Vaccine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Revaccination with measles-mumps-rubella vaccine and hospitalization for infection in Denmark and Sweden – An interrupted time-series analysis

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ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Non-specific effects of vaccines
Heterologous immunity
Vaccination programme
Measles-mumps-rubella vaccine
Interrupted time-series analysis
Hospitalization

ABSTRACT

Background: In a previous cohort study of 4-year-old Danish children, revaccination with the live measles-mumps-rubella vaccine (MMR) was associated with a 16% reduction in the rate of hospitalization lasting two days or longer for non-measles-mumps-rubella infections.
Aim: To examine if the introduction of revaccination with MMR at 4 years of age in Denmark (spring 2008) and at 7–9 years of age in Sweden (autumn 2009), at a time when there was virtually no measles, mumps or rubella cases, was associated with a reduction in the rate of hospitalization-for-infection lasting two days or longer at the population level.
Methods: We included 4-year-olds in Denmark and 7–9-year-olds in Sweden. We obtained the number of hospitalization-for-infection lasting two days or longer from nationwide hospital registers. Person-years at risk were approximated from population statistics for each season and year. We performed an interrupted time series analysis using Poisson regression to estimate the change in hospitalization incidence rates following the introduction of MMR revaccination, adjusting for seasonality. We also performed analyses with control series (3-year-olds in Denmark and 4-year-olds in Sweden).
Results: Comparing the incidence of hospitalization-for-infection lasting two days or longer after the introduction of MMR revaccination with the expected level without an introduction of MMR revaccination resulted in an incidence rate ratio of 1.07 (95% confidence interval [CI] = 0.89–1.28) for 4-year-olds in Denmark and 0.89 (95% CI = 0.77–1.02) for 7–9-year-olds in Sweden in analyses without controls. Analyses with controls gave similar results.
Conclusion: This population-level study of the introduction of MMR revaccination in Denmark and Sweden had inadequate power to confirm or refute the findings from an individual-level Danish study of an association between MMR revaccination and a lower incidence rate of hospitalization-for-infection lasting two days or longer.

Abbreviations: Aut, Autumn; BCG, Bacille Calmette-Guérin (live vaccine against tuberculosis); CI, confidence interval; DTaP-booster, non-live booster against diphtheria, tetanus and pertussis; DTaP-IPV, non-live vaccine against diphtheria, tetanus, pertussis and polio; DTaP-IPV-booster, non-live booster against diphtheria, tetanus, pertussis and polio; DTaP-IPV-Hib, non-live vaccine against diphtheria, tetanus, pertussis, polio and *Haemophilus influenzae* type b; DTaP-IPV-Hib-HepB, non-live vaccine against diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type b and hepatitis B; DT-booster, non-live booster against diphtheria and tetanus; DT-IPV, non-live vaccine against diphtheria, tetanus and polio; Hib, non-live vaccine against *Haemophilus influenzae* type b; ICD-10, 10th revision of the International Statistical Classification of Diseases and Related Health Problems; IRD, incidence rate difference; IRR, incidence rate ratio; IPV-booster, non-live booster against polio; MMR, live vaccine against measles, mumps and rubella; N, number of events; OPV, live oral polio vaccine; PCV, pneumococcal conjugate vaccine (non-live); PYRs, person years at risk; Spr, spring.

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https://doi.org/10.1016/j.vaccine.2021.01.028
0264-410X/

1. Introduction

Vaccines reduce morbidity and mortality from the diseases they target [1]. In addition, numerous studies support that vaccines can also affect morbidity and mortality from non-targeted diseases, i.e. that they have so called non-specific effects [2]. A review commissioned by the Strategic Advisory Group of Experts on immunizations of the World Health Organization showed that the live, attenuated measles vaccine was associated with lower all-cause childhood mortality, mainly in studies from low-income countries [3]. In high-income countries, the live, attenuated vaccine against measles, mumps, and rubella (MMR) has been associated with reductions in the risk of hospitalization for infections [4–8].

Recently, based on a review of the existing literature, the hypothesis was raised that revaccination with live vaccines could lead to further reductions in morbidity and mortality [9]. Such effects would predominantly be non-specific, given that the second dose of most live vaccines do not add much to the protective immunity against the targeted diseases [2,9].

We have previously performed a register-based cohort study in Denmark showing that MMR revaccination was associated with a reduced rate of hospitalizations for non-measles infections. This was mainly due to a 16% (95% CI, 5–36%) reduction in the most severe infections with hospitalizations lasting two days or longer [10]. Such cohort studies might be prone to confounding related to factors both associated with infectious disease morbidity and revaccination with MMR at the individual level. By using population level data to compare children eligible for MMR revaccination with same-aged children that were not eligible for MMR revaccination, the impact of confounding by individual-level confounders should be reduced [11].

In the first decade of the 2000's, Denmark and Sweden both changed the recommended age for MMR revaccination. Consequently, a new age group was offered MMR revaccination [12,13]. Such changes in policy can be regarded as natural experiments and the effect of the policy changes can be analyzed with interrupted time-series analyses [11].

In this study, we used interrupted time-series analyses to examine the hypothesis that the introduction of MMR revaccination at 4 years of age in Denmark and in the first years of school in Sweden was associated with a reduction in the rate of hospitalization-for-infection lasting two days or longer.

2. Material and methods

2.1. Setting

This study used data from the two northern European countries Denmark and Sweden, which both provide recommended childhood vaccinations free-of-charge [14,15]. In Denmark, recommended childhood vaccines are administered by general practitioners throughout childhood [16]. In Sweden, vaccines for children below school age are administered at well-baby clinics, while vaccines after entry into school (in autumn the year children turn 7 years of age) are administered in schools [15]. Hospital care is free-of-charge in Denmark [14], while patient fees up to a maximum annual amount may be charged for hospital care in Sweden, depending on each subnational region's decision [17]. MMR vaccination was introduced in Denmark in 1987 [18] and in Sweden in 1982 [19]. During the study period there were only sporadic cases of measles, mumps and rubella and no endemic transmission [4,10,19,20].

2.2. Selection of pre- and post-intervention periods

The intervention in this study was the change in the recommended age for MMR revaccination. Overall, we aimed for pre- and post-intervention periods of the same duration, as this was expected to increase the statistical power of the analysis [21]. In Denmark, the MMR revaccination age was changed from 12 to 4 years of age in the spring of 2008 [12]. Therefore, we defined the pre-intervention period as March 2005 to February 2008. We did not expect all 4-year-olds to be revaccinated with MMR immediately after the policy change, and therefore defined the post-intervention period as March 2009 to February 2012. Thus, the period March 2008 to February 2009 was defined as a phase-in period and not included in the analyses.

