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REVIEW

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Non-specific effects of MMR vaccines on infectious disease related hospitalizations during the second year of life in high-income countries: a systematic review and meta-analysis

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ABSTRACT

Children who had received MMR as the most recent vaccine had a pooled 35% (95%CI: 12–53%) lower risk for hospitalization due to any infectious disease, compared to children who had received DTaP as the most recent vaccine (three studies, 1,919,192 children). The effect was stronger for respiratory tract infections than for gastrointestinal infections. Two studies investigated MMR alone, compared to concurrent administration of MMR and DTaP vaccines. Here, the pooled estimate for reduction in risk of hospitalization for any infectious disease was smaller and not significant (15%; 95%CI: −9% to 34%). Risk of bias was serious to critical in all studies. Moreover, two of the five studies demonstrated a significantly reduced risk for a control outcome (hospitalization for injuries), strongly indicating healthy vaccinee bias or residual confounding. The available evidence is insufficient to support a change in current vaccination schedules.

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Non-specific effects of vaccines; MMR; DTaP; Review; child hospitalization; high-income countries

Introduction

Non-specific effects of vaccines are vaccine effects that are not mediated by the effect of the vaccine on the targeted pathogen. Such non-specific effects of vaccines on child mortality have first been reported from developing countries.[1] Meanwhile, the non-specific vaccine effects have also been reported for morbidity. While non-specific effects of live vaccines appear to reduce mortality and morbidity, the opposite was found for inactivated vaccines.[2] Strong effects were mainly observed in non-randomized studies. Attempts for confirmation in randomized trials, however, often yielded much smaller and mostly insignificant effects.[3]

More recently this work has been extended to industrialized countries.[4] To measure the effect of live-attenuated vaccines on infectious diseases not targeted by the vaccine the studies investigated hospitalizations due to any infectious disease in infants who received Measles, Mumps and Rubella vaccine (MMR) after having received a Diphtheria, Tetanus and acellular Pertussis vaccine (DTaP), as compared to infants who received the DTaP vaccine after the MMR vaccine or never received MMR after the DTaP (see Figure 1 describing the principle of these studies). A protective effect of MMR vaccine as compared to DTaP containing vaccines as the most recent vaccine on the risk of hospitalizations for infectious diseases in the second year of life was reported.[4]

Exposure to MMR and DTaP containing vaccines as last vaccine in the second year of life is potentially modifiable by adaptation of vaccine recommendations. Such modification might have a substantial effect on the burden of infectious diseases in infants in the second year of life in industrialized countries. We, therefore, attempted to summarize and evaluate the evidence of the effect of MMR as the last vaccine on hospitalization for infectious disease in the second year of life.

Methods

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[5] The review protocol was registered in the International prospective register of systematic reviews (PROSPERO) under the registration number CRD42018100666.

Eligibility criteria

To be eligible, a study had to meet the following PICO (population, intervention, comparator, outcome) criteria:

- P: Children from 12 to 24 months of age, excluding children with any chronic disease, as main population, who could receive further vaccination in the second year of life in accordance with the national vaccination recommendations.
- I: Receipt of MMR comprising vaccine as the most recent vaccine.
- C: Receipt of a DTaP comprising vaccine as the most recent vaccine.

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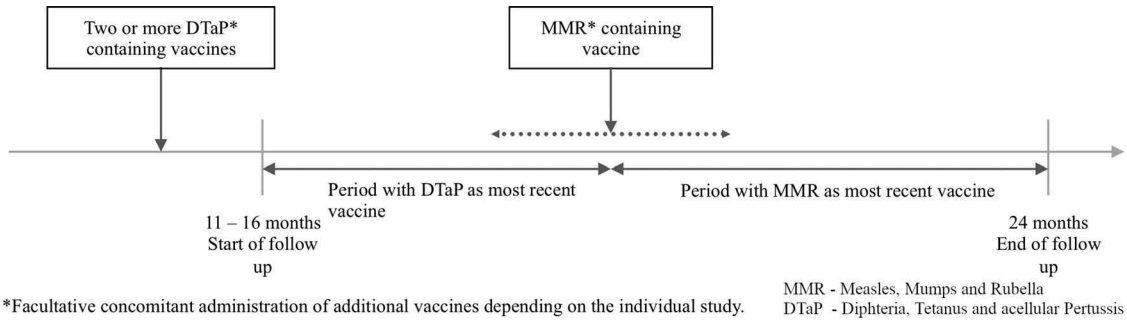

Figure 1. Schematic depiction of the study designs considered for this review.

