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How are children who are delayed in the Childhood Vaccination Programme vaccinated: A nationwide register-based cohort study of Danish children aged 15-24 months and semi-structured interviews with vaccination providers

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ABSTRACT

Aims
Delay of childhood vaccinations is common and influences efforts to reduce targeted
diseases. In Denmark diphtheria, tetanus, pertussis, polio, and Haemophilus influenzae
type b (DTaP-IPV-Hib) vaccine is recommended at age 3, 5, and 12 months and the first
measles-mumps-rubella vaccine (MMR-1) at 15 months. Per guidelines, children delayed
at age 15 months should receive MMR-1 and DTaP-IPV-Hib-3 simultaneously unless
DTaP-IPV-Hib-2 was received less than 6 months ago, then MMR-1 alone is
recommended. We studied compliance with these guidelines and reasons for non-
compliance with a focus on vaccination providers.

Methods
Nationwide register-based cohort study of children born in Denmark between January
2000 and June 2013, who were lacking MMR-1 and DTaP-IPV-Hib-3 at age 15 months
and followed to 24 months. We also performed semi-structured telephone interviews with
vaccination providers.

Results
The study comprised 156,921 children (18% of the children born in the period). Among the
40,060 children who had received DTaP-IPV-Hib-2 less than 6 months ago, 37,892 (95%)
received MMR-1 alone. Among the 88,469 children who had received DTaP-IPV-Hib-2
more than 6 months ago, 6,334 (7%) received DTaP-IPV-Hib-3 and MMR-1
simultaneously. The interviews indicated that some vaccination providers are reluctant to
give multiple vaccinations at the same visit and some have a preference of following the
usual sequence in the programme.

Conclusions
Vaccination providers generally complied with the recommended minimum 6 months’ interval between DTaP-IPV-Hib-2 and DTaP-IPV-Hib-3. Conversely, there was a low compliance with the recommendation to administer DTaP-IPV-Hib-3 and MMR-1 simultaneously. More efforts are needed to ensure timely vaccination.

KEYWORDS
diphtheria-tetanus-acellular pertussis-polio-\textit{Haemophilus influenzae} type b vaccine; measles-mumps-rubella vaccine; delayed vaccinations; vaccination coverage; missed vaccination opportunities
INTRODUCTION

The World Health Organization recommends that the vaccination coverage for the live attenuated vaccine against measles, mumps, and rubella (MMR) should be 95%. However, this goal has not been reached for any Danish birth cohort and increasing vaccination coverage is a high priority for the Danish Health Authorities. Delay of vaccinations is common and could influence vaccination coverage and thereby efforts to reduce or eliminate the targeted diseases. In Denmark, there are national guidelines that describe how to complete the schedule for children who are delayed in the Childhood Vaccination Programme, to minimise delay and increase vaccine coverage.

In Denmark, vaccines in the Childhood Vaccination Programme are free of charge. All citizens are assigned to a general medical practice, where childhood vaccinations are administered by the general practitioners (GPs) or their assistants (usually nurses). The parents are informed about the Childhood Vaccination Programme by the GP at the first visit after the delivery (scheduled for 5 weeks of age); the parents are responsible for booking the subsequent vaccination appointments. The recommended vaccination schedule for Danish children include three inactivated vaccine doses against diphtheria, tetanus, pertussis, polio, and Haemophilus influenzae type b (DTaP-IPV-Hib) at age 3, 5, and 12 months, and the first dose of MMR (MMR-1) at age 15 months (eTable 1). The guidelines recommend at least 6 months between the second and third DTaP-IPV-Hib dose. If children are lacking two or more vaccines, the vaccines can be administered simultaneously.

Vaccination providers play a key role in vaccinating children with delayed vaccines according to these guidelines. Knowing the compliance with these guidelines and determinants of non-compliance is important for future interventions to increase
vaccination coverage. Therefore, the aim of the present study was to examine compliance with the guidelines for administration of delayed vaccination and determinants of non-compliance with focus on the vaccination providers.
The study was conducted in Denmark. We performed a retrospective nationwide register-based cohort study, which describes sequences of DTaP-IPV-Hib-3 and MMR-1 vaccinations in the period from 15 to 24 months of age for Danish children who by age 15 months had received only two doses of DTaP-IPV-Hib and no MMR-1. In this cohort, we also examined if sex, age, months since DTaP-IPV-Hib-2, vaccination period, and province affected the vaccines provided from 15 to 24 months of age. Furthermore, we identified GPs who had vaccinated at least 25 children with delayed childhood vaccinations and eligible for both DTaP-IPV-Hib-3 and MMR-1 (i.e. 6 months had passed since DTaP-IPV-Hib-2), and examined how these GPs would vaccinate delayed children. We conducted qualitative interviews with 12 of these vaccination providers.

The Danish Vaccination Register

In Denmark, GP identification codes identify each general practice, which can include several GPs and assistants. The GP identification code is used to report vaccines to the Danish National Health Service Register for reimbursement and to the national Danish Vaccination Register (DVR). The DVR became operative in February 2013, and has vaccination entries collected from the Danish National Health Service Register dating back to 1996. The purpose with the DVR is to ensure a high quality in monitoring the effectiveness, vaccine safety, and compliance with vaccination.

Cohort

In Denmark, all children are assigned a unique personal identification number at birth including information about the date of birth and sex of the child. This unique personal
identification number is included in the DVR, which enabled us to identify the cohort in the DVR. The cohort included all children born from 1 January 2000 to 30 June 2013 who by age 15 months had received only two doses of DTaP-IPV-Hib, and no MMR-1. We followed the cohort from 15 to 24 months of age; thus, the last follow-up date was 30 June 2015. Since all available children were included, no power calculation was made.