In Sweden, the age of MMR revaccination was changed from 12 years of age to the first or second year of school, beginning in the autumn term of 2009 [13]. Therefore, we defined the pre-intervention period in Sweden as September 2005 to August 2009. As each school decides in which school year and semester to offer the MMR revaccination, children can be between 6.5 and 9.5 years old when vaccinated. Therefore, we decided to define a 3-year phase-in period covering September 2009 to August 2012. The post-intervention period thus became September 2012 to August 2016. The pre- and post-intervention time periods are illustrated in Fig. 1 for Denmark and Fig. 2 for Sweden along with the recommended childhood vaccination program for the included children. More details on the reasons for this selection are included in supplementary Table 1.

2.3. Selection of intervention groups

In our study the intervention group was the age-group subject to receive MMR revaccination after the vaccination schedule was changed. Thus, in Denmark the intervention group was the 4-year-olds. In Sweden, children begin school in the autumn of the calendar year they turn 7 years. This means that the majority of children are above 7 years when they start school and could be offered MMR revaccination in the first school year. In schools that vaccinate in the second grade, many children will be vaccinated when they are 8 years of age and some will even have reached 9 years of age (if vaccinations take place during the spring). Therefore, the intervention group in Sweden was 7–9-year-old children. More details on the reasons for this selection are included in supplementary Table 2.

2.4. Selection of control groups

Using a control group in the interrupted time-series analysis can help to control for confounding by other co-occurring interventions or other time-dependent changes that could equally affect the intervention group and the control group, e.g. changes in practices for hospitalization due to infectious diseases in children [22]. In Denmark we chose 3-year-olds to be the control group and in Sweden the 4-year-olds. These groups were not affected by the changes in MMR revaccination age and no vaccinations were offered within the childhood vaccination program at these ages. More details are included in supplementary Table 2.

2.5. Collection of data on hospitalization and person years at risk

We used national patient registries [23,24] to identify all inpatient hospital contacts with an ICD-10 diagnosis code (primary/-main or secondary/other) for an infectious disease (ICD-10 codes

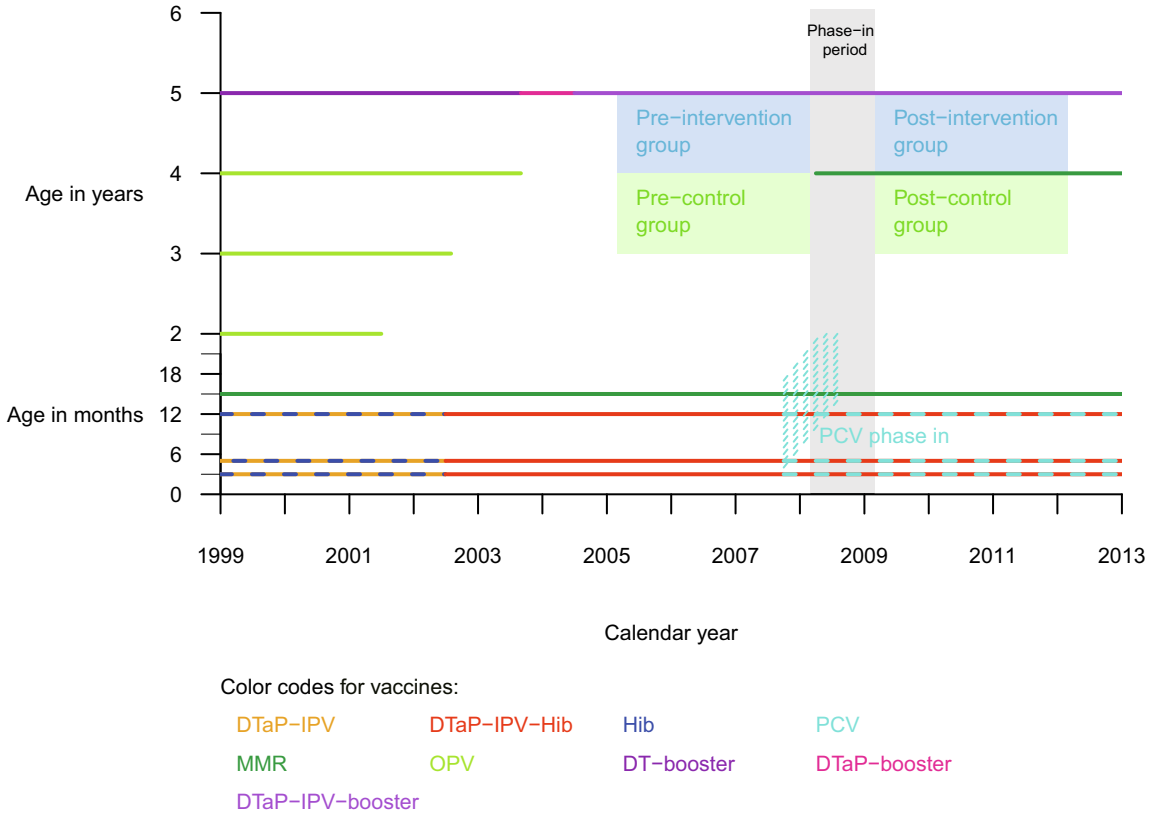

Fig. 1. Overview of the selected intervention (change in MMR revaccination policy) and control groups in Denmark and the recommended childhood vaccination program since the birth of the oldest included children displayed in a lexis diagram. **Abbreviations:** DTaP-IPV = non-live vaccine against diphtheria, tetanus, pertussis and polio; DTaP-IPV-Hib = non-live vaccine against diphtheria, tetanus, pertussis, polio and *Haemophilus influenzae* type b; Hib = non-live vaccine against *Haemophilus influenzae* type b; PCV = non-live pneumococcal conjugate vaccine; MMR = live vaccine against measles, mumps and rubella; OPV = live oral polio vaccine; DT-booster = non-live booster against diphtheria and tetanus; DTaP-booster = non-live booster against diphtheria, tetanus and pertussis; DTaP-IPV-booster = non-live booster against diphtheria, tetanus, pertussis and polio. **Note:** Lines for vaccines including two different colors indicate that the two vaccines have been recommended at the same age. In the lexis diagram, you can draw diagonal lines representing the life line of each child/cohort beginning at their birth date and moving diagonally forward and upward as they age and calendar time passes. Thereby it is possible to see which vaccination recommendation each child/cohort has been recommended.

listed in supplementary Table 3). Hospitalization for infections that occurred ≤14 days from discharge of a previous hospitalization for infection were considered to be related to the same episode of hospitalization for infection. Duration of hospitalization for infection was defined as the number of bed nights within the hospitalization episode. In the present study we only included hospitalizations lasting two bed nights or longer.