- O: As the main outcome hospitalization for any infectious disease was chosen. For subgroup analysis, upper and lower respiratory tract infections as well as gastrointestinal infections were chosen.

This review considered non-randomized studies as well as randomized controlled trials. Only studies from high-income countries were included (see Appendix for definition of high-income countries). Only articles published in the English language were included.

Search strategy

A systematic computerized literature search of three electronic databases including PubMed, EMBASE and Medline was conducted on May 21st 2018 via the Ovid search interface, which provides access to studies published from 1974 onwards. The search strategy combined keywords as shown in the appendix. No filters were applied.

Study selection

EndNote software X7 was used to export identified references. All duplicates were removed. Two researchers (AXS and RvK) completed all stages of the screening process independently and discrepancies were resolved by discussion.

The search term was confined to MMR vaccines. One study,[6] however, included varicella vaccination, another live vaccine, in the analysis, assuming similar effects for MMR and the varicella vaccine. Because it was impossible to disentangle the effects and because the number of children receiving varicella alone was small (of the live vaccines, 88% received MMR containing vaccines by the age of 16 months),[6] we included this study in the analysis.

Also in one study[7] MMR was given with Meningococcal C (MenC), an inactivated vaccine.

For sake of simplicity, we refer to MMR vaccines compared to DTaP containing vaccines throughout the paper, acknowledging the limitation that in one study a small proportion of the presumed MMR effect may be caused by varicella vaccination only and the possible interference of MenC vaccination in another study.

Data extraction and quality assessment

The data were collected into an adapted excel workbook based on the template for data extraction developed by the Editorial Resources Committee of the Cochrane Collaboration.[8] Two reviewers independently extracted data on study characteristics, participant description, intervention characteristics, and outcomes. Differences were resolved by discussion. For included studies, the ROBINS-I tool for assessing risk of bias in non-randomized studies of interventions was used.[9] Any discrepancies were resolved by discussion, if necessary with further reviewers.

Data synthesis

The Hazard Ratios and 95% confidence intervals were synthesized in a random-effects model using Review Manager 5.3.[10] Also, heterogeneity and test for overall effect were assessed using the software.

Quality of the body of evidence

The quality of the body of evidence was evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[11] system. Publication Bias could not be assessed due to the low number of included studies.

Results

Study selection

The database literature search resulted in 574 articles. After removal of duplicates, the titles and abstracts of 452 studies were screened. Four hundred and nineteen studies were excluded because they did not address the topic of interest or were not conducted in the target setting (high-income country). The full texts of 33 papers were further assessed for eligibility. Of these, 12 were excluded because they did not address hospitalization for infectious disease. Two studies were from low-income countries. Three studies had a different intervention than the interventions determined in the protocol. And eleven studies were reviews or comments. Finally, five studies were included in the qualitative and quantitative analysis (see Figure 2 for a PRISMA flowchart).

