases before 12 months of age, history of any registered prescribed antibiotics before 12 months of age, family members with asthma at 12 months of age, family members with atopic dermatitis or allergic rhinoconjunctivitis at 12 months of age, birth month, birth year plus time-dependent accumulations of hospital admissions due to infectious diseases as well as antibiotic prescriptions from 12 months of age and onwards. The inverse probability of not being censored was modelled based on Cox proportional hazards model with the aforementioned covariates plus the time-dependent vaccination status.

Supplementary table 8. Sensitivity analysis. DTaP-IPV-Hib 3 vs DTaP-IPV-Hib 2 and the risk of childhood asthma by sex (outcome related to hypothesis 2)

	Prior vaccination	Last vaccination	Events and person years	Unweighted cumulative incidence per 1,000 children at 15 months of age (95% CI)	weighted cumulative incidence per 1,000 children at 15 months of age (95% CI)	weighted cumulative incidence reduction per 1,000 children at 15 months of age (95% CI)	Additive sex differential effect, p-value	Ratio of weighted cumulative incidence at 15 months of age (95% CI)	Multiplicative sex differential effect, p-value
Overall									
	DTaP-IPV-Hib 1	DTaP-IPV-Hib 2	940/24,781	9.1 (8.4-9.8)	7.6 (7.0-8.2)	0 (ref)		1 (ref)	
	DTaP-IPV-Hib 1+2	DTaP-IPV-Hib 3	1,616/58,008	6.3 (6.0-6.6)	7.0 (6.7-7.3)	0.6 (-0.1 to 1.3)		0.92 (0.84-1.01)	
By sex									
Boys	DTaP-IPV-Hib 1	DTaP-IPV-Hib 2	640/12,843	11.6 (10.6-12.7)	10.0 (9.0-11.0)	0 (ref)		1 (ref)	
	DTaP-IPV-Hib 1+2	DTaP-IPV-Hib 3	1,044/29,435	8.1 (7.6-8.6)	8.8 (8.3-9.4)	1.2 (0.1 to 2.3)		0.88 (0.79-0.99)	
Girls	DTaP-IPV-Hib 1	DTaP-IPV-Hib 2	300/11,938	6.3 (5.5-7.1)	5.1 (4.4-5.8)	0 (ref)	0.09	1 (ref)	0.20
	DTaP-IPV-Hib 1+2	DTaP-IPV-Hib 3	572/28,573	4.5 (4.1-4.9)	5.1 (4.7-5.5)	0.0 (-0.8 to 0.8)		1.00 (0.86-1.19)	

This cohort consisted of the same background cohort as for the analyses for hypothesis 2, however defined to individuals who had had their first two doses of DTP before the age of 12 months and had no missing information on covariates.

Individuals are weighted with stabilised inverse probability of treatment and censoring weights in order to handle potential time variant confounding. The inverse probability of vaccination was modelled based on a Cox proportional hazards model with population density, parents' place of birth, single parenthood, family income level (quartiles), maternal education level, singleton, other children in household, sex, caesarean section, premature (born before the 37th week), birth weight, maternal age, mother smoking during pregnancy, time-varying chronic diseases, history of any registered hospital admission due to infectious diseases before 12 months of age, history of any registered prescribed antibiotics before 12 months of age, family members with asthma at 12 months of age, family members with atopic dermatitis or allergic rhinoconjunctivitis at 12 months of age, birth month, birth year plus time-dependent accumulations of hospital admissions due to infectious diseases as well as antibiotic prescriptions from 12 months of age and onwards. The inverse probability of not being censored was modelled based on Cox proportional hazards model with the aforementioned covariates plus the time-dependent vaccination status.

Supplementary table 9. Overview of previously published papers on MMR or measles vaccine and childhood asthma

Year	Study, setting, and design	Study population (age at enrolment)	Total years that children are followed	Exposure (measurement)	Outcome (measurement)	Adjustment	Adjusted estimate Odds ratio = OR Relative risk = RR Hazard ratio= HR	Sex-differential effect investigated?
2001	Wickens et al., New Zealand, Case-control	474 children aged 6-7 years	Recall the last 12 months	MMR-vaccine histories (collected blindly from the medical notes of the child' s general practitioner) at unknown median age.	Diagnosed with asthma and used asthma medicine within 12 months (reported by parents)	Gender, social class, maternal asthma, parental asthma, maternal eczema, parental eczema, maternal hay fever, paternal hay fever, hepatitis B vaccine, polio vaccine (not explicit if attenuated live or inactivated), family size, measles and pertussis infection, child care use in the first year of life, sheepskin use in the first year of life, current use of a water bed or plastic sheet on mattress, age of mattress and any current smoking in house.	OR: 1.43 (95% CI 0.85-2.41)	No
2002	DeStefano et al., USA, Cohort	167,240 new born	18-72 months	MMR vaccine (Computerized immunization tracking systems) at unknown median age but recommended vaccination age is 12 to 15 months	Asthma within 2 years by ICD9 or at least one prescription for an asthma medication (computerized databases)	Month and year of birth, and adjusted for gender, low birth weight status and DTP, OPV, Haemophilus influenza type b, Hepatitis B.	RR: 0.97 (95% CI 0.91-1.04)	No
2004	Jedrychowski et al., Poland, Cohort	1,129 9-year-old children	3 years	Measles vaccine (individual vaccination records) at unknown median age	Asthma diagnosed by a physician (reported by mothers)	Gender, parental education, environmental tobacco smoke, household heating system and moulds/dampness problems, residence in the city area, and the level of traffic pollution.	OR: 0.50 (95% CI: 0.24–1.00)	No

