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Evaluation of immunogenicity and effectiveness of low dose dTap-IPV vaccine used as booster in 4-8 year old children

A rapid literature review

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Preface

During the last years the demand for combination vaccines used in the National Immunization Programs (NIPs) have increased globally which has led to a shortage of acellular pertussis (aP) containing vaccines, including combination vaccines for primary and booster immunization. Vaccine shortages are expected to last until at least 2018.

During periods of vaccine shortage, the use of low dose dTap-IPV might be an alternative for the current use of full dose DTaP-IPV vaccines in the Norwegian and Swedish NIPs. The aim of this rapid literature review[1] was to identify studies to evaluate the possibility of a replacement for dose 4 in the Norwegian and Swedish NIPs, and furthermore to make an assessment of the consequences of such a vaccine switch. Each country will publish their separate recommendations based on this report.

The report is primarily intended for use by The Public Health Agency of Sweden, Norwegian Institute of Public Health, county councils, vaccine experts and the Medical Products Agency.

Studies identified in the literature search were reviewed by Jann Storsæter, Sara Viksmoen Watle, Tiia Lepp, Bernice Aronsson and Eva Netterlid. This report has been written by Jann Storsæter, Sara Viksmoen Watle and Emma Byström in close collaboration with a Scandinavian expert group (participants in this group were Ann Lindstrand, Ingrid Uhnoo, Marta Granström, Lennart Nilsson, Lena Wehlin, Åke Örtqvist, Helena Hervius-Askling, Sven-Arne Silfverdal, Tiia Lepp, Eva Netterlid, Tine Dalby, Audun Aase and Didrik Vestrheim).

The Public Health Agency of Sweden
Anders Tegnell

1 A presentation of the methodology used for the rapid reviews and the limitations for this methodology is found in Harker and Kleijnen Int J Evid Based Healthc 2012; 10:397-410

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Abbreviations

aP	Acellular pertussis
BCG	Bacillus Calmette-Guérin
DELFIA	Dissociation-enhanced lanthanide fluorescent immunoassay
DT	Diphtheria toxoid
DTaP-IPV	Full dose vaccine against diphtheria, tetanus, pertussis and polio
dTap-IPV	Low dose vaccine against diphtheria, tetanus, pertussis and polio
DU	D-antigen units
ECDC	European Centre for Disease Prevention and Control
EL.U	ELISA units
ELISA	Enzyme-linked immunosorbent assay
EQA	External Quality Assessment
FDA	Food and Drug Administration, USA
FHA	Filamentous hemagglutinin
FIM 2/3	Fimbriae type 2 and 3
GMC	Geometric Mean Concentration
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
GSK	GlaxoSmithKline
Hib	Haemophilus Influenzae, type b
IPV	Inactivated polio vaccine
IU	International units
Lf	Limit of flocculation
MEF-1	Middle East Forces 1
MSIS	Meldingssystem for smittsomme sykdommer (Norwegian Surveillance System for Communicable Diseases)
NACI	National Advisory Committee on Immunization
NIP	National Immunization Program
NIPH	Norwegian Institute of Public Health

NT	Neutralization test
PICO	Population, intervention, control and outcome
Prn	Pertactin
PT	Pertussis toxin
PV	Polio virus
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (The Dutch National Institute for Public Health and the Environment)
SMI	Smittskyddsinstitutet (Swedish Institute for Communicable Disease Control)
SP	Sanofi Pasteur
SPC	Summary of Product Characteristics
SSI	Statens Serum Institut, Denmark
SYSVAK	Nasjonalt vaksinasjonsregister SYSVAK (Norwegian Immunisation Registry SYSVAK)
ToBI	Toxin binding inhibition
TT	Tetanus toxoid