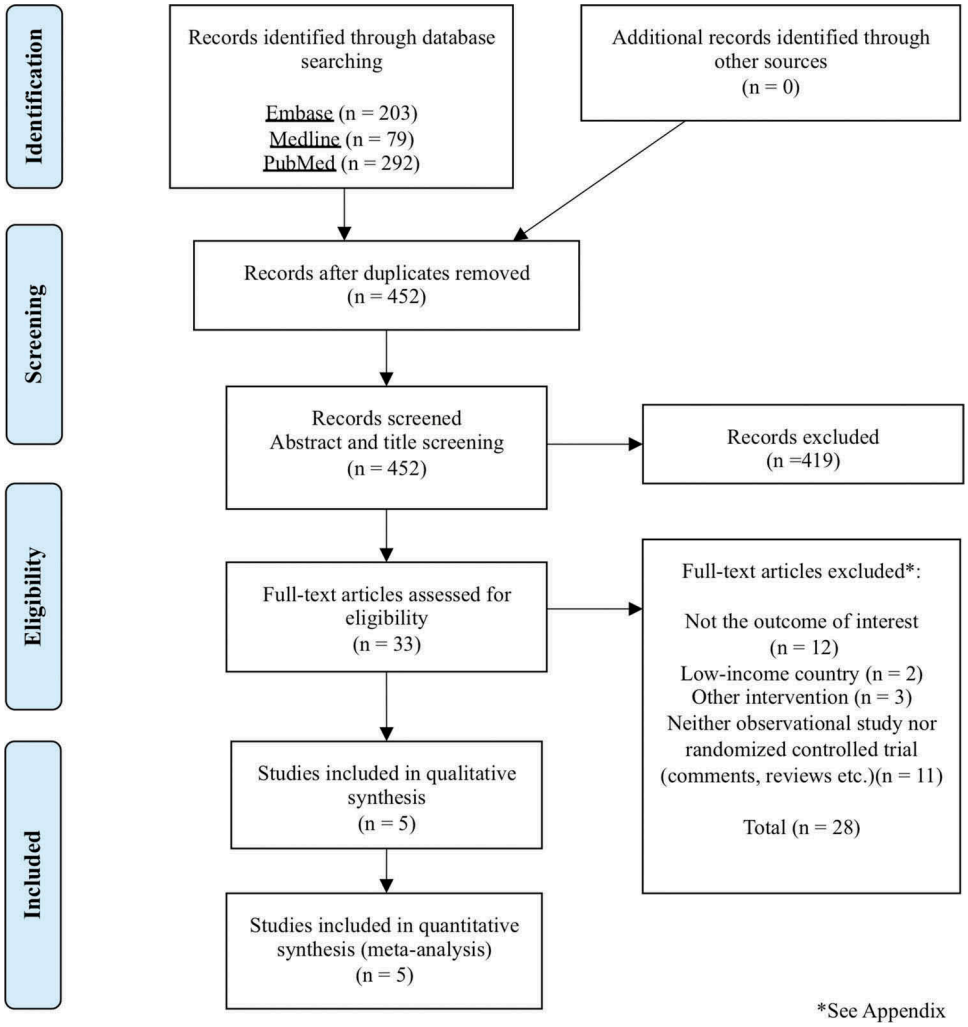

Figure 2. Flowchart of the selection process in accordance with the PRISMA statement adapted by Moher et al.

Study characteristics

The shared exposures analyzed in all studies are depicted in Figure 1. In essence, all studies compare the risk of hospitalization for children because of an infection, by having MMR or DTaP as the most recent vaccine when admitted to hospital. The main characteristics of the included studies are summarized in Table 1. One Danish study examined only MMR as the most recent vaccine for intervention with 510,935 included children.[4] The Dutch study examined MMR combined with Men-C as the most recent vaccine with 1,096,594 included children.[7] One study examining concurrent administration of MMR and DTaP-IPV-Hib vaccines consisted of 520,859 children.[12] The study from the USA investigating both concurrent administration and live vaccine alone as the most recent vaccine included 311,663 children.[6] The study addressing RSV hospitalization had MMR alone for intervention, it included 168,511 children.[13]

The Danish studies[4,12,13] investigating MMR compared to children with DTaP containing vaccine as last vaccine required at least two doses of DTaP containing vaccines as a prerequisite to be included in the study. In the Dutch study,[7] the requirement was four doses DTaP, while it was three doses in the US study.[6] In the three studies with no overlapping populations[4,6,7] MMR containing vaccines as most recent vaccination was assessed as the intervention.

In two study populations, concurrent administration as the most recent vaccine was also reported in the same paper (Bardenheier et al. 2017) or in a separate paper (Sorup et al. 2016).

The main outcome for all studies was hospitalization for an infectious disease. All papers also performed subgroup analysis by stratifying the outcome by upper and lower respiratory tract infection and gastrointestinal tract infections. RSV as an outcome of special interest was addressed in a subpopulation of the Danish study population (Sorup et al. 2015).

The Danish studies[4,12,13] defined exposure as MMR exclusively. In the Dutch[7] study, MMR was administered with MenC on the same day and thus concurrently. In both the Dutch[7] and Danish[4,12,13] studies DTaP was given as a combination vaccine with HiB. Pneumococcal conjugate vaccination was given on the same day in the Dutch study.[7] The US study[6] defined live vaccines as MMR, Varicella or MMRV. In this study, inactivated vaccines included diphtheria-tetanus-acellular pertussis, inactivated polio virus, Haemophilus influenzae type b, pneumococcal conjugate

Table 1. Characteristics of the studies included in the systematic review.