Data and Variables

From the DVR, we obtained information about vaccines, vaccination dates, birthdate, sex, GP identification code, and municipality. Based on birthdate and vaccination date we calculated age at the first vaccination visit after age 15 months, equivalent to the child’s third vaccination visit, and time between DTaP-IPV-Hib-2 and the third vaccination visit. During the study period, there has been some changes in the Danish Childhood Vaccination Programme (eTable 1). Based on the changes in the vaccination programme we defined three calendar periods where the third vaccination visit could comprise two or three injections; from 1 January 2000-30 June 2002, the possible vaccines were DTaP-IPV, Hib, and MMR; from 1 July 2002-30 September 2007, the possible vaccines were DTaP-IPV-Hib and MMR; and from 1 October 2007-30 June 2015 the possible vaccines were DTaP-IPV-Hib, pneumococcal conjugate vaccine (PCV) and MMR. The Danish municipalities were allocated to 11 Danish provinces 11.

Statistical methods

The cohort was divided into two subgroups: children with the third vaccination visit less than 6 months after DTaP-IPV-Hib-2 (“<6 months”), and children with the third vaccination visit more than 6 months after DTaP-IPV-Hib-2 (“6 months+”). For each subgroup, we
calculated the proportion of children who received either DTaP-IPV-Hib-3, MMR-1, or both vaccines simultaneously by sex, age in months at the third vaccination visit, months since DTaP-IPV-Hib-2, vaccination period, and province. Determinants for vaccination among children in the “6 months+” were studied using log binomial regression to obtain adjusted prevalence ratios for receiving the DTaP-IPV-Hib-3 and MMR-1 vaccination simultaneously as recommended compared with receiving either vaccine alone. Stata version 14 was used for the analyses.

**Cohort of GP practices**

We identified all GP practices, which had at least 25 vaccination visits from children in the “6 months+” subgroup. For each GP practice, we calculated the proportion of children receiving DTaP-IPV-Hib-3 alone, MMR-1 alone, or both vaccines simultaneously at the third vaccination visit. These three proportions for each GP practice were plotted in a triplot using Sigmaplot 13.0.

**Qualitative studies**

Based on the cohort of GP practices we identified practices for semi-structured telephone interviews to identify reasons for non-compliance with the vaccination guidelines for children delayed on DTaP-IPV-Hib-3. We aimed at 12 interviews with three practices each following the four strategies: high proportion of MMR-1 alone, high proportion of DTaP-IPV-Hib-3 alone, high proportion of DTaP-IPV-Hib-3 and MMR-1 simultaneously, or approximately same proportion of MMR-1 alone and DTaP-IPV-Hib-3 alone. We included practices with only one GP to increase the likelihood that only one person in the practice
was responsible for vaccinations. Between March and May 2016, CHS performed the semi-structured telephone interviews, which contained both open and closed questions covering three main areas: performance of a regular vaccination visit, vaccination of children delayed on DTaP-IPV-Hib-3, and information on vaccination guidelines. The interview guide was piloted two times on nurses performing childhood vaccinations; resulting in some changes to the interview guide (The final version of the interview guide is in eMethods). The pilot interviews were not used in the analysis. Based on the notes from the interviews SS condensed the information from the interviews and CHS checked the condensation. We regarded that statements like “I would always do…, because…” and “my main concern is..” indicated issues that were important to the interview person.

**Ethics and permits**

Statens Serum Institut has access to the DVR to measure vaccination coverage and to conduct studies on vaccine effectiveness and vaccine safety. The current study was register-based and enclosed at the following notification to the Danish Data Protection Agency: Epidemiological surveillance: jr.nr. 2008-54-0474. Informed oral consent was obtained for the interviews with the vaccination providers.
RESULTS

Among the 855,132 children born in Denmark from January 2000 to June 2013, 12,156,921 children (18%) had received only DTaP-IPV-Hib-1 and -2 and no MMR-1 by age 15 months, and were included in the cohort under study (Figure 1). By age 24 months among children in the included cohort, 41,402 (26%) had received both MMR-1 and DTaP-IPV-Hib-3 either simultaneously or at two separate visits, 18,396 (12%) children had received only DTaP-IPV-Hib-3, 68,731 (44%) had received only MMR-1, and 28,392 (18%) received neither MMR-1 nor DTaP-IPV-Hib-3 before 24 months.

Among the 40,060 children in the “<6 months” subgroup, 37,892 (95%) received MMR-1 as recommended (Figure 1). Of the 88,469 children in the “6 months+” subgroup, only 6,334 (7%) received MMR-1 and DTaP-IPV-Hib-3 simultaneously as recommended (Figure 1).

Vaccination determinants

In the “6 months+” subgroup, sex, age, months since DTaP-IPV-Hib-2, vaccination period, and province were associated with compliance with the vaccination guidelines (Table 1). In the “<6 months” subgroup, the median age when vaccinated was 5 months for DTaP-IPV-Hib-1; 12 months for DTaP-IPV-Hib-2; and 16 months for either DTaP-IPV-Hib-3, MMR-1 or both administered simultaneously (eFigure 1A).

In the “6 months+” subgroup, the median age when vaccinated was approximately 3 months for DTaP-IPV-Hib-1; 5 months for DTaP-IPV-Hib-2; and 16 months for either DTaP-IPV-Hib-3, MMR-1, or both simultaneously (eFigure 1B). There was a larger variation in the “6 months+” group compared with the “<6 months” group (eFigure 1).
Vaccination distribution per GP practice

We identified 1661 (56%) of 2965 GP practices, which had at least 25 vaccination visits from children in the “6 months+” subgroup. Most of these GP practices had a low proportion of children receiving MMR-1 and DTaP-IPV-Hib-3 simultaneously (Figure 2); 526 (31.7%) never administered MMR-1 and DTaP-IPV-Hib-3 simultaneously. All GP practices had administered both MMR-1 alone or DTaP-IPV-Hib-3 alone (Figure 2); some GP practices had a greater proportion of children administered MMR-1 alone and some GP practices had a greater proportion of children administered DTaP-IPV-Hib-3 alone.

