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Infectious Disease Practice

Vaccination against measles-mumps-rubella and rates of non-targeted infectious disease hospitalisations: Nationwide register-based cohort studies in Denmark, Finland, Norway, and Sweden

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SUMMARY

Objectives: To investigate if receipt of measles-mumps-rubella (MMR) vaccine following the third dose of diphtheria-tetanus-acellular pertussis (DTaP3) is associated with reduced rates of non-targeted infectious disease hospitalisations.
Methods: Register based cohort study following 1,397,027 children born in Denmark, Finland, Norway, and Sweden until 2 years of age. Rates of infectious disease hospitalisations with minimum one overnight stay according to time-varying vaccination status were compared using Cox proportional hazards regression analysis with age as the underlying timescale and including multiple covariates. Summary estimates were calculated using random-effects meta-analysis.
Results: Compared with DTaP3 and no MMR vaccine, MMR after DTaP3 was associated with reduced rates of infectious disease hospitalisations: aHR was 0.86 (0.83–0.89) in Denmark, 0.70 (0.64–0.75) in Finland, 0.71 (0.68–0.74) in Norway, and 0.71 (0.65–0.77) in Sweden: summary estimate was 0.75 (0.65 to 0.84). A beneficial association was also seen in a negative control exposure analysis (3 vs. 2 DTaP doses): summary estimate aHR was 0.81 (0.75–0.87).
Conclusions: Having MMR as the most recent vaccine was consistently associated with reduced rates of infectious disease hospitalisation. However, bias may account for at least some of the observed association. Randomised controlled trials are warranted to inform the optimal timing of MMR for both its specific and potential non-specific effects.

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Introduction

Vaccines have been found to have non-specific effects (NSEs), affecting susceptibility towards other infections than the vaccine-targeted diseases.[1] The observed NSEs have varied depending on sex, the type of infection being studied, severity of disease, the type of vaccine being administered, and sequence of vaccinations. Live vaccines have often been associated with beneficial NSEs, which are most pronounced as long as the vaccines are the most recent vaccine administered.[1]

The initial observations were done in settings with high child mortality, where live vaccines were found to reduce child mortality more than what could be explained by the specific disease protection.[2,3] Studies from high-income countries, with low child mortality, have found similar patterns when looking at hospitalisations for non-targeted infectious diseases. Compared with having the non-live vaccine against diphtheria, tetanus, acellular pertussis, polio, and *Haemophilus influenzae* type b as the most recent vaccine, vaccination with the live combination vaccine against measles, mumps and rubella (MMR) has been associated with reduced rates of hospitalisations from non-targeted infections.[4–8] However, it is difficult to draw clear conclusions from these studies due to high risk of residual confounding.[9] Moreover, differences in settings and study protocols hamper comparisons of results.[10–12] Triangulation of results from multiple settings,[13,14] and employing identical analysis plans[15] have been proposed as methods to strengthen the causal deductions that can be made from observational studies.

The aim of this study was to investigate if receipt of MMR vaccine after the third dose of diphtheria-tetanus-acellular pertussis-containing vaccine (DTaP) was associated with lower rates of vaccine non-targeted infectious disease hospitalisation than receipt of three doses DTaP vaccine only, among children below 2 years of age born in Denmark, Finland, Norway, or Sweden, using national register data, similar analysis plans, and extensive control for potential confounders.

Methods

The northern European countries Denmark, Finland, Norway, and Sweden (henceforward referred to as the Nordic countries) all have universal tax-funded health care, comparable socio-demographic characteristics, and extensive nationwide registries holding information on a multitude of health and sociodemographic information.[16] In all countries, the personal ID given upon birth or taking residency in the country makes linkage of data from the different registries possible.[16]

This register-based cohort study utilises the data collected within the Nordic collaboration "NONSEnse". Due to current legislation, data was stored in each country separately. Description of settings, data sources, and harmonisation of data within NONSEnse is published elsewhere.[17]

This study included children born in the respective country from 1 January 2008 in Denmark and Norway, 1 July 2010 in Finland, and 1 January 2013 in Sweden until and including 31 December 2015 in all countries. The study period was based on availability of register data collected for the NONSEnse project, and pneumococcal conjugate vaccines (PCV) being used in the childhood immunisation programmes in all countries. DTaP and PCV were recommended at 3, 5, and 12 months of age in all countries. MMR vaccine was recommended at 15 months of age in Denmark and Norway, and 18 months of age in Sweden. In Finland, MMR was recommended together with DTaP at 12 months of age, but some children still received MMR after the third dose of DTaP. All vaccines within the Nordic childhood immunisation programmes are voluntary and administered free of charge. Individual-level information on administered vaccines, including type and date of vaccination, is recorded in national vaccination registries.[18–20]

Hospitalisations for infections

Hospital care for children is free of charge in Denmark and Norway.[21,22] A small patient fee up to an annual maximum amount may be charged for inpatient contacts in Finland and some regions in Sweden.[23,24] Individual-level information on all hospital contacts, including diagnoses, and dates of admission and discharge, is registered in nationwide patient registries.[25–28] Since 1997, diagnoses have been coded according to the International Classification of Diseases version 10 (ICD-10) in all countries.[29] The primary outcome was defined as inpatient contacts with overnight stays for any type of infection, including primary and secondary diagnoses (sMaterial 1), as this outcome has been found to occur at similar rates across the Nordic countries.[30] Secondary outcomes included inpatient contacts with at least two overnight stays (representing the more severe infections) and inpatient contacts with at least one overnight stay by type of infection, categorised as upper respiratory tract infections (URTI), lower respiratory tract infections (LRTI), gastrointestinal infections (GI) or other infections (OI) (sMaterial 1).

Covariate assessments

From the nationwide registries, we included information on year and season of birth, sex, birth weight, mode of delivery, maternal smoking during pregnancy, singleton, child order, maternal age, maternal origin, household income quintile, single parenthood, maternal highest attained education, number of inpatient hospital contacts before 12 months of age, presence of chronic diseases, and receipt of other live or non-live vaccines (categorisation presented in sMaterial 2).

Study design

We included children who had received the second dose of DTaP but neither the third dose of DTaP, first dose of MMR nor any other measles containing vaccine before 11 months of age (sFigure 1), to minimise bias related to reasons for non-vaccination. In the main analysis, we included children regardless of the number of registered PCV vaccinations.

Vaccination status was time varying and changed on the date of vaccination for each DTaP vaccine or MMR vaccine after baseline. Vaccination status was categorised as: 1) three doses of DTaP (DTaP3), 2) MMR given after three doses of DTaP (MMR-after-DTaP3), 3) concurrent MMR and DTaP3 vaccination (MMR-with-DTaP3), 4) MMR given after DTaP2 (MMR-after-DTaP2), and 5) DTaP3 given after MMR (DTaP3-after-MMR).

Inverse probability of treatment weights (IPTW) predicts the inverse probability of being exposed to different vaccination statuses as a function of the included covariates. We estimated the IPTW given the included covariates using multinominal logistic regression and truncated weights above the 99th percentile.[31–33] The IPTW were estimated in 14-day age intervals reflecting an age-dependent probability of vaccination given the covariates.

We limited follow-up to age intervals where a sufficient number of children had received MMR, i.e., excluding younger ages where only a few children had received MMR earlier than recommended. Baseline was defined based on visual inspection of vaccine exposure distribution (sFigure 2) and IPTW plots according to age (further described in sMaterial 3, sFigure 2–4). Based on this evaluation, baseline was defined as 2 weeks prior to the age of recommended MMR vaccination in Denmark, Norway, and Sweden. In Finland, where MMR is recommended together with DTaP3, children who received MMR separately were generally older than the age of

recommended vaccination, and the baseline in Finland was thus set at 2 weeks after the age of recommended vaccination.

