Original Investigation

Live Vaccine Against Measles, Mumps, and Rubella and the Risk of Hospital Admissions for Nontargeted Infections

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IMPORTANCE In low-income countries, live measles vaccine reduces mortality from causes other than measles infection. Such nonspecific effects of vaccines might also be important for the health of children in high-income settings.

OBJECTIVE To examine whether the live vaccine against measles, mumps, and rubella (MMR) is associated with lower rates of hospital admissions for infections among children in Denmark.

DESIGN, SETTING, AND PARTICIPANTS Population-based cohort study of Danish children born 1997-2006 and followed up from ages 11 months to 2 years (last follow-up, August 31, 2008). Nationwide Danish registers provided data on vaccinations and hospital admissions. The recommended vaccination schedule was inactivated vaccine against diphtheria, tetanus, pertussis, polio, and *Haemophilus influenzae* type b (DTaP-IPV-Hib) administered at ages 3, 5, and 12 months and MMR at age 15 months.

MAIN OUTCOMES AND MEASURES Incidence rate ratios (IRRs) of hospital admissions for any infection, comparing receipt of MMR vs DTaP-IPV-Hib as the most recent vaccine. Risks, risk difference, and number needed to vaccinate were calculated for receiving MMR on time.

RESULTS The study included 495 987 children contributing with 56 889 hospital admissions for any type of infection during 509 427 person-years (rate, 11.2 per 100 person-years). Receiving the live MMR vaccine after the inactivated DTaP-IPV-Hib-vaccine was associated with a lower rate of hospital admissions for any infection.

Most Recent Vaccination	Children, No.	Infectious Disease Admissions per 100 Person-Years (Admissions/Person-Years)	Adjusted Incidence Rate Ratio (95% CI)
Recommended-schedule cohort	456 043		
DTaP-IPV-Hib3 (no MMR)		12.4 (20 743/167 693)	1 [Reference]
MMR after DTaP-IPV-Hib3		8.9 (21 311/239 642)	0.86 (0.84-0.88)
MMR vs DTaP-IPV-Hib2	490 838		
DTaP-IPV-Hib2 (no MMR)		15.1 (13 682/90 691)	1 [Reference]
MMR after DTaP-IPV-Hib2 (no DTaP-IPV-Hib3)		9.9 (1025/10 399)	0.87 (0.80-0.95)
Reversed-schedule cohort	19 219		
MMR after DTaP-IPV-Hib2 (no DTaP-IPV-Hib3)		9.9 (1025/10 400)	1 [Reference]
DTaP-IPV-Hib3 after MMR		12.8 (128/1001)	1.62 (1.28-2.05)

The risk of admission for an infection between ages 16 months and 24 months was 4.6% (95% CI, 4.5%-4.7%) for receiving MMR on time and 5.1% (95% CI, 5.0%-5.2%) for not receiving MMR on time. The risk difference was 0.5 percentage point (95% CI, 0.4-0.6), and the number needed to vaccinate with MMR before age 16 months to prevent 1 infectious disease admission was 201 (95% CI, 159-272).

CONCLUSIONS AND RELEVANCE In a cohort of Danish children, receipt of live MMR vs inactivated DTaP-IPV-Hib as the most recent vaccine was associated with a lower rate of hospital admissions for any infections. These findings require replication in other high-income populations.

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Childhood vaccines are recommended worldwide, based on their protective effect against the targeted diseases.[1] However, observational studies and randomized trials from low-income countries show that vaccines may have nonspecific effects that affect morbidity and mortality from nontargeted diseases.[2-8] These studies have found that live vaccines such as measles and BCG vaccines have beneficial nonspecific effects, ie, reducing nontargeted morbidity and mortality. In contrast, inactivated vaccines, such as diphtheria-tetanus-pertussis,[9] inactivated polio vaccine,[10] and hepatitis B vaccine,[11] have been associated with increased morbidity and mortality in girls.

The specific disease-protective effects of different vaccines are additive, and they are not affected by the sequence in which the vaccines have been administered. However, the nonspecific effects are largely determined by the most recent vaccination. As summarized elsewhere, many studies from low-income countries have found that receipt of measles vaccine as the most recent vaccine after receipt of diphtheria-tetanus-pertussis vaccine is associated with decreased mortality, but receiving an inactivated vaccine as the most recent vaccination after measles vaccine is associated with increased mortality among girls.[9,12]

The mechanisms behind these consistent findings are not understood but may involve epigenetic modulation. Recent research has shown that BCG induces increased H3K4 trimethylation in circulating monocytes, leading to stronger proinflammatory responses and increased protection against unrelated pathogens in humans and animals; blocking the H3K4 methylation reverses this monocyte training.[8,13] Other mechanisms may also be involved, but such epigenetic modifications have the potential to explain how the "most recent vaccine" shapes the nonspecific effects.

So far, most studies of nonspecific effects have been conducted in low-income countries with high infectious disease pressure. In the present study, conducted in a high-income setting (Denmark), we examined whether the rate of hospital admissions for infection in the second year of life differed for children who received live vaccine against measles, mumps, and rubella (MMR) as their most recent vaccination rather than inactivated vaccine against diphtheria, tetanus, pertussis, polio, and *Haemophilus influenzae* type b (DTaP-IPV-Hib). Based on the experience from low-income countries, we hypothesized that the incidence of hospital admission for any infection would be lowest when MMR was the most recent vaccination.