Semi-structured telephone interviews

We performed 12 semi-structured telephone interviews with vaccination providers per selection criteria given in eFigure 2 (online supplement). All informants reported that no children were vaccinated before inspection of the vaccination card or medical record. In most practices, the minimum interval between DTaP-IPV-Hib-2 and 3 was respected, but the choice of vaccine and arguments for the choices differed. Box 1 contains all the mentioned arguments for different vaccine choices. The main argument for providing vaccines simultaneously was to achieve full protection. The main reason for choosing DTaP-IPV-Hib-3 alone was to follow the normal vaccination sequence, while the most important reasons for choosing MMR-1 were reluctance towards administering more than two vaccines at the same visit, and that the child was already partially immune towards diphtheria, tetanus, pertussis, polio, and Haemophilus influenzae type b after two DTaP-IPV-Hib vaccines.

None of the 12 informants stated that the choice of vaccine was influenced by the child’s current health condition (colds, febrile disease), preterm birth, or chronic diseases, except
for one informant who mentioned that immunosuppressed children should not be vaccinated with MMR-1.

Most informants had occasionally experienced parental concern in relation to DTaP-IPV-Hib and MMR-1 vaccines, but all underlined that it was an infrequent occurrence.

None of the informants had any concerns regarding any of the vaccines.

Results regarding vaccination providers considerations about available information on vaccination guidelines are given in the eResults (online supplement).
DISCUSSION

When Danish children lacking DTaP-IPV-Hib-3 and MMR-1 at age 15 months were vaccinated less than 6 months after DTaP-IPV-Hib-2, they were mainly vaccinated with MMR-1 alone as recommended (95%). Only 2% of these children received DTaP-IPV-Hib-3 at a later visit. Children vaccinated 6 months or more after DTaP-IPV-Hib-2 were rarely vaccinated as recommended with DTaP-IPV-Hib-3 and MMR-1 simultaneously. These children usually received DTaP-IPV-Hib-3 alone (54%), but MMR-1 alone was also frequent (39%). The interviews with the vaccination providers indicated that reluctance to give three injections at one visit could give a preference for either DTaP-IPV-Hib-3 alone or MMR-1 alone; a preference for keeping the vaccination sequence could result in administration of DTaP-IPV-Hib-3 alone.

Strengths and weaknesses

We used vaccination information from the DVR, which was based on the Danish National Health Service Register with vaccination information provided for reimbursement purposes. Thus, the GPs have an economic incentive to report the vaccinations. However, previous studies have found underreporting of MMR-1 and DTaP-IPV revaccination scheduled at age 5 years. Underreporting probably occurs for all vaccines. Thus, if registration of DTaP-IPV-Hib-3 before age 15 months is missing, too many children could be included in our cohort. Provided the parent and their GP had correct information on their vaccination status, these children would fall into the category of “MMR-1 alone” in our study, inflating this group. However, based on the numbers, even with considerable underreporting of DTaP-IPV-Hib-3 before age 15 months there would still be
a large group left, who only received MMR-1 even though they had been eligible for MMR-1 and DTaP-IPV-Hib-3.

Children with immune defects or other absolute contraindications to MMR-1 vaccination were present in this study if they fulfilled the inclusion criteria, and would have led to a larger preference for DTaP-IPV-Hib. Nevertheless, such immune defects are rare and would not influence the proportions to any large extent.

We did not have information about change in vaccination provider or number of vaccination providers within each practice. Thus, we cannot determine whether the fact that no GP practices seemed to make the same choice every time reflects one vaccination provider making different choices on different occasions, or more vaccination providers within a practice who had different vaccination choices.

For the interviews, we aimed at including GP practices with different vaccination strategies, but the same limitation as mentioned above could apply.

The vaccination programmes differ between countries and the findings from the current study might not be directly comparable to other settings.

Health consequences of delayed vaccinations

With respect to the specific disease-protective effects of the vaccines, children who are not timely vaccinated have a greater risk at contracting pertussis and measles when there is an epidemic.\(^{15}\)

In addition to their specific effects, vaccines may have important non-specific effects.\(^{17,19}\)

A Danish study found that MMR-1 compared with DTaP-IPV-Hib-3 as the most recent vaccination was associated with a lower rate of admission for any type of infections.\(^{20}\)

Numbers were small, but indicated that if DTaP-IPV-Hib-3 was administered with or after
MMR-1, the same beneficial non-specific effect was not seen.\textsuperscript{20, 21} This supports the importance of receiving the vaccines at the recommended age and in the recommended schedule.

Timely vaccinations and vaccination coverage

The current study included children who had received DTaP-IPV-Hib-2 before age 15 months. Thus, we do not know how many children received no or only one dose of DTaP-IPV-Hib before age 15 months. However, the number of children included in the study indicates that at least 18\% of Danish children have not received DTaP-IPV-Hib-3 by age 15 months and only 26\% of these children are fully vaccinated by age 2 years. Studies from Norway, Belgium, and USA shows similar challenges with timely vaccinations\textsuperscript{5, 22, 23}. One possibility for improving vaccination coverage is to ensure that children lacking vaccines are vaccinated with all lacking vaccines at the first vaccination opportunity. We found that this rarely occurs when both DTaP-IPV-Hib-3 and MMR-1 are lacking for Danish children. This is in line with findings from other studies of occurrence of missed vaccination opportunities\textsuperscript{24, 25}. To overcome this non-compliance, the present study indicates that it would be important to address vaccination providers’ reluctance to give three injections at the same visit and their priority of following the sequence of vaccines. A few of the informants said that parental preference for only one vaccine at a time could also make them deviate from the guidelines. The parents’ wishes regarding vaccination of their child should be respected. However, information about the vaccines can be communicated to the parents in many ways, and perhaps an approach that is not only based on evidence and statistics but narrative communication of the nature of vaccine-preventable diseases and how they affected children and families before the vaccination
era. Some informants placed “lack of child cooperation” as a reason why they did not administer MMR-1 and DTaP-IPV-Hib-3 simultaneously. Pain, anxiety, and stress are crucial factors regarding children’s cooperation and several things can ensure optimal cooperation. A review from 2009 provided advices that could easily be implemented in the daily routines; upright positioning of the child, stroking the skin close to the vaccination before and during vaccination, and most importantly in relation to our study: when multiple vaccines are injected sequentially, choosing the least painful vaccine first. Other studies have shown some beneficial effect of topical anaesthetics.