Authors, Year	Study Design	Setting	Study period	Population	Data origins	Sponsoring	Conflict of interest	Vaccines	Outcomes
Sorup, S., et al., (2014)[4]	Cohort study	Denmark	1997–2008	510,935 children 11–24 months	Danish National Patient Register; Danish Civil Registration System; Danish Medical Birth Register; Data was linked with personal identification number	Health Foundation; Rosalie Petersen Foundation; Novo Nordisk Foundation	None	MMR DTaP-IPV-Hib	Hospital admission for any infectious disease
Sorup, S., et al., (2015)[13]	Cohort study	Denmark	1997–2004	168,511 children 14–23 months	Danish National Patient Register; Danish Civil Registration System; Danish Medical Birth Register; Data was linked with personal identification number	Health Foundation; Rosalie Petersen Foundation; Novo Nordisk Foundation; Danish National Research Foundation	None	MMR DTaP-IPV-Hib	Respiratory syncytial virus hospital contact
Sorup, S., et al., (2016)[11]	Cohort study	Denmark	1997–2009	520,859 Children 15–24 months	Danish National Patient Register; Danish Civil Registration System; Danish Medical Birth Register; Data was linked with personal identification number	Danish Council for Independent Research; Health Foundation; Rosalie Petersens Foundation, Novo Nordisk Foundation; European Research Council; Danish National Research Foundation	None	MMR DTaP-IPV-Hib Concurrent administration of these two	Hospital admission for any infectious disease
Tielemans, S. et al., (2017)[10]	Cohort study	Netherlands	2005–2012	1,096,594 Children 11–24 months	Electronic national immunization register; national medical register; population register; Data was linked with a unique personal identifier	Dutch Ministry of Health	None	MMR + meningococcal C DTaP-IPV-Hib +pneumococcal Vaccination	Hospital admission for any infectious disease
Bardenheier, B. H., et al., (2017)[12]	Cohort study	USA	2005–2014	311,663 children 16–24 months	MarketScan Commercial Claims Databases which provides data from commercial health insurance claims	US Department of Health and Human Services	None	Inactivated vaccines: DTaP, IPV, Hib, pneumococcal conjugate vaccine, hepatitis B vaccine, and hepatitis A vaccine Live vaccines: MMR, Varicella	Hospital admission for any infectious disease

MMR – Measles, Mumps and Rubella vaccine; DTaP – Diphtheria, Tetanus, and acellular Pertussis vaccine; IPV – inactivated Polio virus; Hib – Haemophilus influenzae type B vaccine

vaccine, hepatitis B vaccine, and hepatitis A vaccine (and combined vaccines with these antigens).

Risk of bias within studies

Results of risk of bias assessment are summarized in Table 2. For two studies[4,7] the overall risk of bias was classified as critical because of a significant association to the control outcome in the same direction (reduced risk for injuries with MMR as last vaccine). For the other three studies[6,12,13] risk of bias was classified as serious because structural inequality between intervention and control group could not be ruled out. Design factors seem plausible which influence the time point of the intervention and therefore the group status of a child as well as the observed outcome. Children inherently more prone to infectious disease could have a delayed MMR vaccination and therefore a longer control group status (DTaP as most recent vaccine), while having more hospital admissions for infectious disease accounting for residual confounding.

Additionally, in the Bardenheier et al. study[6] the number of confounders considered for adjustment was lower than in the Danish and Dutch studies: no adjustments for household income, parental education or migration background were made in this study. We did not take account of this limitation to change the risk of bias from serious to critical because the overall impact of including covariates in all studies was only of small size.

Results of individual studies

As shown in Table 3, the main finding of the Sorup 2014 study[4] was a small but significant reduction in the overall risk for hospitalizations after MMR as last vaccine. This was mainly driven by the association between MMR as last vaccine and lower respiratory tract infections. The 95% confidence intervals for upper and lower respiratory tract infections overlapped widely, whereas the respective 95% confidence intervals for gastrointestinal infections were shifted toward unity. The control outcome suggested a small but significant effect on emergency department visits following unintentional injury.

The Sorup 2015 study[13] was based on a sub-sample of the study population analyzed in the 2014 study[4] for which information on RSV was available. The impact on RSV was similar

Table 2. Risk of bias summary applying ROBINS-I.

ROBINS-I risk of bias	Sorup et al., 2014	Sorup et al., 2015	Sorup et al., 2016	Tielemanns et al., 2017	Bardenheier et al., 2017
Bias due to confounding	Critical	Serious	Serious	Critical	Serious
Bias in selection of participants into the study	Low	Low	Low	Low	Low
Bias in classification of interventions	Moderate	Moderate	Moderate	Moderate	Moderate
Bias due to deviations from intended interventions	Low	Low	Low	Low	Low
Bias due to missing data	Low	Low	Low	Low	Low
Bias in measurement of outcome	Moderate	Moderate	Moderate	Moderate	Moderate
Bias in selection of the reported result	Low	Low	Low	Low	Low
Overall risk of Bias	Critical	Serious	Serious	Critical	Serious

Table 3. Findings of the studies included in the systematic review.