Statistical analysis

The analyses were conducted in each country separately, using identical statistical coding in Stata 16 and/or 17. Children were followed from their date of vaccination (first of MMR or DTaP3), or from baseline whichever occurred last, and until 2 years of age, death, emigration, receipt of a fourth dose of DTaP, a second dose of MMR, or 31st December 2017, whichever occurred first (sFigure 1).

Infectious disease hospitalisations were included as recurrent events. Events that occurred within 14 days of a previous event were regarded as belonging to the same infectious disease episode. Therefore, the 13-day period after each event was censored and follow-up was restarted on day 14 after the previous event.

We first calculated crude rates of infectious disease hospitalisations as the number of events per 100 person-years. We used Cox proportional hazards regression model with age as the underlying timescale and repeated events (Andersen-Gill model[34]) to estimate the hazard ratios (HR) of infectious disease hospitalisations according to vaccination status and 95% confidence intervals (CI). We estimated; 1) unadjusted HRs; 2) covariate-adjusted HRs (aHR) and 3) IPTW HRs using time-varying weights. The IPTW model was further adjusted for the included covariates to account for remaining covariate imbalance after weighting.

First, the analyses were performed for hospitalisations with minimum one and two overnight stays, respectively, including all types of infections. Second, the analysis for infectious disease hospitalisations with minimum one overnight stay was performed by type of infection. All analyses were performed for all children combined and by sex. We used the Wald test for interaction to identify potential sex differential effects.

For the primary outcome in the covariate-adjusted model, the proportional hazards assumption was tested using Schoenfeld residuals,[35] if violations were observed between exposure groups, we estimated the HR in 8-week follow-up intervals.

Summary estimates across all countries were calculated using the DerSimonian-Laird method for random-effects meta-analysis accounting for between study heterogeneity.[36]

Sensitivity and subgroup analyses

Children who leave their country of residence temporarily (up to 12 months) are not required to be registered as emigrants, causing loss to follow-up without the possibility to censor them. Children with a parent born abroad may be more likely to leave the country for longer periods of time. MMR is recommended to be given prior to travelling abroad (specific recommendations vary between countries), which could lead to an underestimation of events among children who have received MMR. This could bias the results towards a beneficial effect of MMR. Thus, we performed a subgroup analysis restricted to children with two native-born parents.

Families are generally advised to have the MMR-vaccination postponed if the child has fever. Thus, children will tend to be free from illness at the time of vaccination, introducing healthy vaccinee bias.[37] At the same time, MMR can give transient fever. We therefore conducted a sensitivity analysis excluding the 14 days after vaccination with MMR from follow-up.

In Finland, children are recommended annual seasonal influenza vaccination from 6 months of age; we investigated if receipt of influenza vaccine affected the results by censoring children upon influenza vaccination.

Missing PCV and rota virus vaccine (RV) vaccinations could indicate vaccine hesitancy, which could also apply to MMR. We conducted a subgroup analysis excluding children who had not received two doses of PCV, and RV as recommended in each country, before 11 months of age.

We explored the presence of unmeasured bias attributable to not receiving vaccines as recommended by investigating the rate of infectious disease hospitalisations with minimum one overnight stay among children who had received the third dose of DTaP and no MMR, compared with children who had received two doses of DTaP, as negative control exposure. Post hoc, we further performed this negative control analysis for the different types of infections. In this analysis, we followed children from 11 months of age until 15 months of age, death, migration, or receipt of MMR, whichever came first.

Finally, we calculated the G-value for the strength required by an unmeasured confounder to return the observed aHR of infectious disease hospitalisations in the main analysis to the null.[38]

Ethical approvals

The study was approved by the Regional Ethics Committee, South-East, in Norway and by the Regional Ethical Review Board, Stockholm, Sweden. Ethical approval is not required for registry-based studies in Denmark or Finland, but the study was approved by the Danish Data Protection Agency and the Institutional Review Board of the Finnish Institute for Health and Welfare.

Results

A total of 1,621,643 children were born in the countries during the respective study periods. After exclusions, primarily of children who had received measles-containing vaccines or not received 2 doses of DTaP before 11 months of age, 1,397,027 children were included (Fig. 1).

In Denmark, Norway and Sweden, most children (> 92%) followed the recommended vaccination sequence and received 3 doses of DTaP before any MMR (Fig. 1). In Finland, 25% received DTaP3 before any MMR, whereas most children got the MMR and DTaP3 together as recommended (Fig. 1). The age at vaccination with MMR after DTaP3 varied the most in Finland with an interquartile range (IQR) of 68 days, followed by 54 days in Denmark, compared with an IQR of 32 days in Norway and 27 days in Sweden (sTable 1). Among children with DTaP3, the proportion who subsequently received MMR before 2 years of age was lower in Denmark (90.1%) and Finland (90.7%) compared with Sweden (93.5%) and Norway (97.3%) (Fig. 2, sFigure 2 and calculated from number of children in each exposure group presented in Fig. 1).

The children in the vaccination groups MMR-with-DTaP3, MMR-after-DTaP2, and DTaP3-after-MMR represent small subgroups of the study population (up to 3.4%) who do not follow the recommended vaccination sequence, except for the MMR-with-DTaP3 group in Finland (Fig. 2). The median age at entering the respective vaccination groups (sTable 1) indicated differences across countries concerning whether the children in these subgroups received the vaccines prior to, according to, or later than recommended. The present analysis focused on the effect of having MMR after DTaP3 compared with DTaP3 and no MMR.

Compared to children who had received MMR after DTaP3 one month after recommended MMR vaccination, children who had not yet received MMR were less likely to be firstborn and more likely to come from families with low household income and low maternal education in Denmark, Norway, and Sweden. This pattern was not seen in Finland (Table 1). Overall, the associations between covariates and vaccination status at two years of age were similar to the associations at one month after recommended vaccination (sTable2).