We estimated the person years at risk based on the underlying populations from publicly available national population statistics [25,26]. Due to a limited number of hospitalization-for-infection lasting two days or longer in some months, we estimated the rate of hospitalizations per season and year. We defined the seasons as follows: spring (March-May), summer (June-August), autumn (September-November), and winter (December-February).

2.6. Statistical methods

First, we estimated the overall incidence rates of hospitalization-for-infection lasting two days or longer in the pre- and post-intervention periods, respectively, for the intervention group and the control group. We also estimated the associated incidence rate differences (IRDs) and incidence rate ratios (IRRs) between the post- and pre-intervention periods along with the 95% confidence intervals (CIs) [27].

Secondly, we performed an interrupted time series analysis using Poisson regression where we only included the intervention groups, with number of hospitalization-for-infection lasting two days or longer as events and number of person years as offset [21]. The main variable of interest in the Poisson regression model was the variable for change in the level of the rate of hospitalization-for-infection lasting two days or longer following the introduction of revaccination with MMR in the intervention group. Based on the variable for level change we estimated the corresponding IRR (and associated 95%-CIs) [28]. In addition to the variable for level change, the Poisson regression model included a variable for time indicating the change in the rate per time unit and dummy variables for season. We did not include a variable for change in slope after the intervention, because MMR was introduced at one time point and we expected a rapid up-take within the populations and thus an immediate effect on hospitalizations. We also checked for autocorrelation by visually inspecting plots of the residuals [21], but did not detect any substantial autocorrelation. Therefore, no autocorrelation terms were included in the final models. We tested for overdispersion and in the case of overdispersion in the Poisson model, we used the quasi-Poisson model [29]. To visualize the data and the results of the model we plotted the observed rates per season along with the fitted trend and counterfactual trend from the final model and their associated 95%-CIs, following the advice in Turner et al 2020 [30]. The counterfactual rate is the expected rate in the post-intervention period if the intervention had not been introduced, e.g. what the rate of hospitalization-for-infection lasting two days or longer would have been if the trend from the pre-intervention period continued in the post-intervention period.