2004	Maher et al., USA, Matched-pair case-control	1,778 with mean age of 4.8 years	6-12 months	MMR vaccine (database of medical contacts) at unknown median age	Asthma diagnosed by ICD9 codes or at least one dispensing of asthma medication (computerized database)	Sex, race, birth weight, breastfeeding at 2 months, age and duration of eligibility in 1998, family history of asthma, maternal age, maternal marital status and maternal smoking.	OR: 1.19 (95% CI: 0.78 – 1.82)	No
2004	McKeever et al., UK, Cohort	29.238 children, no information of age	Median follow-up: 2.9 years (0 to 11 years)	MMR-vaccine (database) at median age 1.17 years	Asthma/wheeze (diagnoses in database)	Physician visits	HR: 2.20* (95% CI: 1.50-3.21) * authors regard the association to biased and concluded no association	No
2006	Flöistrup et al., Austria, Germany, the Netherlands, Sweden and Switzerland, Cross-sectional	6.630 children aged 5-13 years	N/A	MMR-vaccine (reported by parents) at unknown median age	Doctor' s diagnosis of asthma (reported by parents)	Age, sex, and country (crude),or maternal smoking during pregnancy, maternal asthma, and/or rhinoconjunctivitis, paternal asthma and/or rhinoconjunctivitis, older siblings, parental education, current smoking in the household and household pets during first year of life	OR: 0.77 (95% CI: 0.57-1.03)	No

2008	Hviid and Melbye, Denmark, Cohort	871,234 children aged 1 year	4 years	MMR-vaccine (national registry) at unknown median age but vaccination programme recommendation at 15 months of age	Asthma diagnosed at hospital contact or based on asthma medicine (national registries)	Age, calendar period, hospitalisation propensity in infancy, birth weight, place of birth, mother's country of birth, child vaccine compliance, birth order, maternal age at birth, and child's sex.	Hospitalised with an asthma diagnosis RR: 0.75 (95% CI: 0.73-0.78) Glucocorticoid inhalants (ATC code R03BA) RR: 0.84 (95% CI: 0.83-0.84)	Hospitalised with an asthma diagnosis: Boys; RR: 0.77 (95% CI: 0.74-0.80), Girls; RR: 0.73 (95% CI: 0.69-0.76). Glucocorticoid inhalants (ATC code R03BA): Boys; RR: 0.81 (95% CI: 0.80-0.82), Girls; RR: 0.89 (0.87-0.90)
2009	Rosenlund et al., Austria, Germany, the Netherlands, Sweden, and Switzerland, Cross-sectional	14,893 children aged 5-13 years	N/A	Measles vaccine (reported by parents) at unknown median age	Doctor's diagnosis of asthma or obstructive bronchitis more than once (reported by parents)	Age, gender, center, study group, smoking during pregnancy, current environmental smoking, maternal asthma and/or rhino conjunctivitis, paternal asthma and/or rhino conjunctivitis, older siblings, parental education, and household pets during first year of life.	Measles vaccine and no measles infection vs. none of each, OR: 1.03 (95% CI: 0.83-1.29) Measles vaccine and measles infection vs. none of each, OR: 0.84 (95% CI: 0.60-1.18)	No

2014	Grabenhenrich et al., Germany, Cohort	1,314 newborns	20 years	Whole-organism vaccines in early childhood (measles, mumps, and rubella; tuberculosis; and tick-borne encephalitis) compared with those who did not receive any at all.	Asthma was defined as satisfying 2 of the following 3 criteria: physician' s diagnosis of asthma ever, asthma medication in the last 12 months, and any indicative symptom in the last 12 months (wheezing, shortness of breath, and dry cough at night).	Parental allergic rhinitis, parental asthma, parents with low education, low family net income, Increased cord blood IgE level, male sex, smoking during pregnancy, day care before 18 months of age, day care after 36 months of age.	Adjusted hazard ratio [HR], 0.66 (95% CI, 0.47-0.93)	No
2015	Timmermann et al., Faroe Islands, cohort	555 children	5,7,13 years	MMR vaccination	Asthma at 5 years of age based on a questionnaire filled by parents	Birth weight and family history of chronic bronchitis/asthma.	aOR: 0.33 (95% CI: 0.12-0.90)	No

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