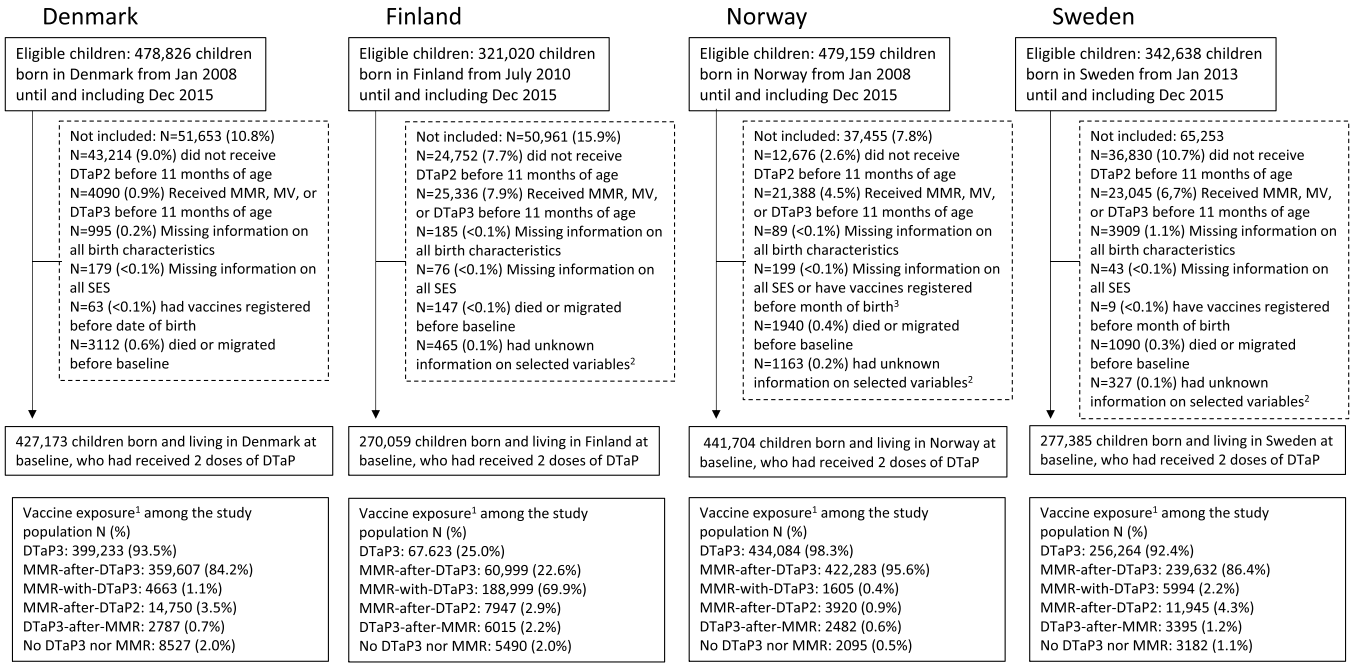

Fig. 1. Flowchart for study population participation including number of children who enter each vaccination group. Abbreviations: MMR: Measles, Mumps, Rubella vaccine; MV: measles containing vaccines; DTaP3: received 3 doses of diphtheria, tetanus, acellular pertussis, polio, and Haemophilus Influenzae type b vaccine; SES: Socioeconomic status; MMR-after-DTaP3: received MMR after DTaP3; MMR-with-DTaP: concurrent MMR and DTaP3 vaccination; MMR-after-DTaP2: MMR after second dose of DTaP; DTaP3-after-MMR: third dose of DTaP received after MMR vaccination. [1]Vaccination statuses of the children in the study population after receipt of the second dose of DTaP (inclusion criteria). The proportion of children in the DTaP3 and MMR-after-DTaP2 vaccination group does not reflect the number of children that contribute with follow-up in these groups as some may have received a subsequent MMR or DTaP3 vaccine before start of follow-up. The groups are not exclusive as the child can contribute to multiple vaccination groups before 2 years of age. [2]we excluded children that had unknown information on a variable where less than 2 per thousand had missing information due to low numbers in these strata. [3]In Norway only months of birth was available. We assigned an exact date of birth to each child as a random integer within the month of birth.

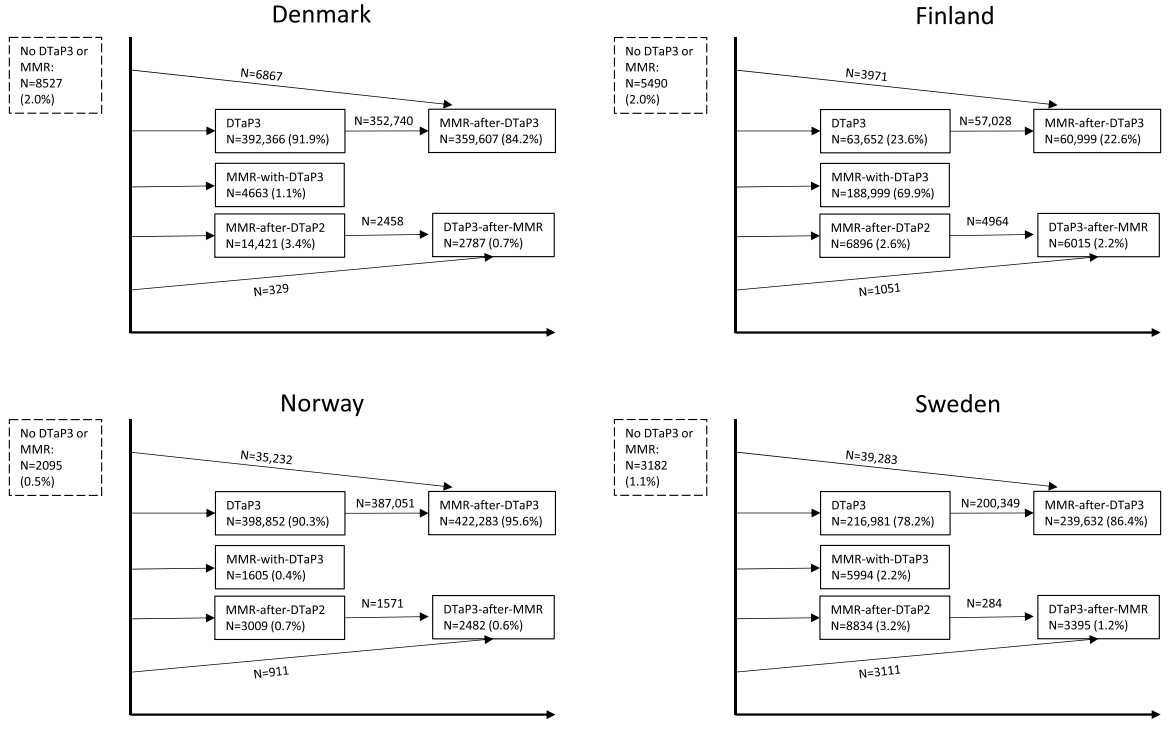

Fig. 2. Changes in vaccination status during follow-up. Abbreviations: DTaP3: received 3 doses of diphtheria, tetanus, acellular pertussis, polio, and Haemophilus Influenzae type b vaccine; MMR-after-DTaP3: received Measles, Mumps, rubella vaccine (MMR) after DTaP3; MMR-with-DTaP3: concurrent MMR and DTaP3 vaccination; MMR-after-DTaP2: MMR after second dose of DTaP; DTaP3-after-MMR: third dose of DTaP received after MMR vaccination. Number of children that belong to the different vaccination groups during follow-up (numbers within the boxes), proportions calculated with number of children included in each of the countries as the denominator: 427,173 in Denmark, 270,059 in Finland, 441,704 in Norway, and 277,385 in Sweden (Fig. 1). Arrows going from the y-axis indicate persons belonging to that vaccination group at start of follow-up (date of DTaP3 or MMR or baseline age, see methods). Arrows between vaccination groups indicate number of children moving from one vaccination group to another vaccination group during follow-up. Note that numbers and proportions do not sum to the total number, because a child can belong to several vaccination groups during follow-up.

Table 1
Characteristics of children exposed to DTaP3 or MMR after DTaP3 at 1 month after age of recommended MMR vaccination[a] in Denmark, Finland, Norway, and Sweden.