Increasing the vaccination coverage has a high priority for the Danish health authorities and in May 2014 a programme was initiated where written reminders are sent to parents of children aged 2, 6.5 and 14 years, who are lacking any of the vaccines recommended for the specific ages. The primary analysis of this initiative indicates a positive effect on vaccination coverage. However, that programme focuses only on catching up. Our study indicates that some of the children might be delayed earlier on, indicated by the median age of DTaP-IPV-Hib-1 and DTaP-IPV-Hib-2. The information to the parents regarding timely vaccinations may not be clear enough and maybe further proactive initiatives should be considered. The DVR provides a unique platform with information on all given vaccines that could be used for generating electronic reminders by mail and/or SMS before scheduled vaccination dates. These could be supplemented by follow-up reminders in case of delay. Noteworthy, by improving the timeliness of DTaP-IPV-Hib-1-3, all children would end up having MMR-1 only as their most recent vaccination, and this may be associated with additional health benefits.

CONCLUSION
This study revealed high compliance with the guidelines regarding minimum intervals between DTaP-IPV-Hib-2 and DTaP-IPV-Hib-3 among Danish vaccination providers. However, there was a low compliance regarding simultaneous administration of DTaP-IPV-Hib-3 and MMR-1 if 6 months or more had passed since vaccination with DTaP-IPV-Hib-2. The qualitative interviews suggested that contributing factors could be vaccination providers’ reluctance towards providing multiple injections, and a preference for following the vaccination sequence in the vaccination programme. Further efforts are needed to improve the timeliness and coverage of vaccines in the Danish Childhood Vaccination Programme.
This work was supported by the Danish Council for Independent Research [grant number DFF- 4183-00316 to S. S.]. The Danish National Research Foundation (DNRF) supports the Research Center for Vitamins and Vaccines [grant number DNRF108]. The funding bodies had no role in the design of the study and collection, analysis, and interpretation of data and in writing of the manuscript.

ACKNOWLEDGEMENTS

Authors’ contributions

KBP, MEH, AKGJ, CHS, CSB, TGK and SS conceptualized and designed the study; AKGJ, CHS, TGK and SS acquired the data; KBP, MEH, AKGJ, and SS analyses the data from the Danish Vaccination Register; CHS and SS analysed the data from the semi-structured telephone interviews; KBP, MEH, AKGJ, CHS, CSB, TGK and SS interpreted the results. KBP and MEH wrote the first draft; KBP, MEH, AKGJ, CHS, CSB, TGK and SS revised the manuscript critically for important intellectual content. All authors approved the final submitted version.

CONFLICTS OF INTERESTS

None declared
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13. Holt N, Mygind A and Bro F. Danish MMR vaccination coverage is considerably higher than reported. Dan Med J 2017; 64.


Table 1. Vaccinations for children aged 15 to 24 months according to time since DTaP-IPV-Hib-2.

<table>
<thead>
<tr>
<th>Time since DTaP-IPV-Hib-2 at the third vaccination visit</th>
<th>&lt;6 MONTHS</th>
<th>6 MONTHS+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine received at the third vaccination visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTaP-IPV- Hib-3 (%) (N)</td>
<td>4.6 (1,830)</td>
<td>54.0 (47,760)</td>
</tr>
<tr>
<td>MMR-1 (%) (N)</td>
<td>94.6 (37,892)</td>
<td>38.9 (34,375)</td>
</tr>
<tr>
<td>DTaP-IPV-Hib-3 (%) (N)</td>
<td>0.8 (338)</td>
<td>7.2 (6334)</td>
</tr>
<tr>
<td>Vaccine received at the third vaccination visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTaP-IPV-Hib-3 (%) (N)</td>
<td>4.8 (984)</td>
<td>54.2 (25,120)</td>
</tr>
<tr>
<td>MMR-1 (%) (N)</td>
<td>94.4 (19,284)</td>
<td>38.4 (17,783)</td>
</tr>
<tr>
<td>DTaP-IPV-Hib-3 and MMR-1 (%) (N)</td>
<td>0.8 (166)</td>
<td>7.4 (3,419)</td>
</tr>
<tr>
<td>PR for DTaP-IPV-Hib-3 and MMR-1 (%) simultaneously (95% CI)</td>
<td></td>
<td>1.06 (1.01-1.11)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys; N=66,756</td>
<td>4.8 (984)</td>
<td>54.2 (25,120)</td>
</tr>
<tr>
<td>Girls; N=61,773</td>
<td>4.3 (846)</td>
<td>53.7 (22,640)</td>
</tr>
<tr>
<td>Age in months at third vaccination visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at third vaccination visit</td>
<td></td>
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</tr>
<tr>
<td>All</td>
<td>4.6 (1,830)</td>
<td>54.0 (47,760)</td>
</tr>
<tr>
<td>Boys; N=66,756</td>
<td>4.8 (984)</td>
<td>54.2 (25,120)</td>
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<tr>
<td>Girls; N=61,773</td>
<td>4.3 (846)</td>
<td>53.7 (22,640)</td>
</tr>
<tr>
<td>Months since DTaP-IPV-Hib-2</td>
<td>N</td>
<td>4.6 (971)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---</td>
<td>-----------</td>
</tr>
<tr>
<td>15; N=54,981</td>
<td>16; N=29,910</td>
<td>4.0 (454)</td>
</tr>
<tr>
<td>16; N=29,910</td>
<td>17; N=16,089</td>
<td>4.7 (252)</td>
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<td>17; N=16,089</td>
<td>18; N=9,677</td>
<td>6.6 (131)</td>
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<td>20; N=4,195</td>
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<td>20; N=4,195</td>
<td>21; N=3,048</td>
<td>-</td>
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<tr>
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<td>-</td>
</tr>
<tr>
<td>22; N=2,133</td>
<td>23; N=2,265</td>
<td>-</td>
</tr>
</tbody>
</table>