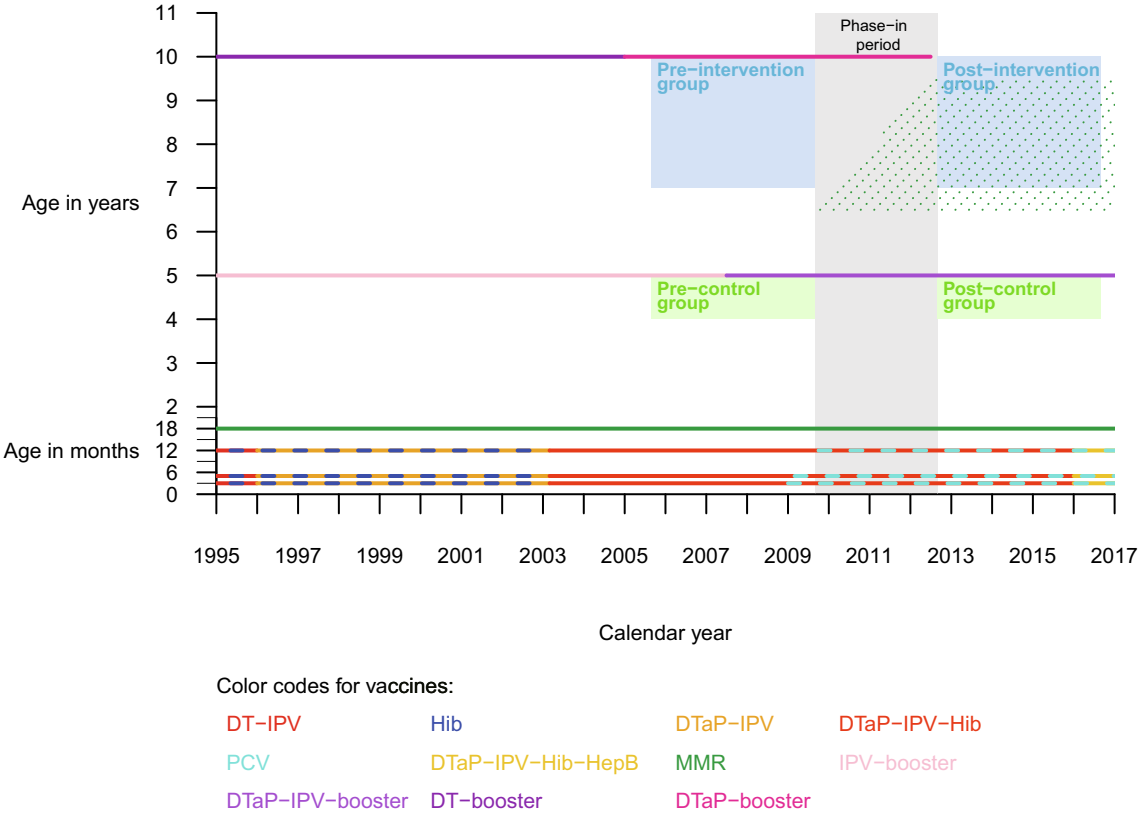

Fig. 2. Overview of the selected intervention (change in MMR revaccination policy) and control groups in Sweden and the recommended childhood vaccination program since the birth of the oldest included children displayed in a lexis diagram. **Abbreviations:** DT-IPV = non-live vaccine against diphtheria, tetanus and polio; Hib = non-live vaccine against *Haemophilus influenzae* type b; DTaP-IPV = non-live vaccine against diphtheria, tetanus, pertussis and polio; DTaP-IPV-Hib = non-live vaccine against diphtheria, tetanus, pertussis, polio and *Haemophilus influenzae* type b; PCV = non-live pneumococcal conjugate vaccine; DTaP-IPV-Hib-HepB = non-live vaccine against diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type b and hepatitis B; MMR = live vaccine against measles, mumps and rubella; IPV-booster = non-live polio vaccine; DTaP-IPV-booster = non-live booster against diphtheria, tetanus, pertussis and polio; DT-booster = non-live booster against diphtheria and tetanus; DTaP-booster = non-live booster against diphtheria, tetanus and pertussis. **Note:** Lines for vaccines including two different colors indicate that the two vaccines have been recommended at the same age. MMR revaccination during year 1 and 2 of primary school (each school decides the timing) was introduced in the autumn term of 2009. Children would usually be between 6.5 and 9.5 years when revaccinated with MMR, this is illustrated by the green dots spanning the age interval 6.5–9.5 years. In the lexis diagram, you can draw diagonal lines representing the life line of each child/cohort beginning at their birth date and moving diagonally forward and upward as they age and calendar time passes. Thereby it is possible to see which vaccination recommendation each child/cohort has been recommended. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Crude incidence rates of hospitalization-for-infection lasting two days or longer in the pre-intervention and post-intervention period for the age groups used in the analyses and incidence rate difference and incidence rate ratio between the two periods comparing the post-intervention period to the pre-intervention period.

	Pre-intervention Incidence rate per 1000 PYRs (N/PYRs)	Post-intervention incidence rate per 1000 PYRs (N/PYRs)	IRD (95%-CI)	IRR (95%-CI)
DENMARK				
Intervention group (4 years)	8.35 (1658/198,643)	7.89 (1553/196,919)	−0.46 (−1.02 to 0.10)	0.94 (0.88 to 1.01)
Control group (3 years)	11.17 (2197/196,668)	10.21 (2013/197,128)	−0.96 (−1.61 to −0.31)	0.91 (0.86 to 0.97)
SWEDEN				
Intervention group (7–9 years)	3.24 (3705/1,142,664)	2.79 (3661/1,314,065)	−0.46 (−0.59 to −0.32)	0.86 (0.82 to 0.90)
Control group (4 years)	7.19 (2818/391,783)	5.77 (2667/462,378)	−1.42 (−1.77 to −1.08)	0.80 (0.76 to 0.85)

Abbreviations: CI = Confidence interval; IRD = incidence rate difference; IRR = Incidence rate ratio; N = number of events; PYRs = person years at risk.
Note: In Denmark the intervention was introduction of revaccination with MMR at 4 years of age. In Sweden the intervention was introduction of revaccination with MMR during year 1 and 2 of primary school (each school decides the timing) resulting in revaccination with MMR between 6.5 and 9.5 years. In Denmark the pre-intervention period was March 1, 2005 to February 28, 2008 and the post-intervention period was March 1, 2009 to February 28, 2012. In Sweden the pre-intervention period was September 1, 2005 to August 31, 2009 and the post-intervention period was September 1, 2012 to August 31, 2016.

Thirdly, we used the methods described above, but with a model also including the control group to adjust for potential time-varying confounders [22]. In this analysis, the Poisson regression model additionally included variables for the intervention group, an interaction term between the intervention group variable and time, and an interaction term between the intervention group variable and level change, corresponding to a difference in level change between the intervention and control group. In this analysis the main variable of interest was the difference in level change between the intervention and control group, because it can be interpreted as the level change in the intervention group over and above the level change in the control group.

All analyses were performed separately for each country.

Table 2
Results of the interrupted time-series analysis without and with controls; expressed as incidence rate ratio for hospitalization-for-infection lasting two days or longer based on the level change associated with introduction of MMR revaccination in the intervention group, main results and results for sensitivity analysis.

	Analysis without control group: Level change in intervention group, IRR (95%-CI)	Analysis with control group: Level change in intervention group over and above the level change in control group IRR (95%-CI)
MAIN RESULTS		
DENMARK		
4 years (intervention group)	1.07 (0.89–1.28)[a]	1.08 (0.84–1.39)[b]
SWEDEN		
7–9 years (intervention group)	0.89 (0.77–1.02)[a]	0.85 (0.65–1.11)[c]
RESULTS ACCORDING TO SEX		
DENMARK		
4 years (intervention group)		
Girls	1.02 (0.75–1.39)[d]	1.23 (0.80–1.90)[e]
Boys	1.12 (0.98–1.28)[a]	0.95 (0.75–1.20)[f]
SWEDEN		
7–9 years (intervention group)		
Girls	0.90 (0.70–1.15)[a]	0.80 (0.56–1.12)[b]
Boys	0.79 (0.63–0.98)[g]	0.87 (0.64–1.19)[h]
SUBDIVISION OF AGE GROUPS		
DENMARK		
4.0–4.5 years (intervention group)	1.16 (0.87–1.55)[a]	1.15 (0.84–1.58)[b]
4.5–5.0 years (intervention group)	1.02 (0.80–1.30)[g]	1.00 (0.74–1.34)[b]
SWEDEN		
7 years (intervention group)	0.78 (0.66–0.92)[a]	0.73 (0.57–0.95)[c]
8 years (intervention group)	0.87 (0.67–1.12)[a]	0.89 (0.62–1.28)[b]
9 years (intervention group)	1.09 (0.84–1.41) [a]	1.04 (0.73–1.49) [c]
SEPARATE ESTIMATION WINTER 2010/2011[£]		
DENMARK		
4 years (intervention group)	0.94 (0.83–1.07)[i]	1.08 (0.84–1.38)[j]
EXTENDED PHASE-IN PERIOD[$]		
DENMARK		
4 years (intervention group)	1.99 (1.36–2.91)[a]	1.34 (0.78–2.31)[b]
SWEDEN		
7–9 years (intervention group)	0.65 (0.51–0.83)[g]	0.89 (0.65–1.21)[k]