Glossary

Booster immunization	Dose given at a time interval after priming doses in order to enhance immunity and protection against disease.
GRADE	Grading of Recommendations, Assessment, Development and Evaluation (GRADE). A methodology to assess the reliability of studies and to rank them according to level of evidence.
Immunogenicity	The capability of a substance to induce an immune response
Incidence	The number of new cases of a particular disease occurring during a defined period of time. Usually written as the number of cases per 100 000 population and year.
NIP	Government program of immunization charged with preventing disease, disability and death from vaccine-preventable diseases.
PICO	Framework to define and specify research questions. Questions always include a population, an intervention, a control group and outcome to meet the aim of the study.
Seroepidemiological studies	Studies of immunity among a sample of the population. Studies are conducted by measuring the levels of serum antibodies against specific antigens.
Vaccine effectiveness	Measure of protection by vaccination in a real life setting, usually outside of a randomized clinical trial
2+1 schedule	Basic immunization schedule for aP-containing vaccines with two primary and one early booster dose during the first two years of life. This schedule is used in Sweden and Norway where primary doses are given at 3 and 5 months and a booster dose at 12 months.
3+1 schedule	Basic immunization schedule for aP-containing vaccines with three primary and one early booster dose during the first two years of life. This schedule is used in several European countries and the US and the timing of vaccination varies between countries.

Summary

Due to an increased global demand for acellular pertussis combination vaccines, Nordic countries have been facing vaccine shortages in national immunization programs which will last until at least 2018. Temporary changes in recommendations for the use of vaccines may be needed.

The main aim of this report was to analyze whether low dose dTap-IPV vaccines might replace the full dose booster in 4-8 year old children during a period of limited access to full dose DTaP-IPV vaccines. The report was based on a rapid review of literature published between 1990 and September 2016. Only data on immunogenicity and effectiveness were reviewed and vaccine safety data were not included in the search strategy.

The review revealed studies on three different full dose DTaP-IPV vaccines, of which only two are marketed in Europe. Full dose vaccines represents today's "standard of care" as a booster dose at school entry in the Norwegian and Swedish NIPs. There were also data on three different low dose dTap-IPV vaccines, all of which are marketed in Europe.

With the limited data on immunogenicity and effectiveness for low dose dTap-IPV vaccines, it is questionable whether there is sufficient evidence for use of these vaccines as replacement for the full dose DTaP-IPV vaccines presently used as booster dose in 4-8 year old (dose 4) in the Norwegian and Swedish vaccination schedules. The preferred option for the Norwegian and Swedish NIPs should be to continue with full dose DTaP-IPV vaccine as dose 4. In case of a temporary shortage of full dose DTaP-IPV vaccine, it will be difficult to make firm conclusions regarding a switch to low dose dTap-IPV vaccine, and changes to the immunization schedule might be needed.

Background

During the last years the demands for combination vaccines used in NIPs have increased globally. The increased demand and production problems in particular with aP-containing vaccines, have led to a shortage of these vaccines for primary and booster immunization. Vaccine shortages are still affecting several countries in the world including countries in Europe. Since the end of 2014, there has been backordering of vaccines used in the Norwegian and Swedish NIPs. According to prognoses from pharmaceutical companies, the risk of vaccine shortage will stand until at least 2018.

In advance of periods of vaccine shortage, temporary changes in recommendations for the use of vaccines may be needed. According to a joint recommendation from the Swedish Association of Local Authorities and Regions and the Public Health Agency of Sweden, available vaccines should be prioritized to infants during periods of vaccine shortage. Infants are in greatest need of protection with vaccines included in the NIP. In particular, the youngest infants are at risk of severe and sometimes life-threatening illness caused by pertussis.

Full dose vaccines against diphtheria and tetanus have been used in Norway and Sweden since the 1940s. Full dose vaccines are now used as basic immunization in immunization programs for infants and young children. The challenge has been to secure an effective booster response with minimum adverse reactions, and low dose vaccines have been developed to ensure long term immunity with acceptable reactogenicity even after repeated doses[2]. Low dose vaccines are used as boosters for adolescents and adults.

Full dose DTaP-IPV vaccines regularly contain ≥ 30 international units (IU) diphtheria toxoid and ≥ 40 IU tetanus toxoid per 0.5 ml vaccine dose. Low dose dTap-IPV vaccines contain various amounts of antigens, but less diphtheria (≥ 2 IU) and tetanus (≥ 20 IU) than full dose DTaP-IPV vaccines. Full dose vaccines contain 20-25 µg PT and low dose vaccines range between 2.5-20 µg per dose. The amounts of polio antigens are the same in full- and low dose vaccines. An overview of vaccine contents are listed in Table 1.