**Months since**

**DTaP-IPV-Hib-2**

<2; N=1,294

| 6.6 (86) | 92.7 (1,199) | 0.7 (9) | - | - | - |

2 and 3; N=28,520

| 2.6 (741) | 96.8 (27,605) | 0.6 (174) | - | - | - |

4 and 5; N=10,246

| 9.8 (1,003) | 88.7 (9,088) | 1.5 (155) | - | - | - |

6 and 7; N=4,195

<p>| - | - | - | 47.8 (3,984) | 46.3 (3,861) | 6.0 (489) | 0.87 (0.79-0.96) |</p>
<table>
<thead>
<tr>
<th>Vaccination</th>
<th>period</th>
<th>N=8,344</th>
<th>N=19,998</th>
<th>N=40,631</th>
<th>N=19,496</th>
<th>N=9,064</th>
<th>N=48,232</th>
<th>N= 71,233</th>
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</thead>
<tbody>
<tr>
<td>8 and 9;</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>68.5 (13,702)</td>
<td>6.1 (1,227)</td>
<td>0.99 (0.93-1.06)</td>
</tr>
<tr>
<td>10 and 11;</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50.8 (20,646)</td>
<td>6.7 (2,702)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>&gt;=12;</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>48.4 (9,428)</td>
<td>9.8 (1,906)</td>
<td>1.27 (1.17-1.37)</td>
</tr>
</tbody>
</table>

**Vaccination period**

<table>
<thead>
<tr>
<th>1.1.2000-</th>
<th>30.6.2002;</th>
<th>6.6 (219)</th>
<th>92.8 (3,063)</th>
<th>0.6 (20)</th>
<th>63.4 (3,653)</th>
<th>31.5 (1,813)</th>
<th>5.1 (296)</th>
<th>0.67 (0.59-0.75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.7.2002-</td>
<td>30.9.2007;</td>
<td>4.4 (676)</td>
<td>95.6 (4,750)</td>
<td>1.0 (153)</td>
<td>48.0 (15,671)</td>
<td>44.0 (14,359)</td>
<td>8.0 (2,623)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>1.10.2007-</td>
<td>30.6.2015;</td>
<td>4.4 (935)</td>
<td>94.8 (20,079)</td>
<td>0.8 (165)</td>
<td>56.8 (28,436)</td>
<td>36.4 (18,203)</td>
<td>6.8 (3,415)</td>
<td>0.85 (0.80-0.88)</td>
</tr>
</tbody>
</table>

26
<table>
<thead>
<tr>
<th>Province</th>
<th>N</th>
<th>4.6 (480)</th>
<th>94.6 (9,972)</th>
<th>0.8 (99)</th>
<th>54.5 (12,784)</th>
<th>37.6 (8,825)</th>
<th>7.9 (1,847)</th>
<th>1 (ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copenhagen;</td>
<td>N=33,996</td>
<td>4.7 (129)</td>
<td>94.5 (2,622)</td>
<td>0.8 (22)</td>
<td>54.1 (3,577)</td>
<td>39.1 (2,586)</td>
<td>6.8 (447)</td>
<td>0.85 (0.77-0.94)</td>
</tr>
<tr>
<td>Northern Sealand; N=9,383</td>
<td></td>
<td>3.3 (51)</td>
<td>96.2 (1,472)</td>
<td>0.5 (7)</td>
<td>51.0 (1,758)</td>
<td>42.8 (1,477)</td>
<td>6.2 (214)</td>
<td>0.83 (0.77-0.94)</td>
</tr>
<tr>
<td>Eastern Sealand; N=4,979</td>
<td></td>
<td>5.7 (213)</td>
<td>93.2 (3,526)</td>
<td>1.1 (43)</td>
<td>52.4 (4,420)</td>
<td>39.5 (3,332)</td>
<td>8.2 (689)</td>
<td>1.03 (0.95-1.12)</td>
</tr>
<tr>
<td>Southwest Sealand; N=12,223</td>
<td></td>
<td>4.4 (157)</td>
<td>94.9 (3,369)</td>
<td>0.7 (26)</td>
<td>53.5 (3,930)</td>
<td>40.4 (2,967)</td>
<td>6.2 (455)</td>
<td>0.79 (0.71-0.87)</td>
</tr>
<tr>
<td>Funen; N=10,904</td>
<td></td>
<td>4.3 (254)</td>
<td>94.9 (5,656)</td>
<td>0.8 (52)</td>
<td>52.5 (6,380)</td>
<td>41.0 (4,990)</td>
<td>6.5 (793)</td>
<td>0.83 (0.77-0.90) &lt;0.001</td>
</tr>
<tr>
<td>Eastern Jutland; N=18,125</td>
<td></td>
<td>5.3 (174)</td>
<td>93.7 (3,095)</td>
<td>1.0 (33)</td>
<td>59.1 (5,037)</td>
<td>34.0 (2,897)</td>
<td>6.9 (585)</td>
<td>0.86 (0.79-0.94)</td>
</tr>
<tr>
<td>Northern Jutland; N=11,821</td>
<td></td>
<td>4.0 (208)</td>
<td>95.3 (4,872)</td>
<td>0.7 (34)</td>
<td>54.5 (6,209)</td>
<td>38.9 (4,428)</td>
<td>6.7 (765)</td>
<td>0.85 (0.78-0.92)</td>
</tr>
<tr>
<td></td>
<td>DTaP-IPV-Hib-3</td>
<td>MMR-1</td>
<td>PR</td>
<td>CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western Jutland; N=9,895</td>
<td>4.8 (158)</td>
<td>94.2 (3,107)</td>
<td>1.0 (32)</td>
<td>51.2 (3,377)</td>
<td>41.2 (2,715)</td>
<td>7.7 (506)</td>
<td>0.96 (0.88-1.06)</td>
<td></td>
</tr>
<tr>
<td>Bornholm N= 630</td>
<td>2.7 (5)</td>
<td>97.3 (178)</td>
<td>0.0 (0)</td>
<td>60.6 (271)</td>
<td>32.4 (145)</td>
<td>6.9 (31)</td>
<td>0.88 (0.63-0.87)</td>
<td></td>
</tr>
<tr>
<td>Missingb N=57</td>
<td>4.0 (1)</td>
<td>92.0 (23)</td>
<td>4.0 (1)</td>
<td>53.1 (17)</td>
<td>40.6 (13)</td>
<td>6.3 (2)</td>
<td>N/Ab</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DTaP-IPV-Hib: Inactivated vaccine against diphtheria, tetanus, pertussis, polio and *Haemophilus influenzae* type b; MMR-1: Live attenuated vaccine against measles, mumps and rubella; PR: prevalence ratio; CI: confidence intervals; N: number of children.