Abbreviations: IRR = Incidence rate ratio; CI = confidence interval.
$: Extending the phase-in period with 1 year on both sides of the original phase-in period.
£: For the intervention group in Denmark, the rate was particularly high in winter 2010/2011, which could be related to a mycoplasma pneumonia epidemic. Winter 2010/2011 was modelled as a separate variable (1 in the winter of 2010/2011, otherwise 0).
a: Estimated based on a Poisson model with the following predictors: time, level change, spring, summer, autumn.
b: Estimated based on a Poisson model with the following predictors: time, intervention, time*intervention, level change, level change*intervention, spring, summer, autumn.
c: Estimated based on a Poisson model with the following predictors: time, intervention, time*intervention, level change, level change*intervention, spring, summer, autumn, post-intervention spring, post-intervention summer, post-intervention autumn, post-intervention spring*intervention, post-intervention summer*intervention, post-intervention autumn*intervention.
d: Estimated based on a quasi-Poisson model with the following predictors: time, level change, spring, summer, autumn.
e: Estimated based on a quasi-Poisson model with the following predictors: time, intervention, time*intervention, level change, level change*intervention, spring, summer, autumn.
f: Estimated based on a Poisson model with the following predictors: time, intervention, time*intervention, level change, level change*intervention, spring, summer, autumn, post-intervention spring, post-intervention summer, post-intervention autumn.
g: Estimated based on a Poisson model with the following predictors: time, level change, spring, summer, autumn, post-intervention spring, post-intervention summer, post-intervention autumn.
h: Estimated based on a Poisson model with the following predictors: time, intervention, time*intervention, level change, level change*intervention, spring, summer, autumn, spring*intervention, summer*intervention, autumn*intervention, post-intervention spring, post-intervention summer, post-intervention autumn, post-intervention spring*intervention, post-intervention summer*intervention, post-intervention autumn*intervention.
i: Estimated based on a Poisson model with the following predictors: time, level change, spring, summer, autumn, post-intervention spring, post-intervention summer, post-intervention autumn, winter2010.
j: Estimated based on a Poisson model with the following predictors: time, intervention, time*intervention, level change, level change*intervention, spring, summer, autumn, winter2010.
k: Estimated based on a Poisson model with the following predictors: time, intervention, time*intervention, level change, level change*intervention, spring, summer, autumn, post-intervention spring*intervention, post-intervention summer*intervention, post-intervention autumn*intervention.
Note: In Denmark the intervention was introduction of revaccination with MMR at 4 years of age. In Sweden the intervention was introduction of revaccination with MMR during year 1 and 2 of primary school (each school decides the timing) resulting in revaccination with MMR between 6.5 and 9.5 years. In Denmark the pre-intervention period was March 1, 2005 to February 28, 2008 and the post-intervention period was March 1, 2009 to February 28, 2012. In Sweden the pre-intervention period was September 1, 2005 to August 31, 2009 and the post-intervention period was September 1, 2012 to August 31, 2016.
Seasons are defined as spring (March, April, May), summer (June, July, August), autumn (September, October, November), and winter (December, January, February).

The more specific procedures for model selection and included variables are described in the supplementary method section and supplementary Table 4.

2.7. Sensitivity analyses

The analyses were performed separately for boys and girls, as non-specific effects of vaccines might differ by sex [2].

It has previously been reported that 50% of Danish children born 2005 had been revaccinated with MMR by approximately 4.2 years age and approximately 68% had been revaccinated with MMR by 5 years of age [31]. Similar statistics are not available in Sweden. However, in both countries we would expect higher coverage of MMR revaccination with increasing age in the intervention group. Therefore, we performed analyses where we divided the intervention group into smaller age groups. In Denmark into 4.0–4.5 and 4.5–5.0 years of age and in Sweden into 7, 8, and 9 years.