In advance of a possible risk of vaccine shortage, there is a need to evaluate the possible use of low dose dTap-IPV vaccines as replacement for full dose DTaP-IPV vaccines as dose 4 in the Norwegian and Swedish NIPs (Table 2 and 3). The consequences of such a switch need to be assessed.

[2] Ref Anders Mark, Studies on adjustments in the Swedish DTP vaccination programme, Thesis, Gothenburg University 1993

Aims

Main aim

Immunogenicity and effectiveness

Collect and present data retrieved from a literature review on immunogenicity and effectiveness for various full dose DTaP-IPV and low dose dTap-IPV combination vaccines used as a booster in children 4-8 years of age previously primed with aP-containing vaccine in a 2+1 or 3+1 schedule. The different low dose dTap-IPV vaccines should be compared with full dose DTaP-IPV vaccines as a benchmark and, where meaningful, the results should be evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework[3].

Secondary aims

a) Vaccine availability and use in European NIPs

To present the currently available DTaP-IPV and dTap-IPV vaccines and identify which of these vaccines that are in use as dose 4 or 5 in the age group 4-8 years in NIPs in European countries.

b) Evaluation of laboratory methods used

Briefly evaluate laboratory methods used in the studies included and to what extent immunogenicity data from these studies may be comparable between laboratories.

c) Discussion of consequences of a possible temporary vaccine switch

Briefly discuss possible consequences of temporary replacing full dose DTaP-IPV vaccine with different low dose dTap-IPV vaccines as dose 4 in the Norwegian and Swedish immunization programs. Furthermore, whether such a replacement would indicate a need for seroepidemiological studies and/or extra vaccine doses later in life.

[3] A description of the framework of GRADE is found in GRADE working group BMJ 2004;328:1490-4

Methods

Main aim

Immunogenicity and effectiveness

This report was based on a rapid, systematic literature review of studies and reviews published between 1990 - September 2016. A literature search was performed 2016-10-06 and articles were retrieved from PubMed, Cochrane Library and Scopus. The search strategy combined controlled vocabulary and free text terms and included words such as: child, preschool, booster, vaccine, vaccination, immunization, diphtheria-tetanus-pertussis vaccine, inactivated poliovirus vaccine. The complete search strategy is listed in Appendix 1. Only articles in English were included.

The articles of the literature search were exported to an EndNote library. As a first selection, title and abstract were reviewed. The search results were divided among four researchers and a fifth researcher reviewed all of the titles and abstracts of included articles. Each abstract was read by at least two persons. Articles were included or excluded based on the exclusion criteria. Disagreements were resolved through discussions among the researchers.

In this report PICO[4] was defined as shown in the box below:

P (Population) = Children primed with acellular pertussis combination vaccines in a 2+1 or 3+1 schedule, and boosted at age 4-8 years

I (Intervention) = Low dose dtap-IPV or full dose DTaP-IPV booster at 4-8 years

C (Comparison) = Control groups in clinical trials / historical controls

O (Outcome) = Immunogenicity or effectiveness

Articles were excluded according to the following criteria:

- Age at booster vaccination with DTaP-IPV/dTap-IPV less than 4 years or more than 8 years
- Primary immunization schedule other than 2+1 or 3+1
- Previously received whole cell pertussis vaccine
- DTaP/dTap and IPV given as two separate injections

Data from studies on full dose vaccines were used as benchmark, and data on low dose vaccines were compared individually to this benchmark.

[4] SBU. Utvärdering av metoder i hälso- och sjukvården - en handbok, Faktaruta 3.1
http://www.sbu.se/globalassets/ebm/metodbok/sbushandbok_kapitel03.pdf

Data on immunogenicity was presented using geometric mean concentration (GMC). Fold-rise and percentages over a putative protective antibody level were not presented as these data were not available in all studies included.

When assessing immunogenicity, general consensus regarding quantitative antibody levels required for long term protection after vaccination for the different antigens included in the vaccines was taken into account (Table 4). For diphtheria, tetanus and polio, there is consensus on the required level of antibody. However, for pertussis exact level of protection has not been determined.