Authors, Year	*Absolute hospital admissions per Person-Years*	*Adjusted parameters*	*Adjusted relative effects (95% CI)*	*Negative control outcomes (95% CI)*
Sorup, S., et al., (2014)[4]	Hospital admission for any infectious disease: DTaP-IPV-Hib3 as most recent vaccine: 20 743/167693 MMR as most recent vaccine: 21 311/239 642 Hospital admission for upper respiratory tract infections: DTaP-IPV-Hib3 as most recent vaccine: 8 516/167 693 MMR as most recent vaccine: 8 599/239 642 Hospital admission for lower respiratory tract infections: DTaP-IPV-Hib3 as most recent vaccine: 7 223/167 693 MMR as most recent vaccine: 6 941/239 642 Hospital admission for gastrointestinal tract infections: DTaP-IPV-Hib3 as most recent vaccine: 2 881/167 693 MMR as most recent vaccine: 3 206/239 642	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	Hospital admission for any infectious disease: MMR as most recent vaccine vs. DTaP-IPV-Hib3: IRR 0.86 (0.84–0.88) Hospital admission for upper respiratory tract infections: MMR as most recent vaccine vs. DTaP-IPV-Hib3: IRR: 0.86 (0.82–0.89) Hospital admission for lower respiratory tract infections: MMR as most recent vaccine vs. DTaP-IPV-Hib3: IRR: 0.80 (0.76–0.84) Hospital admission for gastrointestinal tract infections: MMR as most recent vaccine vs. DTaP-IPV-Hib3: IRR: 0.93 (0.87–1.00)	Emergency department visits following unintentional injury MMR as most recent vaccine vs. DTaP-IPV-Hib3: Unadjusted: IRR 0.96 (0.94–0.98) Adjusted: IRR 0.97 (0.95–0.99)
Sorup, S., et al., (2015)[13]	Respiratory syncytial virus hospital contact: DTaP-IPV-Hib3 as most recent vaccine: 320/35 995 MMR as most recent vaccine: 568/92 593	Sex, birth weight, gestational age, cesarean section, chronicdiseases, number of admissions between 1 month of age and date of DTaP-IPV-Hib3 vaccination, admission from date of DTaP-IPV-Hib3 vaccination until 14 months of age,maternal age at birth of the child, parental place of birth, adult composition of the household, and other children in the household	Respiratory syncytial virus hospital contact: MMR as most recent vaccine vs. DTaP-IPV-Hib3: IRR: 0.78 (0.66–0.93)	Emergency room visits due to accidents MMR as most recent vaccine vs. DTaP-IPV-Hib3: IRR: 1.02 (0.98–1.06)
Sorup, S., et al., (2016)[11]	Hospital admission for any infectious disease: Concurrent administration: 332/2 971 MMR as most recent vaccine: 24 027/267 582	Date of birth, mother smoking during pregnancy, sex, birth weight, gestational age, cesarean section, chronic diseases, number of infectious disease admissions before 15 months of age, 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, adults in the household, income quintiles for the household, other children in the household, and population density	Hospital admission for any infectious disease: Simultaneous MMR and DTaP-IPV-Hib vs. MMR: IRR: 1.04 (0.94–1.17)	Emergency room visits due to accidents Simultaneous MMR and DTaP-IPV-Hib vs. MMR: Unadjusted: IRR: 1.08 (1.03–1.13) Adjusted: IRR: 1.00 (0.95–1.04)

(*Continued*)

Table 3. (Continued).