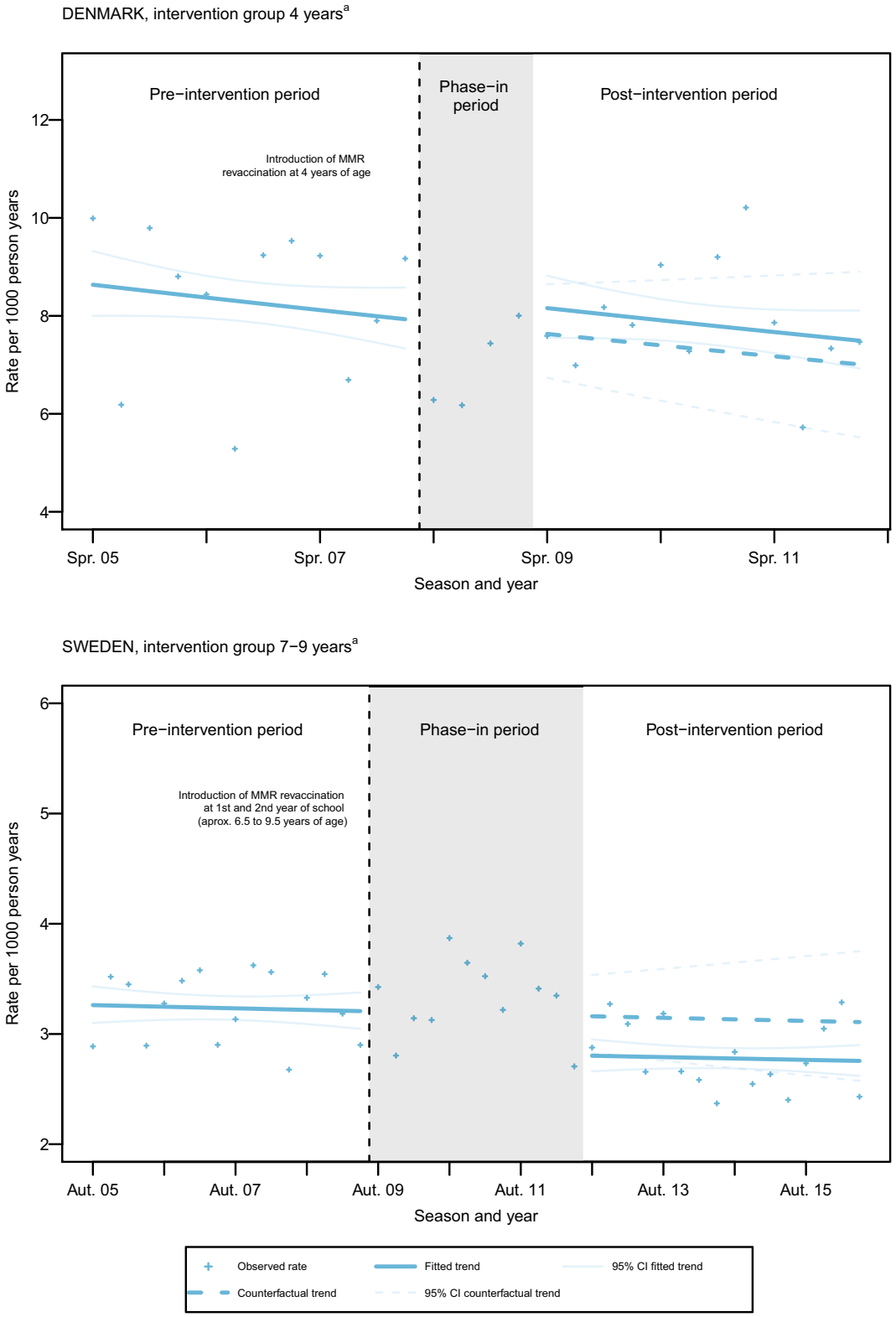

Fig. 3. Observed quarterly incidence rates of hospitalization-for-infection lasting two days or longer (blue dots), fitted trend in the incidence rate (fully drawn lines) and counterfactual trend (dashed line) **Abbreviations:** Aut = Autumn; CI = confidence intervals; MMR = live vaccine against measles, mumps and rubella; Spr = spring. **Notes:** The lines for the trend are estimated based on the final statistical model for each age group and de-seasonalized by setting each season parameter to 0.25. The lines for the counterfactual trend are estimated by setting the parameter for the change in the level to zero. Seasons are defined as spring (March, April, May), summer (June, July, August), autumn (September, October, November), and winter (December, January, February). a: Trends estimated based on a Poisson model with the following predictors: time, level change, spring, summer, autumn. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Based on visual examination of the plots of observed rates, we identified the winter of 2010/2011 (December 2010 to February 2011) in the intervention group in Denmark as a potential outlier. This might have been related to an epidemic of *Mycoplasma pneumoniae* occurring at that time [32]. Therefore, we performed a sensitivity analysis, where we modelled the winter of 2010 as a separate variable in the Danish data.

To examine the sensitivity of the analysis to the length of the pre-intervention, post-intervention and phase-in periods we performed an analysis where we extended the phase-in period with four data points (1 year) on each side of the original phase-in period.

The statistical analyses were performed with R version 3.5.2.

3. Results

3.1. Crude rates

The incidence rates of hospitalization-for-infection lasting two days or longer were lower in the period after the introduction of revaccination with MMR than in the period before introduction of MMR revaccination in the intervention groups in both Denmark (IRR = 0.94; 95% CI = 0.88–1.01) and Sweden (IRR = 0.86; 95% CI = 0.82–0.90; Table 1). Similar decreases were observed in the control groups (Table 1).

3.2. Main interrupted time-series analyses

The interrupted time-series analyses without controls revealed that there were no major differences between the observed and counterfactual incidence rates in the post-intervention period (Fig. 3). The IRR for the level change in hospitalization-for-infection lasting two days or longer following introduction of MMR revaccination was 1.07 in Denmark (95% CI = 0.89–1.28) and 0.89 in Sweden (95% CI 0.77–1.02, Table 2) compared with before the introduction of MMR revaccination in those age groups. The analysis with controls similarly showed no significant level change in the intervention group over and above the level change in the control group in neither Denmark (IRR = 1.08; 95% CI = 0.84–1.39) nor Sweden (IRR = 0.85; 95% CI = 0.65–1.11) (Fig. 4 and Table 2).

3.3. Sensitivity analyses

There was no clear pattern of differences in the results according to sex (Table 2 and Supplementary Table 5). In Denmark, the IRR for level change in analyses without controls was 1.16 (95% CI = 0.87–1.55) for the 4.0–4.5-year-olds and 1.02 (95% CI = 0.80–1.30) for the 4.5–5.0-year-olds (Table 2; crude rates in supplementary Table 6). In Sweden, the IRRs for level change in analyses without controls was 0.78 [95%-CI = 0.66–0.92] for the 7-year-olds and 1.09 [95%-CI = 0.84–1.41] for the 9-year-olds (Table 2; crude rates in supplementary Table 6). Also, the analysis with controls showed similar results for the level change in these smaller intervention groups and in the control groups (Table 2). Modeling of the outlier observation of winter 2010/2011 in Denmark with a distinct variable moved the estimated level change below 1 in the analysis without controls (IRR = 0.94; 95% CI = 0.83–1.07; Table 2). In the analyses without controls, including a longer phase-in period (and consequently shorter pre-intervention and post-intervention periods), the estimated level changes were further from unity than in the main analyses. In Denmark the IRR was 1.99 (95% CI = 1.36–2.91) and in Sweden it was 0.65 (95% CI = 0.51–0.83; Table 2). In the analyses with controls, the level change in the intervention groups and the level change in the control groups did not show significant differences (Table 2).

4. Discussion

The present study used population level data to examine the hypothesis that introduction of MMR revaccination in Denmark and Sweden was associated with a reduction of the incidence rates of hospitalization-for-infection lasting two days or longer. This hypothesis could not be clearly confirmed in the interrupted time series analyses without controls, which take into account the overall trend in the rate of hospitalization-for-infection lasting two days or longer. In Denmark, the point estimate suggested a 7% increase in the rate of hospitalization-for-infection lasting two days or longer following introduction of MMR while the Swedish point estimate suggested an 11% reduction following the introduction of MMR revaccination. The CIs suggested that the data from both countries could be compatible with both increases and reductions in the rates of hospitalization-for-infection lasting two days or longer. The interrupted time-series analyses including a control series gave similar results.

Interrupted time-series analysis evaluate if a policy change affect the overall health in the population, but if the policy is not followed by the population it is a major limitation. In the present study, not all children would be revaccinated with MMR or would not be revaccinated at the recommended age; data from Denmark suggest that around two-thirds of the intervention group was not revaccinated with MMR [31]. The lower the coverage of MMR vaccination in the intervention group, the more attenuated any potential association between revaccination with MMR and hospitalization-for-infection lasting two days or longer would be. We would expect a higher vaccination coverage with higher age of the intervention group, as more children would have had the chance to be vaccinated. Therefore, we conducted analyses categorizing the intervention group into narrow age groups, where we would expect the lowest IRR in the oldest age group as it is presumed to have the highest vaccination coverage. Contrary to expectations, we found the lowest IRR for the 7-year-olds in Sweden, while no significant association was found among the 8- and 9-year-old children and the IRR was above 1 for the 9-year-olds. One explanation for this could be that there is a stronger non-specific effect of the MMR vaccination shortly after the revaccination. However, there was no association for the 4-year-olds in Denmark, who should also have been revaccinated with MMR quite recently in the post-intervention period [10]. Furthermore, many of the 8-year-olds in Sweden would also have been revaccinated with MMR quite recently, whilst many 7-year-olds could have been hospitalized before starting school and receiving the second dose of MMR. The interpretation of the results is hampered by the lack of information on the distribution of the age of revaccination with MMR in Sweden during the years included in this analysis. Overall, there is no clear explanation for these results, but they might have been due to chance or another intervention affecting the 7-year-olds in Sweden.