a PR of receiving DTaP-IPV-Hib-3 and MMR-1 simultaneously compared to a reference defined as DTaP-IPV-Hib-3 alone or MMR-1 alone. Estimated using log binomial regression and adjusted for all variables reported in the table.

b Children lacking information on province were not included in the log binomial regression.

c Wald test statistics examining if the specified variable is related to the prevalence of receiving DTaP-IPV-Hib-3 and MMR-1 simultaneously.
**Box 1. Condensation of arguments for different vaccination choices for children who were lacking both DTaP-IPV-Hib-3 and MMR-1 by 15 months of age, mentioned by 12 Danish vaccination providers during semi-structured telephone interviews, Spring 2016.**

<table>
<thead>
<tr>
<th>Vaccination choice and vaccination providers arguments for the choice</th>
<th>MMR-1</th>
<th>DTaP-IPV-Hib-3³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always simultaneously</td>
<td>Always MMR-1 regardless of maintenance of the minimum interval between DTaP-IPV-Hib-2 and -3</td>
<td>Follow the sequence</td>
</tr>
<tr>
<td>Simultaneously if minimum interval between DTaP-IPV-Hib-2 and -3 maintained</td>
<td>Want to ensure minimum interval between DTaP-IPV-Hib-2 and -3</td>
<td></td>
</tr>
<tr>
<td>To ensure best possible level of protection</td>
<td>Never give three injections at the same time</td>
<td>Never give three injections at the same time</td>
</tr>
<tr>
<td></td>
<td>More important to ensure immunity to measles, mumps, and rubella when already partially immune toward diphtheria, tetanus, pertussis, polio, and <em>Haemophilus influenzae</em> type b from</td>
<td></td>
</tr>
<tr>
<td>Factor</td>
<td>Argument</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Current epidemics of measles or pertussis</td>
<td>Measles epidemics</td>
<td></td>
</tr>
<tr>
<td>Travel abroad</td>
<td>Travel abroad</td>
<td></td>
</tr>
<tr>
<td>Parental preference for both vaccines at the same time</td>
<td>Parental preference for only one vaccine at a time</td>
<td></td>
</tr>
<tr>
<td>Parental preference for MMR</td>
<td>Parental preference for only one vaccine at a time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lacking child cooperation (reacting very negatively on vaccination)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lacking child cooperation (reacting very negatively on vaccination)</td>
<td></td>
</tr>
</tbody>
</table>

...At the time of the interviews, PCV-13 was also included in the Danish childhood vaccination programme to be given together with DTaP-IPV-Hib. All vaccination providers considered PCV-13 and DTaP-IPV-Hib as a joined vaccination, and no one considered splitting them up. Thus, they would consider giving all three vaccines (MMR, PCV-13, and DTaP-IPV-Hib), MMR alone, or PCV-13 and DTaP-IPV-Hib together.

Abbreviations: DTaP-IPV-Hib: Inactivated vaccine against diphtheria, tetanus, acellular pertussis, polio and Haemophilus influenzae type b (the number following this abbreviation indicate dose number); MMR: Live attenuated vaccine against measles, mumps, and rubella; PCV-13 :13-valent pneumococcal conjugate vaccine.

Note: The box includes all the arguments mentioned by at least one vaccination provider during the interviews. Often one provider used more arguments to derive at a decision. One provider could choose DTaP-IPV-Hib-3 if he/she found it most important to follow the sequence of vaccines in the...
ordinary programme. Another provider could choose MMR-1 if he/she found it most important the
provide immunity toward measles, mumps, and rubella compared with providing a modest
additional immunity toward diphtheria, tetanus, pertussis, polio and *Haemophilus influenzae* type b,
as the children already were partially immune toward these diseases, because of the two previous
DTaP-IPV-Hib vaccination. Though the providers might have a preferred choice this could be
altered or further enforced by special circumstances. E.g. current epidemics of the vaccine-
targeted diseases could influence the choice, as could children’s forthcoming travels abroad,
parental preferences, or lacking child cooperation during vaccination sessions.
Figure 1: Overview of the included children and their vaccination patterns from 15 months to 24 months of age.