	Denmark				Finland				Norway				Sweden			
	DTaP3		MMR after DTaP3		DTaP3		MMR after DTaP3		DTaP3		MMR after DTaP3		DTaP3		MMR after DTaP3	
Study population	169,638		215,597		46,557		12,543		100,600		329,202		63,494		192,035	
Sex																
Male	87,823	51.8%	108,907	50.5%	23,588	50.7%	6389	50.9%	52,482	52.2%	168,184	51.1%	33,135	52.2%	98,463	51.3%
Female	81,815	48.2%	106,690	49.5%	22,969	49.3%	6154	49.1%	48,118	47.8%	161,018	48.9%	30,359	47.8%	93,572	48.7%
Year of birth																
2008	23,672	14.0%	25,982	12.1%	0	0.0%	0	0.0%	17,064	17.0%	36,876	11.2%	0	0.0%	0	0.0%
2009	22,601	13.3%	26,695	12.4%	0	0.0%	0	0.0%	15,690	15.6%	39,840	12.1%	0	0.0%	0	0.0%
2010	21,801	12.9%	29,418	13.6%	6876	14.8%	1980	15.8%	14,131	14.0%	41,182	12.5%	0	0.0%	0	0.0%
2011	22,073	13.0%	26,011	12.1%	10,133	21.8%	3231	25.8%	13,807	13.7%	40,304	12.2%	0	0.0%	0	0.0%
2012	21,789	12.8%	25,594	11.9%	10,036	21.6%	2552	20.3%	12,291	12.2%	41,288	12.5%	0	0.0%	0	0.0%
2013	20,117	11.9%	24,850	11.5%	7749	16.6%	1846	14.7%	10,968	10.9%	41,690	12.7%	22,526	35.5%	61,352	31.9%
2014	17,893	10.5%	27,243	12.6%	6276	13.5%	1510	12.0%	8486	8.4%	43,438	13.2%	21,302	33.5%	63,600	33.1%
2015	19,692	11.6%	29,804	13.8%	5487	11.8%	1424	11.4%	8163	8.1%	44,584	13.5%	19,666	31.0%	67,083	34.9%
Season of Birth																
Winter (December to February)	38,888	22.9%	51,611	23.9%	11,323	24.3%	3155	25.2%	19,393	19.3%	80,549	24.5%	16,468	25.9%	43,116	22.5%
Spring (March to May)	41,247	24.3%	53,327	24.7%	9909	21.3%	2602	20.7%	28,477	28.3%	82,589	25.1%	15,436	24.3%	51,732	26.9%
Summer (June to August)	45,366	26.7%	58,643	27.2%	12,190	26.2%	3222	25.7%	27,304	27.1%	87,980	26.7%	18,483	29.1%	48,645	25.3%
Autumn (September to November)	44,137	26.0%	52,016	24.1%	13,135	28.2%	3564	28.4%	25,426	25.3%	78,084	23.7%	13,107	20.6%	48,542	25.3%
Birth weight (grams)																
< 2000	3250	1.9%	3455	1.6%	776	1.7%	202	1.6%	2003	2.0%	5301	1.6%	813	1.3%	1864	1.0%
2001–2500	5598	3.3%	7059	3.3%	1240	2.7%	303	2.4%	3059	3.0%	9379	2.8%	1737	2.7%	4917	2.6%
2501–3000	20,749	12.2%	27,550	12.8%	5204	11.2%	1399	11.2%	11,498	11.4%	37,689	11.4%	7160	11.3%	21,743	11.3%
3001–3500	53,689	31.6%	71,066	33.0%	15,083	32.4%	4134	33.0%	31,781	31.6%	106,235	32.3%	20,494	32.3%	61,957	32.3%
3501–4000	56,384	33.2%	71,518	33.2%	16,522	35.5%	4481	35.7%	34,651	34.4%	114,077	34.7%	21,500	33.9%	66,471	34.6%
4001–4500	22,896	13.5%	27,316	12.7%	6621	14.2%	1736	13.8%	14,482	14.4%	46,662	14.2%	9520	15.0%	28,527	14.9%
> 4500	4673	2.8%	5284	2.5%	1111	2.4%	288	2.3%	3126	3.1%	9859	3.0%	2270	3.6%	6556	3.4%
Unknown	2399	1.4%	2349	1.1%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Preterm (born before 37 full weeks of gestation)																
Not preterm	157,034	92.6%	201,064	93.3%	43,913	94.3%	11,872	94.7%	93,415	92.9%	308,167	93.6%	60,040	94.6%	182,683	95.1%
Preterm	10,790	6.4%	12,885	6.0%	2644	5.7%	671	5.3%	6632	6.6%	19,486	5.9%	3454	5.4%	9352	4.9%
Unknown	1814	1.1%	1648	0.8%	0	0.0%	0	0.0%	553	0.5%	1549	0.5%	0	0.0%	0	0.0%
Delivered by caesarean section																
Not delivered by caesarean section	132,077	77.9%	167,416	77.7%	38,600	82.9%	10,417	83.1%	83,055	82.6%	274,523	83.4%	52,204	82.2%	158,379	82.5%
Delivered by caesarean section	37,561	22.1%	48,181	22.3%	7957	17.1%	2126	16.9%	17,545	17.4%	54,679	16.6%	11,290	17.8%	33,656	17.5%
Unknown	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Maternal smoking or snuff during pregnancy																
No smoking or snuff during pregnancy	144,745	85.3%	189,727	88.0%	38,506	82.7%	10,539	84.0%	73,232	72.8%	251,367	76.4%	56,778	89.4%	175,571	91.4%
Smoking or snuff during pregnancy	20,802	12.3%	21,627	10.0%	7009	15.1%	1758	14.0%	10,387	10.3%	26,836	8.2%	4337	6.8%	9266	4.8%
Unknown	4091	2.4%	4243	2.0%	1042	2.2%	246	2.0%	16,981	16.9%	50,999	15.5%	2379	3.7%	7198	3.7%
Singleton																
No	7450	4.4%	8677	4.0%	1350	2.9%	304	2.4%	3751	3.7%	10,102	3.1%	1986	3.1%	5149	2.7%
Yes	162,188	95.6%	206,920	96.0%	45,207	97.1%	12,239	97.6%	96,849	96.3%	319,100	96.9%	61,508	96.9%	186,886	97.3%
Unknown	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Child order																
Firstborn	62,559	36.9%	112,345	52.1%	18,292	39.3%	5677	45.3%	36,451	36.2%	146,584	44.5%	23,073	36.3%	85,077	44.3%
1 older sibling	69,486	41.0%	72,136	33.5%	16,046	34.5%	4170	33.2%	39,248	39.0%	116,945	35.5%	25,120	39.6%	71,524	37.2%
2 older siblings	27,247	16.1%	23,033	10.7%	7304	15.7%	1759	14.0%	17,334	17.2%	48,017	14.6%	10,088	15.9%	25,155	13.1%
3 or more older siblings	9032	5.3%	6116	2.8%	4915	10.6%	937	7.5%	7567	7.5%	17,656	5.4%	5213	8.2%	10,279	5.4%
Unknown	1314	0.8%	1967	0.9%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Maternal age at delivery																
< =20 years	4161	2.5%	4464	2.1%	1828	3.9%	440	3.5%	3884	3.9%	10,133	3.1%	1719	2.7%	3807	2.0%
21–25 years	22,723	13.4%	30,613	14.2%	8103	17.4%	2074	16.5%	17,694	17.6%	56,545	17.2%	11,385	17.9%	31,661	16.5%
26–30 years	55,477	32.7%	78,531	36.4%	15,333	32.9%	4245	33.8%	33,154	33.0%	112,720	34.2%	20,664	32.5%	64,203	33.4%

(*continued on next page*)

Table 1 (*continued*)