A simulation study using a Poisson time-series with a conditional mean model showed that the power to detect an association was very low for a model such as ours, with 24 time points, no autocorrelation and a modest true association [10,33]. Therefore, our study is likely hampered by low power. Moreover, our sensitivity analyses showed that particularly the analyses without controls was hugely affected by reducing the number of data points in the pre- and post-intervention periods and removal of outliers.

This study was inspired by a previous individual-based Danish register-based cohort study showing an association between revaccination with MMR and hospitalization-for-infection lasting

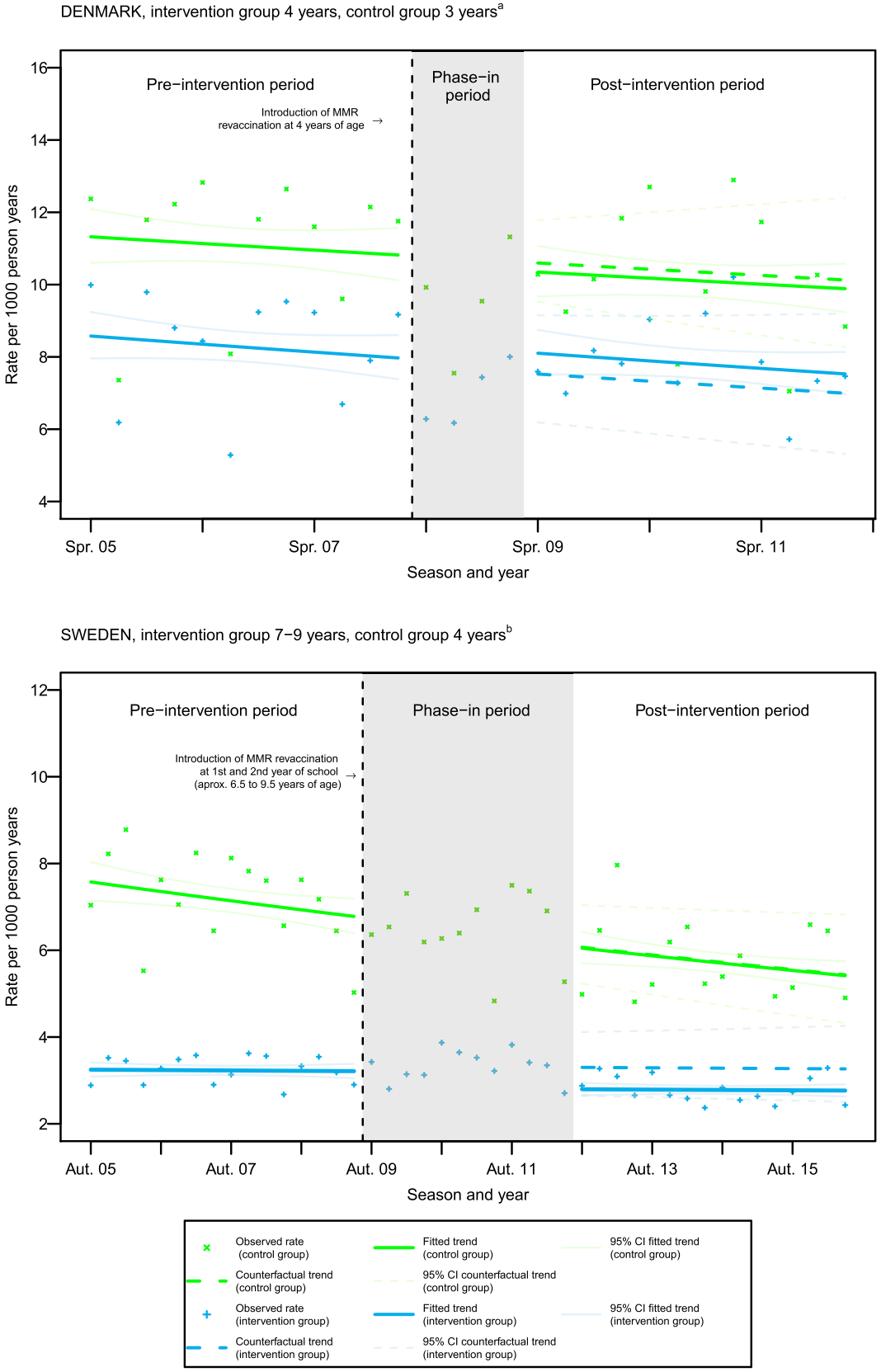

Fig. 4. Observed quarterly incidence rates of hospitalization-for-infection lasting two days or longer, fitted trend and counterfactual trend in analyses including a control group. Abbreviations: Aut = Autumn; CI = confidence intervals; MMR = live vaccine against measles, mumps and rubella; Spr = spring. Notes: The lines for the trend are estimated based on the final statistical model for each age group and de-seasonalized by setting each season parameter to 0.25. The lines for the counterfactual trend are estimated by setting the parameter for the change in the level to zero. Seasons are defined as spring (March, April, May), summer (June, July, August), autumn (September, October, November), and winter (December, January, February). a: Estimated based on a Poisson model with the following predictors: time, intervention, time*intervention, level change, level change*intervention, spring, summer, autumn. b: Estimated based on a Poisson model with the following predictors: time, intervention, time*intervention, level change, level change*intervention, spring, summer, autumn, post-intervention spring, post-intervention summer, post-intervention autumn, post-intervention spring*intervention, post-intervention summer*intervention, post-intervention autumn*intervention.

two days or longer. The analyses in the cohort study adjusted for many potential health-related and socio-economic confounders, but might have been affected by confounding by unmeasured individual level confounders (for example overall frailty of the child or acute infectious diseases that may have delayed vaccination and led to hospitalizations for infections thereby inflating the rate in the group not revaccinated with MMR) [10]. The interrupted time-series analysis presented in the current paper would not be prone to individual-level confounders, as comparisons are made on the population level based on same-aged children before and after the introduction of revaccination with MMR. However, the interrupted time-series analysis, like all analyses based on observational data, is prone to confounding by other time-dependent factors that could affect the rate of hospitalization-for-infection lasting two days or longer for all children [22] e.g. new treatment modalities, co-occurring interventions, or changes in the guidelines for treatment of infections in children. If such time-dependent factors occurred, we would expect that they also affected other age groups than those who were recommended revaccination with MMR in the post-intervention period. Therefore, we conducted analyses with controls where we observed similar level changes in the intervention group and the control group. This indicates that time dependent factors affecting all age groups did not influence the results of the analyses without controls.