Methods

The study included children born in Denmark from January 1, 1997, to August 31, 2006, when the recommended vaccination schedule until age 2 years consisted of 3 doses of DTaP-IPV-Hib at ages 3, 5, and 12 months and MMR (Enders-Edmonston, Jeryl Linn, Wistar RA 27/3) at age 15 months. In Denmark all recommended childhood vaccinations are noncompulsory and are administered free of charge by general practitioners. For the purpose of reimbursement, general practitioners report vaccinations along with information on the unique personal identification number of the recipient to the Danish National Board of Health.[14] The personal identification number is used by all Danish registers, making linkage possible.[15] Until 1996, all childhood vaccines were registered with the parent's identification number. Occasionally, childhood vaccinations were reported for adults (4.3%). In these cases, we assigned the vaccinations to that adult's child who was closest to the recommended age for that vaccine (eBox 1 in Supplement).

The Danish Data Protection Agency approved the study; no informed consent from the participants was required.

Hospital Admissions for Any Infection

The Danish National Patient Register contains information about discharge diagnoses, which are coded according to the *International Statistical Classification of Diseases, Tenth Revision (ICD-10)*.[16] We identified all inpatient contacts with a primary or secondary discharge diagnosis of any infection as defined in eTable 1 in Supplement. In Denmark, general practitioners have limited access to diagnostic tools such as acute blood tests and radiography. Hence, children with suspected severe infections are usually admitted to hospitals free of charge for further diagnostic testing; children with the mildest infections are often discharged the same day.

Other Registers

The Danish Civil Registration System contains information on births, deaths, and emigration, which we used to define inclusion and follow-up and to obtain information about the child's parents and household.[15] The Danish Medical Birth Register contains information about birth weight, cesarean delivery, gestational age, and maternal smoking.[17] Information on household income[18] and maternal education[19] was obtained from Statistics Denmark.

Design

We included children who had received 2 doses of DTaP-IPV-Hib before age 11 months to limit the possibility of bias attributable to factors related to low vaccination coverage. We used 2 cohorts with different sequences of vaccinations. The recommended-schedule cohort included children who received the third dose of DTaP-IPV-Hib after the second dose (and possibly MMR later), whereas the reversed-schedule cohort received MMR after DTaP-IPV-Hib2 (and possibly DTaP-IPV-Hib3 later). We excluded children with missing information on any of the potential confounders. The children were followed up from administration of DTaP-IPV-Hib3 (recommended-schedule cohort) or administration of MMR (reversed-schedule cohort) until age 2 years, administration of other vaccines, migration, death, whereabouts unknown to the Danish authorities, or uncertainty about vaccine allocation for twins. The latest date of follow-up was August 31, 2008, in the main analysis.

As a supplemental analysis to examine the rate of hospital admissions for infection among children receiving MMR after DTaP-IPV-Hib2, we included children who had received

DTaP-IPV-Hib2 before age 11 months and provided follow-up from age 11 months until age 2 years or receipt of vaccines other than MMR.

Statistical Methods

We used a generalized linear model for the binomial family with log-link to estimate the risk ratios for entering the reversed-schedule cohort compared with the recommended-schedule cohort. This model was also used to examine the determinants of having received the next vaccine at age 16 months.

We used Cox regression to estimate the incidence rate ratios (IRRs) and 95% CIs of hospital admission for any infection according to the most recent vaccination. The assumption of proportional hazards for vaccination status was evaluated by Schoenfeld residuals,[20] and no violations were detected. We used age as the underlying time scale and stratified by date of birth to control completely for any effect of age, season, and year. All hospital admissions for infection were included, so one child could have several admissions. However, several admissions within a short period could be attributable to the same infection; therefore, we defined admissions occurring less than 14 days after a previous discharge as 1 episode. To account for repeated admissions we used the Andersen-Gill model (counting process approach), for which each individual is allowed to be present only once in a particular risk set at a particular age, ensuring that a child will never be compared with him or herself.[21] Vaccination was included as a time-varying variable changing at the date of vaccination; thus, we analyzed the association with the most recent vaccine.

We performed both unadjusted and adjusted analyses in Stata 12 (StataCorp) (variables and categorization are included in **Table 1**). All tests were 2-sided, and the threshold for statistical significance was $P < .05$ or, for IRRs, a 95% CI not overlapping 1.0.

In-Depth Examination of the Association With Vaccination

We analyzed the association with time since vaccination and tested for trend using the likelihood ratio test. We used a competing-risks analysis[22] with Wald test statistics to test equality between different types of infections and duration of admission. We also examined whether the association differed according to background factors and tested for homogeneity with Wald test statistics.

Sensitivity Analyses

We repeated the analyses including only those children for whom all vaccines had been registered with their own personal identification number. Vaccines are only registered with the week of vaccination; we therefore coded the date of vaccination as Wednesday of the specified week. This made some misclassification inevitable, and we examined the importance of this by excluding admissions and person-years occurring during the week of vaccination. We examined the results according to administration of MMR before and after age 15 months in the reversed-schedule cohort, because early MMR vaccination could be attributable to travel to low-income countries and related to a different hospital admission pattern.

Control Outcome

We performed analyses of vaccinations and emergency department visits registered in the Danish National Patient Register as resulting from unintentional injury,[16] because we do not believe vaccination is causally related to such events. Most such visits are diagnosed as injuries. We also examined the association between vaccination status and emergency department visits related to infectious diseases.