	Denmark				Finland				Norway				Sweden			
	DTaP3		MMR after DTaP3		DTaP3		MMR after DTaP3		DTaP3		MMR after DTaP3		DTaP3		MMR after DTaP3	
Study population	169,638		215,597		46,557		12,543		100,600		329,202		63,494		192,035	
31–35 years	58,462	34.5%	70,058	32.5%	14,071	30.2%	3942	31.4%	30,447	30.3%	100,643	30.6%	18,976	29.9%	60,573	31.5%
36 years and older	28,815	17.0%	31,931	14.8%	7222	15.5%	1842	14.7%	15,421	15.3%	49,161	14.9%	10,750	16.9%	31,791	16.6%
Unknown	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Maternal origin																
Born in-country	140,522	82.8%	183,115	84.9%	42,998	92.4%	11,506	91.7%	76,839	76.4%	256,075	77.8%	45,360	71.4%	146,411	76.2%
Born abroad	29,116	17.2%	32,482	15.1%	3559	7.6%	1037	8.3%	23,761	23.6%	73,127	22.2%	18,134	28.6%	45,624	23.8%
Unknown	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Household income quintile at birth																
First (lowest)	32,153	19.0%	32,655	15.1%	8968	19.3%	2261	18.0%	21,671	21.5%	58,235	17.7%	13,354	21.0%	31,476	16.4%
Second	32,865	19.4%	39,235	18.2%	9773	21.0%	2444	19.5%	21,237	21.1%	64,808	19.7%	13,994	22.0%	38,416	20.0%
Third	32,663	19.3%	42,174	19.6%	9825	21.1%	2559	20.4%	20,422	20.3%	67,484	20.5%	13,126	20.7%	41,051	21.4%
Fourth	31,545	18.6%	44,940	20.8%	9415	20.2%	2697	21.5%	19,030	18.9%	69,277	21.0%	12,116	19.1%	41,308	21.5%
Fifth (highest)	29,893	17.6%	46,359	21.5%	8399	18.0%	2533	20.2%	18,240	18.1%	69,398	21.1%	10,904	17.2%	39,784	20.7%
Unknown	10,519	6.2%	10,234	4.7%	177	0.4%	49	0.4%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Single parenthood																
Lives with 2 parents	155,052	91.4%	200,696	93.1%	42,974	92.3%	11,650	92.9%	89,480	88.9%	300,289	91.2%	55,367	87.2%	173,889	90.6%
Lives with single parent	14,073	8.3%	14,430	6.7%	3350	7.2%	840	6.7%	11,120	11.1%	28,913	8.8%	8127	12.8%	18,146	9.4%
Unknown	513	0.3%	471	0.2%	233	0.5%	53	0.4%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Maternal highest attained education[b]																
Low education	26,816	15.8%	25,998	12.1%	5682	12.2%	1368	10.9%	21,088	21.0%	55,742	16.9%	9661	15.2%	20,013	10.4%
Medium education	57,764	34.1%	73,008	33.9%	19,494	41.9%	5008	39.9%	27,498	27.3%	88,081	26.8%	18,796	29.6%	58,647	30.5%
High education	81,206	47.9%	112,414	52.1%	21,381	45.9%	6167	49.2%	48,173	47.9%	175,069	53.2%	20,353	32.1%	73,203	38.1%
Unknown	3852	2.3%	4177	1.9%	0	0.0%	0	0.0%	3841	3.8%	10,310	3.1%	14,684	23.1%	40,172	20.9%
Chronic diseases[c]																
No chronic diseases	163,870	96.6%	209,110	97.0%	43,238	92.9%	11,759	93.7%	93,408	92.9%	309,630	94.1%	61,187	96.4%	186,335	97.0%
Chronic diseases	5768	3.4%	6487	3.0%	3319	7.1%	784	6.3%	7192	7.1%	19,572	5.9%	2307	3.6%	5700	3.0%
Received other live vaccines																
Yes	691	0.4%	1325	0.6%	42,310	90.9%	12,103	96.5%	25,652	25.5%	99,080	30.1%	0	0.0%	0	0.0%
Unknown[d]	168,947	99.6%	214,272	99.4%	4247	9.1%	440	3.5%	74,948	74.5%	230,122	69.9%	63,494	100.0%	192,035	100.0%
Received other non-live vaccines[e]																
Yes	4183	2.5%	9422	4.4%	7567	16.3%	3524	28.1%	27,663	27.5%	79,529	24.2%	39	0.1%	98	0.1%
Unknown[d]	165,455	97.5%	206,175	95.6%	38,990	83.7%	9019	71.9%	72,937	72.5%	249,673	75.8%	63,455	99.9%	191,937	99.9%
Number of hospital contacts before 12 months of age																
0	98,581	58.1%	126,764	58.8%	35,142	75.5%	9581	76.4%	75,001	74.6%	249,862	75.9%	50,639	79.8%	156,559	81.5%
1	47,048	27.7%	60,882	28.2%	8568	18.4%	2305	18.4%	18,922	18.8%	62,201	18.9%	9784	15.4%	28,141	14.7%
2	14,684	8.7%	17,923	8.3%	1787	3.8%	421	3.4%	4005	4.0%	11,388	3.5%	1989	3.1%	5168	2.7%
3	5054	3.0%	5542	2.6%	565	1.2%	117	0.9%	1332	1.3%	3112	0.9%	545	0.9%	1284	0.7%
4 or more	4271	2.5%	4486	2.1%	495	1.1%	119	0.9%	1340	1.3%	2639	0.8%	537	0.8%	883	0.5%

Abbreviations: DTaP3 = third dose of the non-live vaccine against diphtheria, tetanus, acellular pertussis, polio, and Haemophilus Influenzae type b; MMR= vaccination against measles, mumps, and rubella.

[a] One month after age of recommended vaccination with MMR reflects the date the child turns 13 months of age in Finland, 16 months of age in Denmark and Norway, and 19 months of age in Sweden.

[b] Highest attained education classified according to ISCED2011.

[c] Chronic diseases are defined according to the definition provided by Kristensen et al.[46]

[d] Reporting of vaccines not belonging to the immunisation programme was not mandatory in all countries, thus lacking registration of other vaccines may not reflect that no other vaccines was given.

[e] PCV was recommended to all children throughout the study period. PCV was not included in other non-live vaccines.