Authors, Year	*Absolute hospital admissions per Person-Years*	*Adjusted parameters*	*Adjusted relative effects (95% CI)*	*Negative control outcomes (95% CI)*
Tielemans, S. et al., (2017)[10]	Hospital admission for any infectious disease: DTaP-IPV-Hib+PCV as most recent vaccine: 4 111/284 786 MMR+MenC as most recent vaccine: 6 850/776 456 Hospital admission for upper respiratory tract infections: DTaP-IPV-Hib+PCV as most recent vaccine: 1 664/285 664 MMR+MenC as most recent vaccine: 2 765 / 782 900 Hospital admission for lower respiratory tract infections: DTaP-IPV-Hib+PCV as most recent vaccine: 1 234/285 731 MMR+MenC as most recent vaccine: 2 120/783 457 Hospital admission for gastrointestinal tract infections: DTaP-IPV-Hib+PCV as most recent vaccine: 1 816 /285 657 MMR+MenC as most recent vaccine: 2 942/782 668	Sex, chronic disease, admission for any reason at age 8 months, birth weight, gestational age, maternal age and parity, parental country of birth, and postcode	Hospital admission for any infectious disease: MMR+MenC as most recent vaccine: HR: 0.62 (0.57 to 0.67) Hospital admission for upper respiratory tract infections: MMR+MenC as most recent vaccine: HR: 0.54 (0.48 to 0.62) Hospital admission for lower respiratory tract infections: MMR+MenC as most recent vaccine: HR: 0.56 (0.49 to 0.66) Hospital admission for gastrointestinal tract infections: HR: 0.70 (0.61 to 0.80)	Admitted to hospital for more than one day because of injury or poisoning MMR+MenC as most recent vaccine vs. DTaP-IPV-Hib +PCV: Unadjusted: HR: 0.81 (0.71 to 0.93) Adjusted: HR: 0.84 (0.73 to 0.96)
Bardenheier, B. H., et al., (2017)[12]	Hospital admission for any infectious disease: Live as most recent vaccine: 241/16 002 Inactivated as most recent vaccine: 1 807/137 156 Hospital admission for upper respiratory tract infections: Live as most recent vaccine: 103/16 093 Inactivated as most recent vaccine: 665/137 650 Hospital admission for lower respiratory tract infections: Live as most recent vaccine: 108/16 086 Inactivated as most recent vaccine: 958/137 519 Hospital admission for gastrointestinal tract infections: Live as most recent vaccine: 28/16 138 Inactivated as most recent vaccine: 146/137 884	Chronic conditions, low birth weight, premature, number of hospitalizations prior to age 16 months, number of outpatient visits prior to age 16 months, region, urban/rural, and mother's age	Hospital admission for any infectious disease: Live as most recent vaccine: HR: 0.50 (0.43, 0.57) Hospital admission for upper respiratory tract infections: Live as most recent vaccine: HR: 0.41 (0.32, 0.51) Hospital admission for lower respiratory tract infections: Live as most recent vaccine: HR: 0.45 (0.36, 0.56) Hospital admission for gastrointestinal tract infections: HR: 0.92 (0.59, 1.42)	Emergency room visit for an unintentional injury Live vs. inactivated: HR: 1.16 (0.90, 1.48)

MMR – Measles, Mumps and Rubella vaccine; DTaP – Diphtheria, Tetanus, and acellular Pertussis vaccine; IPV – inactivated Polio virus; Hib – Haemophilus influenzae type B vaccine; PCV – Pneumococcal Conjugate Vaccine; HR – Hazard Ratio; IRR – Incidence Rate Ratio; CI – Confidence Interval.

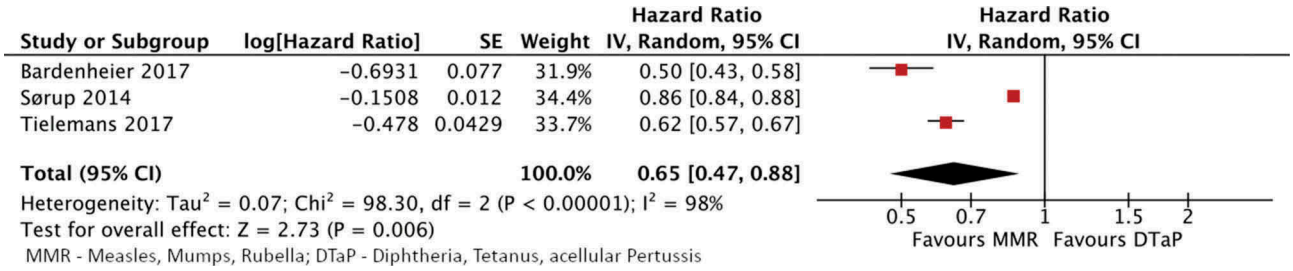

Figure 3. Hospital admissions for any infectious disease MMR vs. DTaP as most recent vaccine (confounder-adjusted estimates were used from the primary studies).