Risk Difference and Number Needed to Vaccinate

Two methods were applied. First, we estimated the risks for the first admission related to infection from age 16 to 24 months for children who received MMR before age 16 months and for those who had received DTaP-IPV-Hib3 as the most recent vaccine by age 16 months (received MMR later or never). The risks were calculated using estimates from an adjusted Cox regression analysis comparing the 2 groups. Based on these risks, the risk difference and the number needed to vaccinate with MMR to avoid 1 hospital admission for an infection were calculated. Confidence intervals were estimated based on nonparametric bootstrap method with 2000 bootstrap samples.[23] This method provides a conservative (too high) estimate of the number needed to vaccinate, because it does not account for children receiving MMR after age 16 months and only includes first hospital admissions.

Second, an estimate of the risk difference between MMR and DTaP-IPV-Hib3 was calculated as $[1 - \exp(-IR)] - [1 - \exp(-IR \times \text{adjusted IRR})]$, where the adjusted IRR is the estimate from the adjusted Cox regression for MMR vs DTaP-IPV-Hib3 as the most recent vaccine and IR is the crude rate of infectious disease admissions among those most recently vaccinated with DTaP-IPV-Hib3. We used the rate over the course of an 8-month period for comparability with the conservative method. The obtained risk difference was used to calculate the number needed to vaccinate. This method provides a liberal (too low) estimate, because it is based on the crude admission rate when DTaP-IPV-Hib3 was the most recent vaccine, ie, among the youngest children.

Results

The study included 456 043 children in the recommended-schedule cohort and 19 219 in the reversed-schedule cohort (**Figure**). The characteristics of the 2 cohorts are reported in Table 1. The children were followed up until the first of the following events: age 2 years (n = 436 258 [91.8%]), administration of vaccines other than MMR and DTaP-IPV-Hib3 (n = 38 533 [8.1%]), migration (n = 413 [0.1%]), death (n = 39 [0.0%]), uncertain vaccine allocation for twins or triplets (n = 11 [0.0%]), and unknown whereabouts (n = 8 [0.0%]). The supplemental analysis examining MMR vs DTaP-IPV-Hib2 included 490 838 children. A total of 495 987 different children were included in at least 1 of the analyses.

Vaccination Status

The number of MMR-vaccinated children increased from ages 15 months to 16 months in both cohorts (eTable 2 in

Table 1. Characteristics of Participants Entering the Reversed-Schedule Cohort Compared With the Recommended-Schedule Cohort

Characteristic	No. (%)		Risk Ratio (95% CI)[a]	*P* Value
	Entering Recommended-Schedule Cohort	Entering Reversed-Schedule Cohort		
Sex				
Male	232 709 (95.9)	9946 (4.1)	1 [Reference]	.11
Female	223 334 (96.0)	9273 (4.0)	0.98 (0.95-1.01)	
Maternal smoking during pregnancy				
No	374 375 (95.9)	15 812 (4.1)	1 [Reference]	.16
Yes	81 668 (96.0)	3407 (4.0)	0.97 (0.94-1.01)	
Birth weight, g				
≤2000	8129 (96.3)	315 (3.7)	0.88 (0.77-1.00)	.24
2001-2500	14 658 (96.2)	575 (3.8)	0.90 (0.82-0.99)	
2501-3000	54 998 (96.0)	2283 (4.0)	0.97 (0.92-1.01)	
3001-3500	143 704 (95.9)	6137 (4.1)	1 [Reference]	
3501-4000	153 173 (96.0)	6453 (4.0)	0.99 (0.96-1.02)	
4001-4500	65 745 (96.0)	2768 (4.0)	0.99 (0.94-1.03)	
>4500	15 636 (95.8)	688 (4.2)	1.02 (0.94-1.10)	
Gestational age, wk				
<37	27 394 (96.1)	1108 (3.9)	0.99 (0.92-1.07)	.86
≥37	428 649 (95.9)	18 111 (4.1)	1 [Reference]	
Cesarean delivery				
No	375 920 (96.0)	15 719 (4.0)	1 [Reference]	.003
Yes	80 123 (95.8)	3500 (4.2)	1.06 (1.02-1.10)	
Chronic diseases				
No	442 750 (96.0)	18 636 (4.0)	1 [Reference]	.42
Yes	13 293 (95.8)	583 (4.2)	1.03 (0.95-1.12)	
No. of admissions for infections before age 11 mo				
None	413 930 (96.0)	17 253 (4.0)	1 [Reference]	<.001
1	37 061 (95.6)	1721 (4.4)	1.10 (1.05-1.15)	
2	4210 (95.2)	214 (4.8)	1.19 (1.04-1.36)	
≥3	842 (96.4)	31 (3.6)	0.87 (0.61-1.23)	
Admitted to hospital for any cause within the last mo				
No	448 148 (96.0)	18 882 (4.0)	1 [Reference]	.92
Yes	7895 (95.9)	337 (4.1)	0.99 (0.89-1.11)	
Maternal age at birth of child, y				
≤19	6042 (95.0)	316 (5.0)	1.16 (1.03-1.30)	.04
20-24	53 191 (95.9)	2293 (4.1)	1.01 (0.96-1.06)	
25-29	163 692 (96.0)	6741 (4.0)	0.99 (0.95-1.02)	
30-34	162 427 (96.0)	6849 (4.0)	1 [Reference]	
35-39	61 631 (95.9)	2666 (4.1)	1.01 (0.97-1.06)	
≥40	9060 (96.2)	354 (3.8)	0.91 (0.82-1.01)	
Highest educational level for the female adult in the household				
Primary school	89 475 (95.8)	3970 (4.2)	1.01 (0.97-1.06)	<.001
High school examination	45 920 (96.0)	1934 (4.0)	1.01 (0.96-1.07)	
Vocational training	157 168 (96.1)	6428 (3.9)	1 [Reference]	
Bachelor or academy profession	125 622 (96.1)	5152 (3.9)	1.02 (0.98-1.05)	
Master's degree or higher	37 858 (95.6)	1735 (4.4)	1.15 (1.09-1.22)	