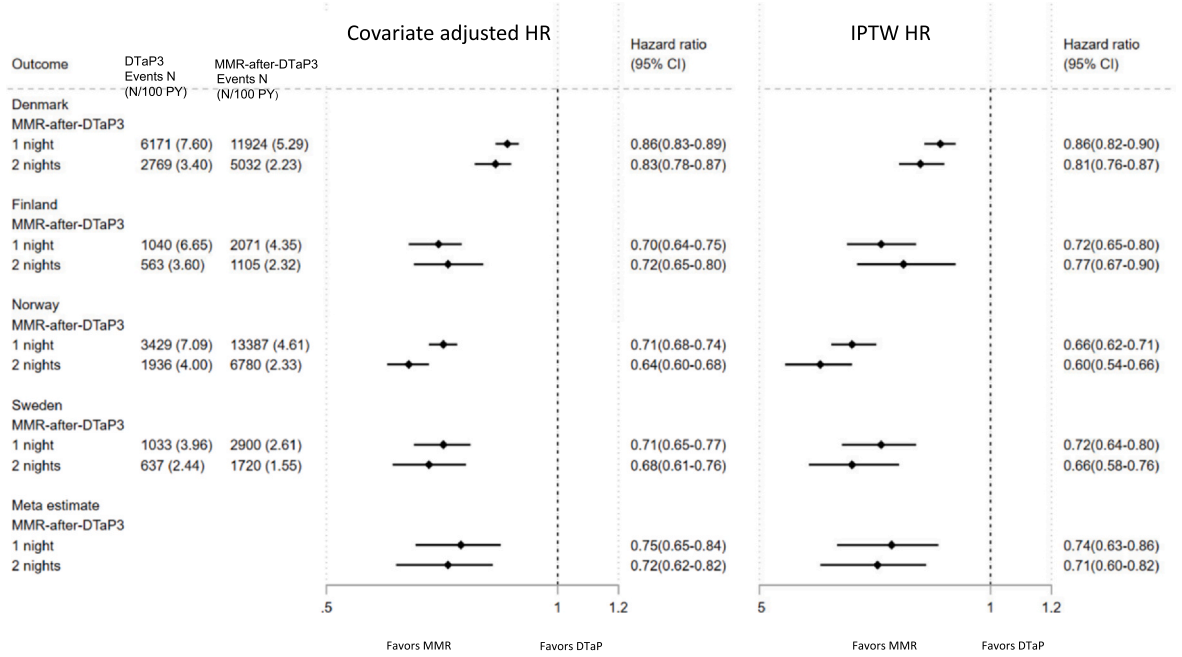

Fig. 3. Hazard ratios of infectious disease hospitalisations with a minimum of 1 or 2 overnight stays among children with MMR after three doses of DTaP compared with 3 doses of DTaP without MMR, by country and combined in summary estimate. Abbreviations: DTaP3: Received 3 doses of diphtheria, tetanus, acellular pertussis, polio, and Haemophilus Influenzae type b vaccine; MMR-after-DTaP3: Received measles, mumps, rubella vaccine after DTaP3; HR: Hazard Ratio; IPTW: Inverse probability of treatment weighted Estimated using an extended Cox regression with age as the underlying time scale, vaccination status included as time-varying exposure and infectious disease hospitalisations included as recurrent events. Summary estimate is calculated using DerSimonian-Laird method for random-effects meta-analysis. Covariates included in both the adjusted and weighted model: Year and season of birth, sex, birth weight, mode of delivery, maternal smoking during pregnancy, singleton, child order, maternal age, maternal origin, household income quintile, single parenthood, maternal highest attained education, number of inpatient hospital contacts before 12 months of age, chronic diseases, and receipt of other live or non-live vaccines.

Infectious disease hospitalisations

In all countries, children with MMR after DTaP3 had a lower rate of infectious disease hospitalisations with overnight stays compared with children not vaccinated with MMR (the DTaP3 exposure group): the unadjusted HR was 0.81 (0.78 to 0.84) in Denmark, 0.68 (0.63 to 0.73) in Finland, 0.64 (0.61 to 0.67) in Norway, and 0.66 (0.61 to 0.71) in Sweden (sTable3). The aHRs were 0.86 (0.83–0.89) in Denmark, 0.70 (0.64–0.75) in Finland, 0.71 (0.68–0.74) in Norway, and 0.71 (0.65–0.77) in Sweden (sTable 3, Fig. 3). The summary estimate for the aHR across countries was 0.75 (0.65 to 0.84) (Fig. 3). The summary estimate was 0.73 (0.62 to 0.84) for boys and 0.78 (0.69 to 0.87) for girls (sFigure 5). The summary estimate for hospitalisations with at least two overnight stays was 0.72 (0.62 to 0.82) (Fig. 3). The IPTW HRs were similar to the aHRs (Fig. 3, sTable 3, sTable 4). There were non-proportional hazards in Norway with the highest aHR for infectious disease hospitalisations with minimum one overnight stay of 0.83 (0.77 to 0.90) observed in the first 8 weeks of follow-up (sTable 5).

Type of infection

The hazard of infectious disease hospitalisations among children exposed to MMR after DTaP3 compared with DTaP3 was lower for all types of infections (Fig. 4, sTable6). The association was strongest for LRTI in Denmark, strongest for GI in Finland and OI in Sweden (Fig. 4). In Norway the results differed between the two models. The association was strongest for LRTI in the covariate adjusted model and for URTI in the IPTW model (Fig. 4). The associations by type of infection were similar for boys and girls (sFigure 6).

Sensitivity- and subgroup analyses

Restricting the analyses to children of parents born in the respective countries (sTable 7), censoring 14 days after receipt of MMR (sTable 8), censoring upon influenza vaccination in Finland (sTable 9), or restricting the study population to children who had received two doses of PCV before 11 months of age, and RV as recommended, (sTable 10) did not substantially change the results.

Having received three doses of DTaP (DTaP3) compared with two (DTaP2) was associated with reduced rates of infectious disease hospitalisations in all countries: aHR was 0.83 (0.79 to 0.86) in Denmark, 0.89 (0.80 to 1.00) in Finland, 0.74 (0.70 to 0.79) in Norway, and 0.81 (0.73 to 0.89) in Sweden, yielding a summary estimate across countries of 0.81 (0.75 to 0.87) (Fig. 5, sTable 11). The summary estimates across countries were similar for the different types of infections.

G-values for the required strength of confounding to return the observed aHR in the main analysis to the null was 1.6 in Denmark, 2.12 in Finland and Sweden, and 2.40 in Norway if the confounding factor is present in 100% of children with DTaP3 (sTable 12).

Discussion

Receipt of MMR after DTaP3 was consistently associated with lower rates of infectious disease hospitalisations compared with not having received MMR after DTaP3. The reduction was smaller in Denmark (14%) than in the other Nordic countries (approximately 30%). Similar protective associations were seen after receipt of DTaP3 when compared to DTaP2. We did not find any consistent differences in the results by sex, duration of hospitalisation, or type of infection across countries and statistical models.

Strengths and limitations

The study was based on population-based registers that contained information on exposures, outcomes, and potential confounders. Further strengths pertain to the comparable data structure across countries by use of a common data model,[17] and previous