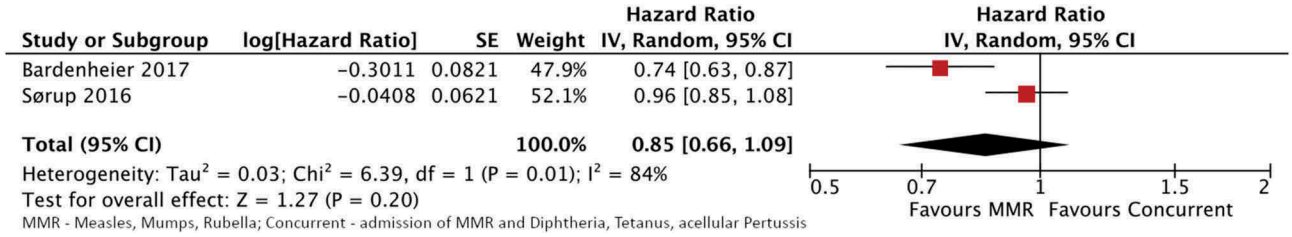

Figure 4. Hospital admissions for any infectious disease MMR vs. concurrent administration of MMR and DTaP (confounder-adjusted estimates were used from the primary studies).

in size to that observed for lower respiratory infections in the entire population.

The Dutch study[7] suggested a substantially higher impact of MMR on the rate of hospitalizations, as compared to those observed in the studies[4,12,13] from Denmark. The control outcome suggested a similar and significant effect on emergency department visits following unintentional injury. As in the Sorup studies[4,12,13] the effect was stronger for upper and lower respiratory tract infections and not as strong for gastrointestinal infections.

The US study[6] reported an even more pronounced effect of MMR on hospitalization. As in the Sorup[4,12,13] and Dutch[7] studies, the effect was stronger for lower and upper respiratory tract infections. There was no significant effect on hospital admissions for gastrointestinal infections. Interestingly, in this study no effect on the control outcome "emergency room visits for unintentional injury" was observed.

For two populations[6,12] the potential effect of MMR on hospitalization for infections was also addressed if MMR was given with a DTaP containing vaccine compared to MMR alone. The Danish paper[12] did not find a significant relative effect, whereas the US study[6] observed a favorable effect of the administration of MMR alone.

Synthesis of results

Figure 3 shows the result of the meta-analysis for hospital admissions due to any infectious disease after receipt of MMR as the most recent vaccine, as compared to receipt of DTaP as the most recent one. The pooled overall effect suggested a reduction of the relative risk by about one third with large heterogeneity between the studies.

Figure 4 shows the result of the meta-analysis for hospitalization due to any infectious disease after receipt of MMR as the most recent vaccine, as compared to concurrent administration of a MMR and DTaP vaccine as the most recent vaccination. Here, a smaller and non-significant reduction in risk was observed, while heterogeneity was high again.

GRADE evidence quality

GRADE evidence quality was very low for all outcomes. This was mainly due to high risk of bias and substantial heterogeneity between studies (see Supplementary Table 6).

Discussion

The results of this systematic review show that five studies performed in high-income countries reported a non-specific protective effect of MMR as the most recent vaccine for prevention of hospitalizations related to infectious diseases in the second year of life compared to children with DTaP containing vaccine as the most recent vaccine. The summary effect estimate from three studies suggests a reduction by 35%. High risk of bias in the individual studies and substantial inconsistency between study results, however, preclude any firm conclusions for potential modification of time schedules in national immunization programs.

We used the ROBINS-I tool[9] for assessment of risk of bias. This recently developed tool applies the approach of comparing a given non-randomized study to a hypothetical randomized "target trial" to analyze potential sources of bias in the former. Identification of and adjustment for potential confounders is one of the key domains of ROBINS-I, including the issue of residual confounding. Residual confounding, however, appears possible for the main Danish[4] and Dutch[7] studies because of significant effects on the control outcome in the same direction. Robins-I explicitly recommends that any association seen for a control outcome (or so-called negative outcome) in the same direction as the main outcome

should be considered as indication of bias, irrespective of difference in the strength of effect. In conclusion, all studies were considered to be at serious to critical risk of bias. The confidence regarding the overall effect estimate was further reduced by substantial inconsistency between studies, because of differences in concurrent administration of vaccines and strength of the effect.

The authors of the Dutch study[7] doubt the validity of their findings themselves, because of a relatively strong and significant effect on the control outcome. Additionally, comparing infectious disease hospitalization rates after 4 versus 3 DTaP vaccinations, they found a protective effect of the fourth DTaP dose, similar in size to that of MMR. Consequently, these authors concluded that the effects observed in studies on this subject might not be specific for live vaccines, but may indicate healthy vaccinee bias.