(continued)

Table 1. Characteristics of Participants Entering the Reversed-Schedule Cohort Compared With the Recommended-Schedule Cohort (continued)

Characteristic	No. (%) Entering Recommended-Schedule Cohort	No. (%) Entering Reversed-Schedule Cohort	Risk Ratio (95% CI)[a]	*P* Value
Parental place of birth				
Denmark	382 104 (96.0)	15 821 (4.0)	1 [Reference]	<.001
Denmark and foreign	40 130 (95.8)	1773 (4.2)	1.06 (1.01-1.11)	
Foreign	33 809 (95.4)	1625 (4.6)	1.11 (1.05-1.17)	
Adult composition of the household				
Two adults	429 074 (96.0)	17 888 (4.0)	1 [Reference]	<.001
Single parent	26 869 (95.3)	1326 (4.7)	1.12 (1.06-1.19)	
No parents	100 (95.2)	5 (4.8)	1.12 (0.48-2.65)	
Income quintiles for the household				
1st (lowest)	82 520 (95.5)	3893 (4.5)	1.09 (1.04-1.15)	<.001
2nd	92 110 (96.0)	3845 (4.0)	1.00 (0.96-1.05)	
3rd	96 926 (96.0)	4053 (4.0)	1.02 (0.97-1.06)	
4th	95 202 (96.2)	3724 (3.8)	0.96 (0.91-1.00)	
5th	89 285 (96.0)	3704 (4.0)	1 [Reference]	
Other children in the household				
No	192 843 (96.1)	7926 (3.9)	1 [Reference]	.08
Yes	263 200 (95.9)	11 293 (4.1)	1.03 (1.00-1.06)	
Population density, inhabitants per km^2				
<50	30 829 (96.3)	1196 (3.7)	1 [Reference]	<.001
50-499	267 932 (95.8)	11 604 (4.2)	1.10 (1.04-1.17)	
500-1999	84 201 (96.1)	3379 (3.9)	1.00 (0.94-1.07)	
2000-4999	20 334 (95.8)	884 (4.2)	1.08 (0.99-1.18)	
≥5000	52 747 (96.1)	2156 (3.9)	1.00 (0.93-1.07)	

[a] Generalized linear model for the binomial family with log-link for risk ratio of entering the reversed-schedule cohort compared with the recommended-schedule cohort, adjusted for all variables in the table.

Supplement). The median age of MMR vaccination was 15.8 months (interquartile range, 15.2-17.0 months) in the recommended-schedule cohort and 15.9 months (interquartile range, 15.2-17.4 months) in the reversed-schedule cohort. In the reversed-schedule cohort, 1981 children (10.3%) received DTaP-IPV-Hib3 after MMR.

In the recommended-schedule cohort, most background variables were significantly associated with MMR vaccination by age 16 months, although most estimates were close to 1 (eTable 3 in Supplement). In the reversed-schedule cohort there were fewer significant determinants of vaccination status (eTable 3 in Supplement).

Hospital Admissions for Infections

In total the study included 56 889 admissions attributable to any type of infection during 509 427 person-years of follow-up in the recommended-schedule cohort, reversed-schedule cohort, and the supplemental analysis examining MMR vs DTaP-IPV-Hib2 (incidence rate, 11.2 admissions per 100 person-years); 39 670 children were admitted once, whereas 7187 children were admitted several times during follow-up. Generally, the rate of admissions declined with age (eTable 4 in Supplement).

In the recommended-schedule cohort, the rate of admission was significantly lower in the adjusted model for children who received MMR compared with those who still had DTaP-IPV-Hib3 as their most recent vaccination (IRR, 0.86 [95% CI, 0.84-0.88]) (**Table 2** and eTable 5 in Supplement). When comparing children who received MMR after DTaP-IPV-Hib2 with those receiving DTaP-IPV-Hib2 as the most recent vaccine, the association was similar (adjusted IRR, 0.87 [95% CI, 0.80-0.95]) (Table 2). In the reversed-schedule cohort, DTaP-IPV-Hib3, compared with MMR as the most recent vaccination, was associated with a higher rate of admission (adjusted IRR, 1.62 [95% CI, 1.28-2.05]) (Table 2 and eTable 5 in Supplement).