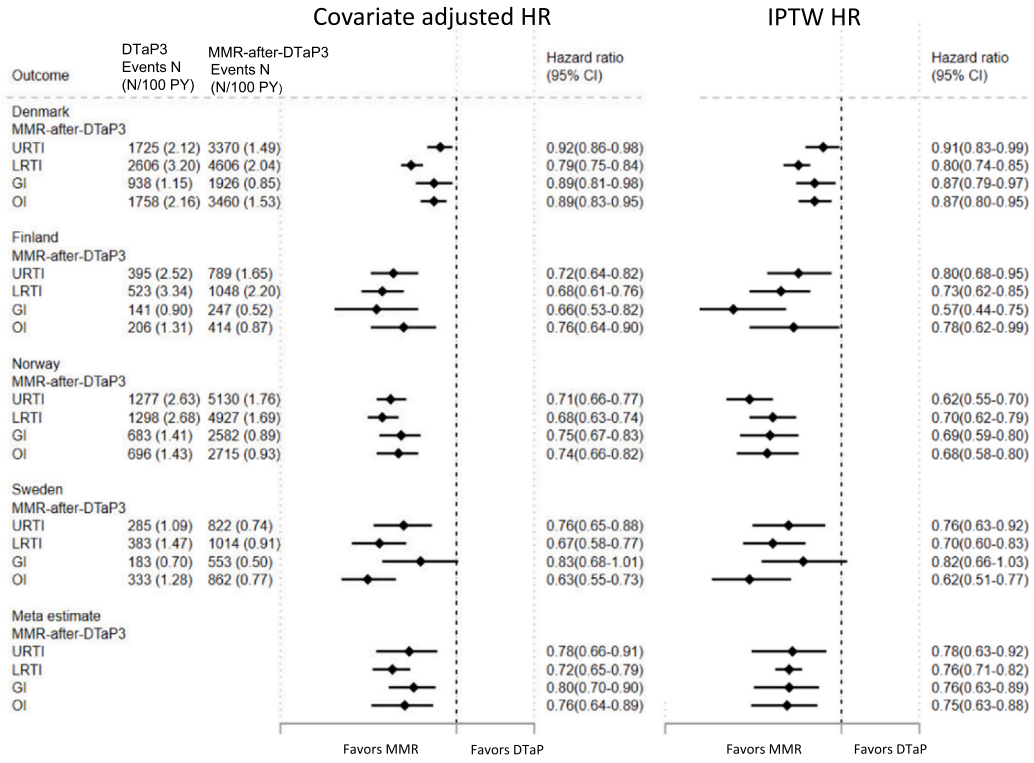

Fig. 4. Covariate adjusted, and inverse probability of treatment weighted (IPTW) Hazard Ratio of infectious disease hospitalisations with minimum 1 overnight stay for different types of infections for children with MMR after three doses of DTaP compared with 3 doses of DTaP without MMR, by country and combined in meta estimate. Abbreviations: DTaP3: received 3 doses of diphtheria, tetanus, acellular pertussis, polio, and Haemophilus Influenzae type b vaccine; MMR-after-DTaP3: received Measles, Mumps, rubella vaccine after DTaP3; HR: Hazard Ratio; IPTW: Inverse probability of treatment weighted; URTI: upper respiratory tract infections; LRTI: Lower respiratory tract infections; GI: Gastrointestinal infections; OI: Other infections. Estimated using an extended Cox regression with age as the underlying time scale, vaccination status included as time varying exposure and infectious disease hospitalisations included as recurrent events. Summary estimate is calculated using DerSimonian-Laird method for random-effects meta-analysis. Covariates included in both the adjusted and weighted model: Year and season of birth, sex, birth weight, mode of delivery, maternal smoking during pregnancy, singleton, child order, maternal age, maternal origin, household income quintile, single parenthood, maternal highest attained education, number of inpatient hospital contacts before 12 months of age, chronic diseases, and receipt of other live or non-live vaccines.

investigations of the outcomes to ensure comparability of measures across countries.[30]

However, observational studies such as ours are limited by an inherent risk of residual confounding. To reduce the risk of bias attributable to complete non-vaccination, we restricted the study population to children who had followed the vaccination programme for DTaP and MMR until 11 months of age. We used age as the underlying timescale, to ensure complete adjustment for age. We furthermore adjusted for a range of potential confounders, which attenuated the effect estimates in all countries to some extent. The IPTW model is based on the time-varying function of the covariates, which may offer better adjustment for reasons for delayed vaccination, but the results were quite similar in both the covariate-adjusted and the IPTW models. Noteworthy, estimated G-values indicate that unmeasured confounders must be associated with a 60–140% greater risk of infectious disease hospitalisations if present among 100% of children with DTaP3 to return the observed aHR to 1 – thus unmeasured confounders must represent stronger predictors of both vaccination status and risk of infectious disease hospitalisations than the combined covariates included in our analyses to return the observed aHR to 1.

Country-specific considerations

In all countries, the observed association may be biased towards a beneficial effect of receiving MMR if reasons for not receiving MMR as recommended are connected to an increased risk of infectious diseases. The lower MMR uptake with more delays in Denmark has previously been ascribed to parents forgetting appointments or re-scheduling due to busy lives.[39] These more random delays may increase comparability of children who have received MMR vaccine and those who have not in Denmark. In contrast, in the other Nordic countries, particularly in Norway, with high and steep MMR uptake, the few children who remain MMR unvaccinated probably represent a more selected group, which may result in a greater bias towards a beneficial effect of MMR. Bias must be suspected to account for at least some of the observed association in all countries. In general, it has been observed that the higher and steeper the MMR uptake, the more beneficial the estimated effect (see also below). Thus, the greater beneficial association observed in the countries other than Denmark, likely reflects a greater degree of bias.

Negative control exposure

In the main analysis the reduction in hospitalisation following MMR vaccination was 25% (16–35%) across countries. However, the negative control analysis of DTaP3 vs DTaP2 also yielded a reduction in the rates of infectious disease hospitalisations (19% (95% CI: 13–25%) across countries, indicating that bias related to not following the recommended vaccination schedule accounts for at least some of the observed association.

Tielemans et al.[8] also used a negative control exposure. In their main analysis, they found MMR+Meningococcal C vaccination compared with DTaP4 to be associated with a 38% (33–43%) lower rate of admission to hospital for infection. In their negative control