Note: Percentage is calculated from the number in the previous box.

Abbreviations: DTaP-IPV-Hib: Inactivated vaccine against diphtheria, tetanus, pertussis, polio, and Haemophilus influenzae type b (the number following this abbreviation indicate dose number);
MMR-1: The first dose of the live attenuated vaccine against measles, mumps, and rubella; <6 months: Less than 6 months since receiving DTaP-IPV-Hib-2 at the third vaccination visit; 6 months+: 6 months or more since receiving DTaP-IPV-Hib-2 at the third vaccination visit; N: number of children.

Figure 2: Triplot of the proportion of vaccination visits resulting in administration of DTaP-IPV-Hib-3 and MMR-1 simultaneously, DTaP-IPV-Hib-3 alone, or MMR-1 alone for children with 6 months or more since DTaP-IPV-Hib2 at the third vaccination visit for each GP practise.

Note: The plot is based on data from 1661 GP practises, which had at least 25 different children having a vaccination visit more than 6 months after DTaP-IPV-Hib-2. Each cross in the plot represent one GP practise. The cross is placed on the coordinate that represents the joint distribution of the proportion of children vaccinated with DTaP-IPV-Hib-3 and MMR-1 simultaneously, the proportion of children vaccinated with DTaP-IPV-Hib-3 alone, and the proportion of children vaccinated with MMR-1 alone for each GP practise. The reading direction for the distribution of the vaccine choice is indicated by the arrows and the gridlines. E.g. a cross in the top apex would indicate that 100% of the children vaccinated by the GP practise had received DTaP-IPV-Hib-3 and MMR-1 simultaneously, 0% had...
received DTaP-IPV-Hib-3 alone, and 0% MMR-1 alone. Abbreviations: DTaP-IPV-Hib-3: Inactivated vaccine against diphtheria, tetanus, pertussis, polio and *Haemophilus influenzae* type b; MMR-1: Live attenuated vaccine against measles, mumps and rubella; GP: General Practitioner;
Online supplement for

How are children who are delayed in the Childhood Vaccination Programme vaccinated: A nationwide register-based cohort study of Danish children aged 15-24 months and semi-structured interviews with vaccination providers
Kenneth B Pedersen, Marie E Holck, Aksel K G Jensen, Camilla H Suppli, Christine S Benn, Tyra G Krause, Signe Sørup
**eTable 1.** Overview of the Danish Childhood Vaccination Programme for children below 2 years of age since 1.1.1997

<table>
<thead>
<tr>
<th>Recommended vaccination age</th>
<th>Date of change and the recommended vaccines</th>
<th>Interval between DTaP-IPV-Hib vaccines**</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>DTaP-IPV and Hib 1.1.1997</td>
<td>DTaP-IPV-Hib 1.7.2002</td>
<td>DTaP-IPV-Hib 1.10.2007</td>
<td>DTaP-IPV-Hib 19.4.2010</td>
</tr>
<tr>
<td>5 months*</td>
<td>DTaP-IPV and Hib 3 months</td>
<td>DTaP-IPV-Hib 1.7.2002</td>
<td>DTaP-IPV-Hib and PCV7 1.10.2007</td>
<td>DTaP-IPV-Hib and PCV13 19.4.2010</td>
</tr>
<tr>
<td>12 months*</td>
<td>DTaP-IPV and Hib 5 months*</td>
<td>DTaP-IPV-Hib 1.7.2002</td>
<td>DTaP-IPV-Hib and PCV7 1.10.2007</td>
<td>DTaP-IPV-Hib and PCV13 19.4.2010</td>
</tr>
<tr>
<td>15 months</td>
<td>MMR 12 months</td>
<td>MMR 1.7.2002</td>
<td>MMR 1.10.2007</td>
<td>MMR 19.4.2010</td>
</tr>
</tbody>
</table>

Abbreviations: DTaP-IPV: Inactivated vaccine against diphtheria, tetanus, pertussis, and polio; Hib: Inactivated vaccine against *Haemophilus influenzae* type b; DTaP-IPV-Hib: Inactivated vaccine against diphtheria, tetanus, pertussis, polio and *Haemophilus influenzae* type b; MMR-1: Live attenuated vaccine against measles, mumps and rubella; PCV7: 7-valent pneumococcal conjugate vaccine; PCV13 :13-valent pneumococcal conjugate vaccine.

* Simultaneously with a routine medical check-up performed by the general practitioner.

** Same interval for all vaccination years.
eMethods: Questionnaire for semistructured telephone interviews

The original interview guide was in Danish, below is the authors English translation.

1) About respondent
   a) What is your professional background?
   b) How long have you been employed in the practice?
   c) How large a proportion of the 15 months vaccinations do you perform, approximately?
2) Who else in your practice perform 15 months vaccinations?
   a) No one else
   b) Medical doctor
   c) Nurse
   d) Other
3) How many in total perform childhood vaccinations?
4) How do you perform a vaccination consultation?
   (Ticking off and additional comments to the different issues below based on the open question.
   Directly asked questions should be marked with A. Spontaneously reported should be marked with S)
   □ Check vaccination status
   □ Inform about vaccination and adverse events
   □ Address and discuss parental considerations/concerns
   □ Check the child's health status
   □ Check the parents expectation – what vaccine
   □ Other

5) Which factor do you in general include in your considerations about vaccination of a child above 15 months, who are lacking both MMR and the third dose of DTaP-IPV-Hib?
   (Ticking off and additional comments based on the open question. Focus on which vaccine is chosen and why. If some of the issues below are not mentioned, then you subsequently ask: We have considered that ...(lacking issue) might sometimes influence what you chose?
   S=Spontaneously reported ; A= Directly asked questions)

<table>
<thead>
<tr>
<th>Issue</th>
<th>A/S</th>
<th>&lt; 6 months since DTaP-IPV-Hib</th>
<th>&gt; 6 months since DTaP-IPV-Hib</th>
</tr>
</thead>
</table>
6) Which factors have the greatest impact on what you chose (and is there any difference according to time since the latest DTaP-IPV-Hib)?