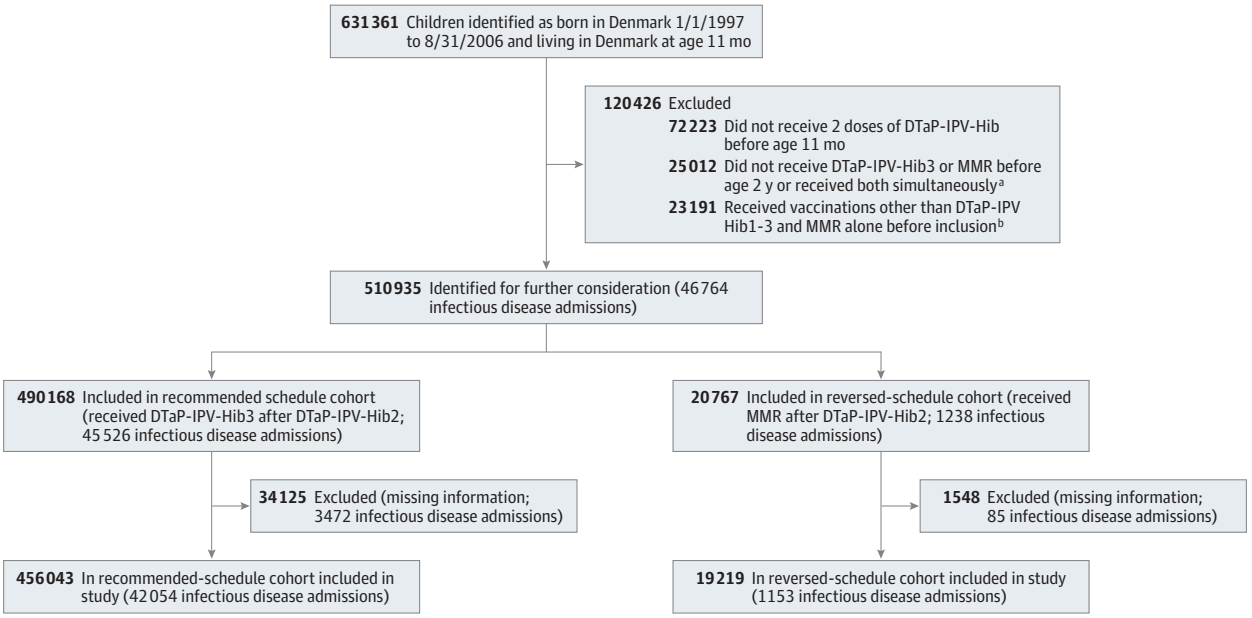
Timing of Associations

There was no significant difference in the rate of admissions in the first 15 days following a new vaccination (**Table 3**). In the recommended-schedule cohort there was a significant trend toward lower IRRs with time since MMR vaccination.

Type and Severity of Infection

In adjusted analyses of the recommended-schedule cohort, receiving MMR as the most recent vaccination had the strongest association with lower respiratory tract infections (IRR, 0.80 [95% CI, 0.76-0.84]), significantly ($P < .001$) stronger than for other types of infection (**Table 4**). About one-third of admissions in the recommended-schedule cohort and the

Figure. Study Flow of the Recommended-Schedule and Reversed-Schedule Cohorts



Infectious disease admissions are counted from the latest of the following events: 11 months of age, received diphtheria, tetanus, pertussis (acellular), polio, and *Haemophilus influenzae* type b (DTaP-IPV-Hib) vaccine (recommended-schedule cohort) or measles, mumps, and rubella (MMR) vaccine (reversed-schedule cohort) and until date of censoring for the children included in the study or until age 2 years for the children excluded from the study.

[a] Of these children, 5403 (21.6%) received DTaP-IPV-Hib3 and MMR together.

[b] DTaP or Hib alone (n = 14 277 [61.6%]), not recommended combination of vaccines (n = 5055 [21.8%]), booster dose against different combinations of diphtheria, tetanus, pertussis (acellular), and polio (n = 1649 [7.1%]), whole-cell pertussis vaccine (n = 862 [3.7%]), vaccine against hepatitis B (n = 783 [3.4%]), oral polio vaccine (n = 392 [1.7%]), fourth dose of DTaP-IPV-Hib (n = 144 [0.6%]), pneumococcal conjugate vaccine (n = 28 [0.1%]), and second dose of MMR (n = 1 [0.0%]).

Table 2. Incidence Rate and Incidence Rate Ratios of Hospital Admissions for Any Infection According to Most Recent Vaccination

	Admissions per 100 Person-Years (No. of Admissions/Person-Years)	Unadjusted IRR[a] (95% CI)	*P* Value	Adjusted IRR[b] (95% CI)	*P* Value
Recommended-schedule cohort[c]					
Most recent vaccination					
DTaP-IPV-Hib3	12.4 (20 743/167 693)	1 [Reference]		1 [Reference]	
MMR	8.9 (21 311/239 642)	0.81 (0.79-0.84)	<.001	0.86 (0.84-0.88)	<.001
Reversed-schedule cohort[d]					
Most recent vaccination					
DTaP-IPV-Hib3	12.8 (128/1001)	1.71 (1.37-2.12)		1.62 (1.28-2.05)	
MMR	9.9 (1025/10 400)	1 [Reference]	<.001	1 [Reference]	<.001
MMR vs DTaP-IPV-Hib2[e]					
Most recent vaccination					
DTaP-IPV-Hib2	15.1 (13 682/90 691)	1 [Reference]		1 [Reference]	
MMR	9.9 (1025/10 399)	0.77 (0.71-0.84)	<.001	0.87 (0.80-0.95)	.002

Abbreviations: DTaP-IPV-Hib, vaccination against diphtheria, tetanus, pertussis (acellular), polio, and *Haemophilus influenzae* type b (the number indicates the dose number); MMR, vaccination against measles, mumps, and rubella; IRR, incidence rate ratio.