Vaccination with pneumococcal conjugate vaccines (PCV) has been associated with a reduction of the risk of hospitalization for community acquired pneumonia, particularly among the youngest children [34]. In Denmark, PCV was introduced in the National vaccination program in October 2007 and included a catch-up program covering children born after April 2006 [35]. In Sweden, PCV was included in the national childhood vaccination program from the beginning of 2009, but some subnational regions had started PCV vaccination already by the end of 2007 [36,37]. Thus, in the post-intervention period, most children in the control groups and some children in the intervention groups would have received PCV in both Denmark and Sweden. Therefore, PCV vaccination could be a time-dependent factor that could affect the rate of hospitalizations differently in different age-groups. In the analyses without controls, the estimates might be lower than what would have been observed without the introduction of PCV, because PCV vaccination might contribute to a lower rate of hospitalization for infections in the post-intervention period. In the analyses with controls, the estimates of IRRs for the level change in the intervention group over and above the level change in the control might be higher than what would have been observed without introduction of PCV. This is based on the assumption that PCV would have contributed to a greater reduction in the rate of hospitalization in the younger control groups than in the older intervention groups in the post-intervention period [34] and thus a greater reduction in the rate of hospitalization for infections explained by PCV in the control group than in the intervention group.

Some studies, mainly from low-income countries, have shown that the magnitude of non-specific effects of vaccines differ by sex; girls benefitting more from non-specific effects than boys [3]. Studies from high-income countries have generally not shown the same sex-differences [4,5,7,10,38] and in the present study there was no indication of major sex differential patterns.

It has been suggested to use triangulation methods in the assessment of non-specific effects of vaccines, whereby results from different settings and study designs with different bias structures are evaluated together [39]. Therefore, the present study needs to be evaluated together with all the evidence regarding potential beneficial non-specific effects of revaccination with measles containing vaccines. Overall, the present study does not confirm or refute our previous individual-level observation in the Danish register-based cohort study of an IRR for hospitalization-for-infection lasting two days or longer of 0.84 (95%-CI = 0.64–0.95) for 4-year-old children revaccinated with MMR compared with those children not revaccinated with MMR [10]. The estimates of the present study had wide confidence intervals, some of which include the point estimate from the previous individual-based Danish study [10]. Furthermore, the point estimates for the intervention group in Sweden were quite close to the point estimate from the previous Danish study [10].

Several studies from low-income countries have investigated if revaccination with measles vaccine was associated with mortality reductions. One randomized trial compared a two dose measles vaccine schedule (at 4–6 months and 9 months of age) with a one dose measles vaccine schedule (9 months of age); they found that children revaccinated with measles vaccine (the two dose schedule) had lower mortality after 9 months of age compared with those with one dose of measles vaccine [40]. Another similar trial could not confirm this finding, but might have been affected by co-occurring oral polio vaccine campaigns [41]. Two studies have shown that children revaccinated with measles vaccine in a measles vaccination campaign had lower mortality than those who received their first dose of measles vaccine [42,43]. Other studies have shown that vaccination with the first dose of measles vaccine in the presence of maternal measles antibodies reduces mortality in African infants [44,45]. The present study did not confirm or refute these previous observations of beneficial effects of vaccinating with measles-containing vaccines in the presence of pre-existing measles immunity either from maternal antibodies or previous vaccination. However, the association might differ between different age groups, settings, and different outcomes.

5. Conclusion

We did not detect an association between the change in recommended age for revaccination with MMR and hospitalization-for-infection lasting two days or longer among children in the high-income countries Denmark and Sweden. However, the study had low power and the CIs suggested that the data could be compatible with both increases and reductions in the rates of hospitalization-for-infection lasting two days or longer following the introduction of MMR revaccination in both countries. We used interrupted time-series analysis, a population-based ecological design, which limits confounding by unmeasured individual-level confounders. However, the study was sensitive to changes in time-periods and intervention groups, and to outliers. Furthermore, the study had limited power due to an expected modest association and limited number of time points and the wide range of possible vaccination ages in Sweden further hampered the interpretation of the results. To guide policy, more studies examining the association between revaccination with measles-containing vaccines and non-targeted outcomes are needed to create a stronger evidence-base.

Funding

The project was supported by NordForsk [grant number 83839]. The funder had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication

CRediT authorship contribution statement

Signe Sørup: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization, Funding acquisition. **Hélène Englund:** Methodology, Software, Investigation, Data curation, Writing - review & editing.

Ida Laake: Methodology, Software, Writing - review & editing. **Heta Nieminen:** Methodology, Writing - review & editing, Funding acquisition. **Lise Gehrt:** Methodology, Software, Data curation, Writing - review & editing. **Berit Feiring:** Methodology, Writing - review & editing, Funding acquisition. **Lill Trogstad:** Methodology, Writing - review & editing, Funding acquisition. **Adam Roth:** Methodology, Writing - review & editing, Supervision, Funding acquisition. **Christine Stabell Benn:** Methodology, Writing - review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: HN is an employee of the Finnish Institute for Health and Welfare, which has received research funding from GlaxoSmithKline, Sanofi-Pasteur and Pfizer for clinical trials. All other authors report no conflicts of interest.

Acknowledgements

We would like to thank Ilias Galanis for fruitful discussions on methodology.

Contribution

SS conceived the study; SS, HE, IL, HN, LG, LT, BF, AR and CSB designed the study; SS and HE acquired the data; SS, HE and LG analyzed the data; SS, HE, IL, HN, LG, LT, BF, AR and CSB interpreted the data; SS drafted the article; SS, HE, IL, HN, LG, LT, BF, AR and CSB revised the article critically for important intellectual content: all authors approved the final submitted version.

Data statement

Data for the approximation of person years at risk was based on data from publicly available data sources as detailed in the method section. Data on hospitalization for infection was obtained from national registers and we are not allowed to share the individual level data according to data protection rules. However, we are allowed to share the aggregated data and statistical code which is available from Mendeley data.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.01.028.

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