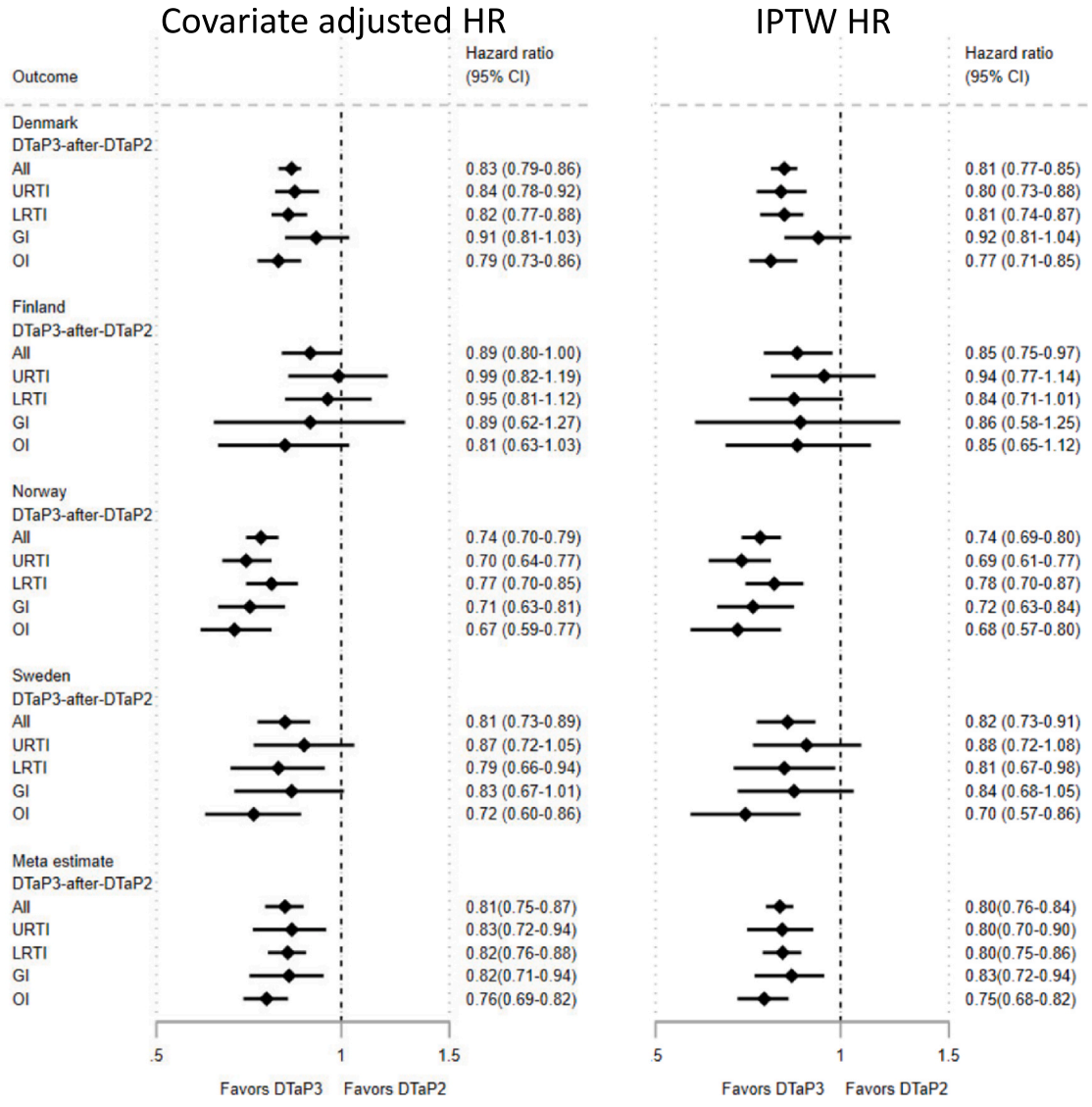

Fig. 5. Negative control exposure analysis: Hazard ratio of infectious disease hospitalisation when exposed to three doses of DTaP compared with two doses of DTaP for and hospitalisations combined and by type of infection, by country and combined in meta estimate. Abbreviations: DTaP2: received 2 doses of diphtheria, tetanus, acellular pertussis, polio, and Haemophilus Influenzae type b vaccine; DTaP3: Received 3 doses of DTaP; HR: Hazard Ratio; IPTW: Inverse probability of treatment weighted; All: all types of infections; URTI: upper respiratory tract infections; LRTI: Lower respiratory tract infections; GI: Gastrointestinal infections; OI: Other infections. Estimated using an extended Cox regression with age as the underlying time scale, vaccination status included as time-varying exposure and infectious disease hospitalisations included as recurrent events. Infectious disease hospitalisations that occur within 14 days from a previous infectious disease hospitalisation are regarded to belong to the same infectious disease episode. Children were followed from 11 months of age until 15 months of age, death, migration, or receipt of MMR, whichever occurred first. Adjusted for year and season of birth, sex, birth weight, mode of delivery, maternal smoking during pregnancy, singleton, child order, maternal age, maternal origin, household income quintile, single parenthood, maternal highest attained education, number of inpatient hospital contacts before 11 months of age, chronic diseases and receipt of other live or non-live vaccines.

analysis, having 4 doses of DTaP vs. DTaP3 was associated with a 31% (24–37%) lower rate of infectious disease hospitalisations.

We observed a more beneficial association in our main analysis than in the negative control analysis in all countries except Denmark, which is noteworthy, given that the uptake of DTaP3 was steeper, and the coverage was higher than for MMR (sMaterial 4), indicating a bigger potential for healthy vaccinee bias in the negative control analysis. However, there may be other differences in the underlying bias structures in the two analyses and therefore any comparison of results should be interpreted with caution.

Comparison with other studies

Previous cohort studies have found lower rates of infectious disease hospitalisation when MMR as most recent vaccine is compared with DTaP,[4–7] also when MMR was given together with the non-live vaccine against meningitis C.[8] The greatest protective associations were observed in countries with high and steep MMR uptake, and thus also an assumed larger degree of healthy vaccinee bias,[5,7,8] similar to what was observed in our study. Two previous studies have been conducted using Danish registry data, with divergent conclusions.[5,7] The first study found an aHR of 0.86 (0.84 to 0.88),[5] similar to the Danish estimates in our study (aHR: 0.86 (0.83 to 0.89)), ascribing it partly to an effect of MMR on hospital admissions for infections. The other study reported an aHR of 0.93 (0.92 to 0.94), but ascribed the association to residual confounding.[7] The latter study, however, did not make the same restrictions to the study population and followed children longer, up to 5 years of age, which may have contributed to the divergent conclusions.[11]

The beneficial effect of having MMR after DTaP was not found in a self-controlled case series analysis,[12] and was less clear[40] or weaker[41] when MMR was co-administered with DTaP.

Previous studies have found beneficial NSE of measles-containing vaccines to be most pronounced for LRTI.[5,6,42,43] This was not so clear in this study, and estimates were inconsistent between statistical models and countries. We have previously found variation across countries in the rates of infectious disease hospitalisations for the different types of infections.[30] Differences in coding practices may affect the results on type of infection differently in different countries. Furthermore, some of the previous studies that showed beneficial NSEs of MMR for respiratory tract infections were conducted among children not offered PCV. In all Nordic countries, PCV is offered together with DTaP, which may make the potential NSE of MMR vaccine less pronounced.

NSEs have also been found to vary by sex in studies from low-income settings.[1] We did not find consistent patterns of sex differential effects, in line with other studies from high income countries.[5,6,8]

Immunological mechanisms

Trained innate immunity has been proposed as a concept and mechanism for NSEs of vaccines.[44–46] This involves long-term functional reprogramming of innate immune cells by stimulation with eg a live vaccine, leading to an altered innate immune response at future stimulation.[44,45] Most immunological studies have focused on the live Bacille Calmette-Guérin (BCG) vaccine against tuberculosis, but recently, transcriptional and functional alterations consistent with introduction of trained immunity in γδ T cells following MMR vaccination have been observed.[47]

Conclusion and perspectives

In all four countries, we observed a lower rate of infectious disease hospitalisations among children who had MMR as their most recent vaccine compared with children who had not yet received MMR. Despite careful considerations of study design and control for numerous potential confounders, we cannot exclude residual confounding. This was illustrated by the protective association also seen for the control exposure (DTaP3). To further explore NSEs of MMR in high-income settings, randomised trials are warranted. Such randomised trials could be designed to examine the optimal age of MMR vaccination, with respect to both measles control and the occurrence of non-targeted infections.

Transparency

The guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

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Contributors

LG, SM, HE, IL, HN, BF, AAP, LT, CSB, and SS conceptualized the study. All authors directed the analyses, which were carried out by LG with supervision of SM. LG, IL, HE, and ML managed data curation, undertook the country specific coding, and produced the country-specific results. LG, HE, IL, HN, BF, AAP, LT, and SS obtained the data to be included in this study. All authors contributed to the discussion and interpretation of the results. LG drafted the first version of the manuscript. SM, HE, IL, HN, BF, ML, AAP, LT, CSB, and SS critically revised the draft. LG produced the visualizations. LG, IL, HN, BF, ML, AAP, LT, CSB, and SS obtained the funding for the present project. All authors approved the final version for submission. LG is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors had full access to all of the statistical reports and tables in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data availability

Due to data protection rules, we are not allowed to share the individual-level data, but other researchers fulfilling the requirements could obtain similar data from the register controllers.

Declaration of Competing Interest

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/http://www.icmje.org/disclosure-of-interest/ and declare: All authors had financial support from NordForsk (grant number: 83839) and LG had financial support from Odense University Hospital Research fund (A-number: 2519) and the faculty scholarship from the University of Southern Denmark for the submitted work; Finnish Institute for Health and Welfare (THL) has conducted Public-Private Partnership with vaccine manufacturers and has received research funding from Sanofi Inc., Pfizer Inc., and GlaxoSmithKline Biologicals SA. HN, ML, and AAP have been investigators in these studies, but they have received no personal remuneration; no other relationships or activities that could appear to have influenced the submitted work. Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital, receives institutional research funding from public and private entities for studies of medicines and vaccines, to and administered by Aarhus University. None of these are relevant to the current study. SS is a salaried employee of Department of Clinical Epidemiology.

Acknowlegdements

NA.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106365.

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