[a] Cox proportional hazards model with age as underlying time and stratified by date of birth thereby controlling for season.

[b] Cox proportional hazards model with age as underlying time, stratified by date of birth and adjusted for sex, maternal smoking during pregnancy, birth weight, gestational age, cesarean delivery, chronic diseases, number of admissions for infections before age 11 months, admitted to hospital for any cause within the last 30 days, maternal age at birth of the child, highest educational level for the female adult in the household, parental place of birth, adult composition of the household, income quintiles for the household, other children in the household, and population density (the IRR estimates for these variables for the recommended-schedule cohort and reversed-schedule cohort are given in eTable 5 in Supplement).

[c] Cohort included 456 043 children who received DTaP-IPV-Hib3 after DTaP-IPV-Hib2. They contribute with 42 054 infectious disease admissions during 407 335 person-years at risk.

[d] Cohort included 19 219 children who received MMR after DTaP-IPV-Hib2. They contribute with 1153 infectious disease admissions during 11 401 person-years at risk.

[e] This includes 490 838 children followed up from age 11 months until age 2 years or receipt of other vaccines than MMR (including DTaP-IPV-Hib3).They contribute with 14 707 infectious disease admissions during 101 090 person-years at risk.

Table 3. Incidence Rate and Incidence Rate Ratios of Infectious Disease Admission According to Time Since MMR Vaccination for the Recommended-Schedule Cohort and Time Since DTaP-IPV-Hib3 Vaccination for the Reversed-Schedule Cohort

	Admissions per 100 Person-Years (No. of Admissions/Person-Years)	IRR (95% CI)	
		Unadjusted[a]	Adjusted[b]
Recommended-schedule cohort[c]			
DTaP-IPV-Hib3 most recent vaccination	12.4 (20 743/167 693)	1 [Reference]	1 [Reference]
Time after MMR, d			
1-15	11.8 (1863/15 773)	0.94 (0.89-0.99)	0.97 (0.93-1.02)
16-30	10.4 (1621/15 656)	0.83 (0.79-0.88)	0.87 (0.83-0.92)
31-60	10.0 (3085/30 975)	0.83 (0.79-0.86)	0.86 (0.83-0.90)
61-90	9.7 (2946/30 432)	0.81 (0.77-0.84)	0.85 (0.81-0.89)
91-120	9.1 (2694/29 767)	0.77 (0.74-0.81)	0.82 (0.78-0.86)
>120	7.8 (9102/117 039)	0.75 (0.73-0.78)	0.81 (0.78-0.84)
P for trend		<.001	<.001
Reversed-schedule cohort[d]			
MMR most recent vaccination	9.9 (1025/10 400)	1 [Reference]	1 [Reference]
Time after DTaP-IPV-Hib3, d			
1-15	11.3 (9/80)	1.37 (0.62-3.06)	1.06 (0.45-2.48)
16-30	15.5 (12/77)	2.10 (1.02-4.34)	2.35 (1.12-4.95)
31-60	16.8 (25/149)	2.00 (1.21-3.29)	2.06 (1.21-3.51)
61-90	10.7 (15/140)	1.53 (0.84-2.79)	1.15 (0.60-2.21)
91-120	13.2 (17/128)	1.68 (0.96-2.93)	1.75 (0.97-3.16)
>120	11.7 (50/427)	1.66 (1.19-2.31)	1.60 (1.11-2.29)
P for trend		.11	.09

Abbreviations: DTaP-IPV-Hib3, vaccination with the third dose against diphtheria, tetanus, pertussis (acellular), polio, and *Haemophilus influenzae* type b; IRR, incidence rate ratio; MMR, vaccination against measles, mumps, and rubella.

[a] Cox proportional hazards model with age as underlying time and stratified by date of birth thereby controlling for season.

[b] Cox proportional hazards model with age as underlying time, stratified by date of birth and adjusted for sex, maternal smoking during pregnancy, birth weight, gestational age, cesarean delivery, chronic diseases, number of admissions for infections before age 11 months, admitted to hospital for any cause within the last 30 days, maternal age at birth of the child, highest educational level for the female adult in the household, parental place of birth, adult composition of the household, income quintiles for the household, other children in the household, and population density.

[c] Cohort included 456 043 children who received DTaP-IPV-Hib3 after DTaP-IPV-Hib2. They contribute with 42 054 infectious disease admissions during 407 335 person-years at risk.

[d] Cohort included 19 219 children who received MMR after DTaP-IPV-Hib2. They contribute with 1153 infectious disease admissions during 11 401 person-years at risk.

reversed-schedule cohort lasted less than 1 day (14 627 admissions [33.9%]); in the recommended-schedule cohort the adjusted IRR for admissions lasting less than 1 day was 0.86 (95% CI, 0.82-0.90), comparable with the estimate for admissions lasting at least 1 day (adjusted IRR, 0.86 [95% CI, 0.83-0-89]) (eTable 6 in Supplement). The adjusted IRR was 0.83 (95% CI, 0.79-0.86) for admissions lasting more than 1 day, 0.80 (95% CI, 0.76-0.84) for those lasting more than 2 days, and 0.80 (95% CI, 0.75-0.86) for those lasting more than 3 days (eTable 6 in Supplement). In the reversed-schedule cohort, there was no significant difference according to type of infection (Table 4) or duration of admission (eTable 6 in Supplement).