The US study[6] reports the strongest effects. However, adjustment for confounders was less complete than in the other studies. Moreover, there was a discrepancy between the reported rates for hospitalization for any infectious disease after live vaccine and inactivated vaccine and the derived adjusted relative risks for any infectious disease hospitalization. The adjusted relative risk was almost halved whereas the absolute risk for live vaccine was higher than after inactivated vaccine. This discrepancy could not be resolved by correspondence with the first author or the institution (neither responded).

In the studies[6,12] that compared the effect of MMR alone to concurrent MMR and DTaP administration, the within study effects appear to be lower after concurrent administration, which might indicate effect modification by administration of DTaP. However, pooling the estimates of the two studies led to high heterogeneity and a non-significant pooled estimate.

Heterogeneity also pertains to the exposures compared. In the Netherlands,[7] MMR was consistently given concurrently with MenC, an inactivated vaccine. In the US study,[6] any live vaccine (including MMRV or Varicella alone) was considered and compared to DTaP or to a number of different potential other inactivated vaccines.

Some consistency between the studies may indicate a shared causal principal or shared confounding directed at the prevention of respiratory infections: In all studies, the effect was more pronounced against respiratory than gastrointestinal infections. The considerable effect size against RSV reported in the Danish study[13] published in 2015 points to a potential clinical relevance of MMR as last vaccine since RSV is a major cause of life-threatening acute respiratory infections in children, globally.[14]

So far the data of the Danish group[5] elaborating further on indirect evidence against selection bias are unique. The emergence of the MMR effect only 2 weeks after MMR vaccination hints to plausibility: Immune modulation after MMR vaccination is unlikely to emerge immediately after vaccination, whereas a healthy vaccinee effect related to the timing of vaccination would be present immediately after vaccination. Additionally, the similar findings regarding the reverse schedule cannot be explained by vaccinating healthier children with MMR earlier. Further study in populations where the reverse schedule is more widely used is needed for confirmation of these findings.

Strengths and Limitations

A limitation of this systematic review is the paucity and heterogeneity of the published studies on this issue. Additionally, the individual studies were of limited quality.

In the ROBINS-I[9] tool studies are considered as critical for the risk of bias, if the control outcome "strongly suggests unmeasured confounding". In fact, it is not entirely clear what the authors of ROBINS-I mean by "strongly suggests unmeasured confounding". If "strongly" is interpreted with regard to effect size and confidence intervals, one has to admit that the effect sizes of the negative control outcomes are smaller than those of the target outcomes, while the confidence intervals of the former are sometimes close to 1. However, "strongly" might also be interpreted as "we have robust evidence for the presence of residual confounding". In this sense, analyses showed that in the studies under discussion here, an effect on the negative control outcomes was observed in the unadjusted data, but also after adjustment for (known and observable) confounders. We would like to interpret this as robust evidence for the presence of residual confounding. Moreover, we do not know to what extent the unmeasured confounding influences the target outcome. Even a weak effect on the control outcome could mean a strong effect on the target outcome, because of unmeasured variables. It is uncertain if the control outcome and the measured outcome are influenced equally.

Despite the limitations of the individual studies, we did a meta-analysis to summarize the findings of the three relevant studies since the effect was in a similar direction. The justification for performing a meta-analysis on heterogeneous studies of limited quality might be questioned. We presented the meta-analysis nevertheless, to provide a summary, while acknowledging the limitations of the summary estimate presented.

In conclusion, in non-randomized studies, having received a live vaccine as the most recent vaccine is associated with a decreased risk of hospitalization for any infectious disease during the second year of life in high-income countries. However, due to severe study limitations, the available evidence is insufficient to support a change in current vaccination schedules. In vaccination programs in populations with persistent measles circulation and only one MMR dose in the first 2 years postponing MMR to make it the most recent vaccination would evidently put the most vulnerable by measles, infants and young toddlers, at risk for acquiring measles. Because of the small but relevant risk of primary MMR vaccine failures, this may also apply to the second dose in countries where this is recommended. For these populations, the risk of measles due to postponement of the MMR dose, which depends on the size of measles circulation in the population, must be balanced against the potential benefit of a reduced risk for respiratory infections.

In a population with an ongoing 2 dose MMR vaccination in the first 2 years of life and successful measles elimination, it might be possible to randomize the timing of the second MMR dose in order to obtain irrefutable evidence for a reduced risk for respiratory infections related to MMR given as the last vaccine.

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