<table>
<thead>
<tr>
<th>Time since DTaP-IPV-Hib</th>
<th>The child’s current health status (e.g. colds, fever)</th>
<th>The child’s potential chronic conditions</th>
<th>The child is born to early</th>
<th>Current epidemics (e.g. measles or pertussis)</th>
<th>Number of jabs the child should have</th>
<th>The parents attitudes/ideas/preferences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

_________________________________________________________________________________
_________________________________________________________________________________
_________________________________________________________________________________
7) Do you in general have any concerns in relation to vaccination with DTaP-IPV-Hib?

_________________________________________________________________________________
_________________________________________________________________________________
_________________________________________________________________________________
_________________________________________________________________________________

8) Do you experience that parents have any concerns in relation to vaccination with DTaP-IPV-Hib?

_________________________________________________________________________________
_________________________________________________________________________________
_________________________________________________________________________________
_________________________________________________________________________________

9) Do you in general have any concerns in relation to vaccination with MMR?

_________________________________________________________________________________
_________________________________________________________________________________
_________________________________________________________________________________
_________________________________________________________________________________

10) Do you experience that parents have any concerns in relation to vaccination with MMR?

_________________________________________________________________________________
_________________________________________________________________________________
_________________________________________________________________________________
_________________________________________________________________________________

Next is some questions on information regarding vaccination recommendations

11) Do you know recommendations in case of delayed vaccination?

_________________________________________________________________________________

(If yes on 11)

12) Where do you have your knowledge from?

_________________________________________________________________________________
_________________________________________________________________________________

13) If you have any doubts regarding which vaccines a delayed child should receive, where do you seek information?

_________________________________________________________________________________
_________________________________________________________________________________
14) How satisfied are you with the availability of information regarding how to handle children who are delayed according to the childhood vaccination program?
_________________________________________________________________________________
_________________________________________________________________________________

15) How satisfied are you with the content of the information?
_________________________________________________________________________________
_________________________________________________________________________________

16) If you could decide, how should you receive information regarding vaccination recommendations?
_________________________________________________________________________________
_________________________________________________________________________________

17) Does it affect your compliance if it is called a "vaccination recommendation" or a "vaccination instruction"?
_________________________________________________________________________________
_________________________________________________________________________________

18) Other comments?
_________________________________________________________________________________
_________________________________________________________________________________
**eFigure 1:** Median age with interquartile range and spread at vaccination per type of vaccine for children having less than 6 months, or 6 months or more between DTaP-IPV-Hib2 and their third vaccination visit.

**Abbreviations:** DTaP-IPV-Hib: Inactivated vaccine against diphtheria, tetanus, pertussis, polio, and Haemophilus influenzae type b. MMR-1: Live attenuated vaccine against measles, mumps and rubella; <6 months: Less than 6 months since receiving DTaP-IPV-Hib-2 at the third vaccination visit; 6 months+: 6 months or more since receiving DTaP-IPV-Hib-2 at the third vaccination visit; N: number of children.

**Note:** The gray box represents the interquartile ranges (values from the 25th percentile to the 75th percentile) and the horizontal line in the box is the median. The vertical lines outside the box ending in a horizontal line are defined as follows: the largest observed value less than the 75th percentile plus 1.5 times the interquartile range (upper line) and the lowest observed value above the 25th percentile minus 1.5 times the interquartile range (lower line). Dots outside these lines indicates extreme values.
eFigure 2. Overview of selection criteria, possible participating GP practices, and number of completed semi-structured interviews

Legend: Only GP practices which were registered as solo-practices (i.e. only one GP attached to the GP identification code) and who between January 1st 2000 to June 30th 2015 had vaccinated at least 25 children who were lacking both DTaP-IPV-Hib-3 and MMR-1 after 15 months of age and who had been vaccinated with DTaP-IPV-Hib2 for more than 6 months ago at the time of the vaccination visit.

*Each selected GP practice was contacted by telephone 3 times during regular office hours to arrange an interview.

Abbreviations: DTaP-IPV-Hib: Inactivated vaccine against diphtheria, tetanus, pertussis, polio, and Haemophilus influenzae type b (the number following this abbreviation indicate dose number); MMR-1: First dose of the live attenuated vaccine against measles, mumps, and rubella; GP: General Practitioner.
eResults:

Most informants used the homepage of Statens Serum Institut (www.ssi.dk) to obtain information about vaccination recommendations for delayed children, but some also mentioned the weekly newsletter “EPI-NYT” and the telephone hotline at the Department of Infectious Disease Epidemiology and Prevention at Statens Serum Institut as sources of information.

Most informants were satisfied with the availability and content of the information about vaccination of delayed children on the homepage, but it was mentioned that it could be difficult to navigate on the homepage and some information was missing.

Overall, some informants preferred information about vaccination guidelines on the homepage of Statens Serum Institut, while others preferred written information sent out by mail and others again the newsletter “EPI-NYT” sent out by e-mail. One informant found the telephone hotline important.

Some informants stated that their compliance would be the same irrespective of whether the term "vaccination recommendation" or the term "vaccination instruction" was used; some preferred "vaccination recommendation" and others "vaccination instruction".