Variability According to Background Factors

There were statistically significant interactions between the most recent vaccination and the following variables in adjusted analyses in the recommended-schedule cohort: chronic diseases, hospital admission within the last 30 days, hospital admission for infection before age 11 months, parental origin, and other children in the household. Receiving MMR as the most recent vaccination was associated with a lower rate of admission for all groups except children admitted to the hospital within the last 30 days, those with chronic conditions, and those with both parents born outside Denmark (eTable 7 in Supplement). In the reversed-schedule cohort, the only significant interaction was between most recent vaccine and chronic diseases (eTable 8 in Supplement). There was no statistically significant interaction between the most recent vaccination and sex (eTable 7 and eTable 8 in Supplement).

Sensitivity Analyses

Among the 410 872 children (90.1%) from the recommended-schedule cohort who had all vaccines registered with their own personal registration number, the adjusted IRR for MMR as the most recent vaccination was 0.86 (95% CI, 0.84-0.89; 38 022 admissions). In the reversed-schedule cohort 17 658 children (91.9%) had all vaccines registered with their own personal registration number; among these children the adjusted IRR for receiving DTaP-IPV-Hib3 after MMR was 1.68 (95% CI, 1.31-2.14; 1062 admissions). In the reversed-schedule cohort the results were similar for those receiving MMR before age 15 months (adjusted IRR, 1.79 [95% CI, 0.81-3.97]) and after age 15 months (adjusted IRR, 1.71 [95% CI, 1.22-2.38]). The results were similar with exclusion of admissions in the week of vac-

Table 4. Incidence Rate and Incidence Rate Ratio for Hospital Admissions for Any Infection According to Type of Infection

	Recommended-Schedule Cohort			Reversed-Schedule Cohort		
Type of Infection	Admissions per 100 Person-Years (No. of Admissions/ Person-Years)	IRR (95% CI) Unadjusted[a]	IRR (95% CI) Adjusted[b]	Admissions per 100 Person-Years (No. of Admissions/ Person-Years)	IRR (95% CI) Unadjusted[a]	IRR (95% CI) Adjusted[b]
Upper respiratory tract						
DTaP-IPV-Hib3	5.1 (8516/167 693)	1 [Reference]	1 [Reference]	5.7 (59/1001)	2.17 (1.55-3.02)	1.89 (1.31-2.74)
MMR	3.6 (8599/239 642)	0.82 (0.79-0.86)	0.86 (0.82-0.89)	4.0 (420/10 400)	1 [Reference]	1 [Reference]
Lower respiratory tract						
DTaP-IPV-Hib3	4.3 (7223/167 693)	1 [Reference]	1 [Reference]	3.8 (38/1001)	1.58 (1.07-2.34)	1.64 (1.06-2.54)
MMR	2.9 (6941/239 642)	0.73 (0.70-0.76)	0.80 (0.76-0.84)	3.1 (322/10 400)	1 [Reference]	1 [Reference]
Gastrointestinal tract						
DTaP-IPV-Hib3	1.7 (2881/167 693)	1 [Reference]	1 [Reference]	1.5 (15/1001)	1.21 (0.65-2.28)	1.41 (0.71-2.78)
MMR	1.4 (3206/239 642)	0.91 (0.85-0.98)	0.93 (0.87-1.00)	1.5 (159/10 400)	1 [Reference]	1 [Reference]
Other						
DTaP-IPV-Hib3	2.7 (4454/167 693)	1 [Reference]	1 [Reference]	2.8 (28/1001)	1.34 (0.85-2.11)	1.32 (0.80-2.16)
MMR	1.9 (4626/239 642)	0.87 (0.82-0.92)	0.92 (0.87-0.99)	2.3 (234/10 400)	1 [Reference]	1 [Reference]
P for equality		<.001	<.001		.23	.68

Abbreviations: DTaP-IPV-Hib3, vaccination with the third dose against diphtheria, tetanus, pertussis (acellular), polio, and *Haemophilus influenzae* type b; IRR, incidence rate ratio; MMR, vaccination against measles, mumps, and rubella.

[a] Cox proportional hazards model with age as underlying time and stratified by date of birth, thereby controlling for season.

[b] Cox proportional hazards model with age as underlying time, stratified by date of birth and adjusted for sex, maternal smoking during pregnancy, birth weight, gestational age, cesarean delivery, chronic diseases, number of admissions for infections before age 11 months, admitted to hospital for any cause within the last 30 days, maternal age at birth of the child, highest educational level for the female adult in the household, parental place of birth, adult composition of the household, income quintiles for the household, other children in the household, and population density.

cination (eTable 9 and eTable 10 in Supplement), exclusion of 38 admissions because of the vaccine-targeted infections (eAppendix in Supplement), and exclusion of admissions because of chronic infections (eTable 11 in Supplement).

Emergency Department Visits

In the recommended-schedule cohort, the adjusted IRR of emergency department visits following unintentional injury was 0.97 (95% CI, 0.95-0.99) for MMR compared with DTaP-IPV-Hib3 as the most recent vaccination (eTable 12 in Supplement). The equivalent adjusted IRR of infections registered at emergency department visits was 0.84 (95% CI, 0.78-0.91) (eTable 13 in Supplement).

Risk Difference and Number Needed to Vaccinate

Children vaccinated with MMR before age 16 months had a 4.6% (95% CI, 4.5%-4.7%) risk of being admitted at least once for an infection between ages 16 and 24 months, whereas the risk for those not vaccinated with MMR before age 16 months was 5.1% (95% CI, 5.0%-5.2%). Hence, the conservative estimate of the risk difference was 0.5 percentage point (95% CI, 0.4-0.6), and the number needed to vaccinate with MMR before age 16 months to prevent 1 hospital admission for an infection before age 24 months was 201 (95% CI, 159-272). The liberal estimate of the risk difference was 1.1 percentage points (95% CI, 0.9-1.2) for DTaP-IPV-Hib3 vs MMR as the most recent vaccine, and the number needed to vaccinate with MMR to prevent 1 hospital admission for an infection during an 8-month period was 93 (95% CI, 82-109).

Discussion

Receiving the live MMR vaccine after the inactivated DTaP-IPV-Hib vaccine was associated with a lower rate of hospital admissions for any infection. The association was particularly strong for lower respiratory tract infections and for longer hospital admissions. Children who received DTaP-IPV-Hib after MMR had a significantly higher rate of infectious disease admission.

Vaccinations were registered by general practitioners to obtain reimbursement; we therefore believe that the information is reliable, but there might have been some underreporting.[24] Any misclassification or underreporting of vaccinations would bias the estimates toward no association. There was no possibility for residual confounding by age, because the Cox regression model was specified to compare children of the exact same age but who have received different vaccinations.

To observe nonspecific effects of vaccines it is necessary to go beyond measurement of protective antibody responses or protection against the specific disease and examine the overall effect on morbidity or mortality. Before measles vaccine was recommended, 2 community studies randomized some areas

to receive measles vaccine or no vaccine, and the reduction in overall mortality was 30% to 50%.[25,26] After measles vaccination at age 9 months became global policy, it was not possible to compare measles-vaccinated with measles-unvaccinated children, but randomized trials have measured the effect of introducing an additional dose of measles vaccine before age 9 months compared with the current policy. Reduction in overall mortality and hospital admissions was 30% to 50% and was not explained by prevention of measles infection.[3,27-29] Our finding that MMR as the most recent vaccine was associated with lower risk of hospital admissions for nontargeted infections is consistent with these reports.

In high-income countries, some studies also found an association with MMR and lower risk of infectious diseases.[30-32] However, these studies have not focused on the most recently administered vaccine and are therefore not directly comparable with the present study. It has been a consistent observation in low-income countries that the most recent vaccination most strongly influences susceptibility to unrelated infections.[1,9,12,33] The immunological mechanisms for how different vaccinations induce such changes—from DTaP-IPV-Hib3 to MMR or from MMR to DTaP-IPV-Hib3 in the present study—have not been studied. Both cross-reactivity of T cells in the adaptive immune system and trained innate immunity have been suggested as potential explanations of nonspecific effects of vaccines.[8]

It might be speculated that our results were attributable to selection bias if the healthiest children received MMR first.[34] However, many of our observations cannot be explained by selection bias. First, if the association was attributable to healthy children being vaccinated first, the association should have been apparent in the first 2 weeks. This was not the case. Second, the association should be similar for all types of infection; however, we observed a significantly lower rate of lower respiratory tract infections. Third, a similar association was seen when MMR was administered out of sequence after DTaP-IPV-Hib2. Fourth, MMR was only associated with a 3% reduction in emergency department visits following unintentional injury, which suggests that our results are not explained by a health-seeking bias.

Furthermore, when DTaP-IPV-Hib3 was given after MMR in the reversed-schedule cohort, vaccination was associated with an increase in admissions. In the reversed-schedule cohort, there was also no significant association in the first 15 days after DTaP-IPV-Hib3 vaccination, there was no association with emergency department visits following unintentional injury, and the association was also present among normal birth weight children and children without chronic conditions.

The high-quality data, the strict control for confounders, and the consistency with prior observations from low-income countries[1,8,28] all support that vaccines also have nonspecific effects on susceptibility to infections in high-income countries.

The coverage with MMR is suboptimal in many high-income countries[35]; in the present study, about 50% of children were not vaccinated on time. Physicians should encourage parents to have children vaccinated on time with MMR and avoid giving vaccinations out of sequence, because the present study suggests that timely MMR vaccination averted a considerable number of hospital admissions for any infection between ages 16 and 24 months. The conservative estimate of the number needed to vaccinate to avoid 1 admission for an infection between ages 16 and 24 months was 201, whereas the liberal estimate was 93. The true number needed to vaccinate probably lies somewhere between these 2 estimates. The estimates are affected by the rate of admissions, which is higher in Denmark than in many other countries, including the United States, because of different organization of health care, including free hospital care and limited diagnostic options in primary care.[36-38]

Conclusions

In a nationwide cohort of Danish children, receipt of the live MMR vaccine vs inactivated DTaP-IPV-Hib as the most recent vaccine was associated with a lower rate of hospital admissions for any infections. The findings require replication in other high-income populations.

ARTICLE INFORMATION

Author Contribution: Dr Sørup had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition of data: Sørup, Ravn.
Analysis and interpretation: All authors.
Drafting of the manuscript: Sørup.
Critical revision of the manuscript for important intellectual content: Benn, Poulsen, Krause, Aaby, Ravn.
Statistical analysis: Sørup, Ravn.
Obtained funding: Sørup, Benn, Aaby, Ravn.
Administrative, technical, and material support:
Study supervision: Benn, Poulsen, Krause, Aaby, Ravn.

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