When assessing effectiveness, data were considered from countries that fulfilled the following criteria:

- Only one brand of DTaP-IPV/dTap-IPV vaccine had been used in the NIP as dose 4 or 5 for 4-8 year old children for a prolonged period of time (more than five years).
- The country has had a nationwide surveillance system to provide reliable age-specific pertussis incidence numbers before and after the booster vaccine introduction.

When estimating the effectiveness of preschool booster as an intervention, the formula below was used[5].

$$\text{Vaccine effectiveness} = \frac{\text{Risk unvaccinated group - Risk vaccinated group}}{\text{Risk unvaccinated group}} \times 100\ \%$$

Judgement about the quality of evidence with GRADE was based on the framework described by the GRADE Working Group, see footnote page 14.

GRADE evaluations are primarily based on study design. The studies evaluated are given a number of points on a scale from one to four plus (⊕). Randomized studies typically start with ⊕ ⊕ ⊕ ⊕ and the GRADE is reduced if there are problems with study quality, inconsistencies, imprecision or high probability of reporting bias. Typically such problems will reduce the number of points with one ⊕ for each of the above elements. Points can also be added if there is strong evidence of association based on consistent evidence from two or more studies with no plausible confounders.

Overall quality of evidence was defined using the following terms:

- *High* (⊕⊕⊕⊕) = Further research is very unlikely to change our confidence in the estimate of effect.

[5] Principles of Epidemiology in Public Health Practice, Third Edition, An Introduction to Applied Epidemiology and Biostatistics, Center for Disease Control and Prevention.
https://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson3/section6.html

- *Moderate* (⨁⨁⨁) = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- *Low* (⨁⨁) = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- *Very low* (⨁) = Any estimate of effect is very uncertain.

Secondary aims

a) Vaccine availability and use in European NIPs

In addition to literature search as mentioned above, direct contact was made with vaccine producers and with European Centre for Disease Prevention and Control (ECDC) in order to obtain an updated overview of DTaP-IPV and dTap-IPV vaccines used for 4-8 year old children in Europe.

b) Evaluation of laboratory methods used

Analyses on immunogenicity have been conducted by different laboratories. Methods and assays used in these laboratories were evaluated against each other in order to make assumptions regarding comparability between results from different laboratories.

c) Discussion of consequences of a possible temporary vaccine switch

Analysis of consequences of a vaccine switch was essentially outside the scope of this literature review which by necessity had to be retrospective. Possible scenarios and recommendations are found in Appendix 2 and need to be further discussed in a larger forum.

Results

Vaccine availability and use in European NIPs (Secondary aim a)

NIPs differ between countries with respect to use of full dose DTaP-IPV or low dose dTap-IPV vaccines for booster immunization in the age group 4-8 years[6].

For the age groups of interest in this report (4-8 years of age), the situation in Europe regarding booster vaccine can be summarized as follows:

- Full dose DTaP-IPV vaccines are used in Austria, Belgium, Finland, Iceland, Portugal, Norway, Sweden, France and Switzerland (also used in Australia, Canada and New Zealand). Most countries have more than one brand of DTaP-IPV on the market simultaneously.
- Low dose dTap-IPV vaccines are used in Denmark and Israel, and were recently introduced in the NIPs in Ireland and the Netherlands.

A very limited number of European countries have consistently used only one brand of booster vaccine for a prolonged period of time in the age group 4-8 years. The crude intervention effectiveness of the introduction of DTaP-IPV booster vaccine could be evaluated in Norway and Finland. Both these countries had used Tetravac® for a long time period.

Effectiveness data could also be obtained for low dose dTap-IPV vaccine from Israel where Boostrix-Polio® was used, and from Denmark where DiTeKiPol Booster® was used.

Immunogenicity and effectiveness (Main aim)

Results of literature review

The literature search yielded a total of 4334 articles after duplicates had been excluded. A total of 22 articles were included from Cochrane Library, 3667 articles from PubMed and 645 articles from Scopus.

The review did not aim to evaluate data on reactogenicity or safety.

It was decided that the review did not aim to compare different full dose vaccines with each other. Likewise, different low dose vaccines should not be compared with each other. The low dose vaccines should not be analyzed as a group. Comparisons of low dose to full dose vaccines should be vaccine specific.

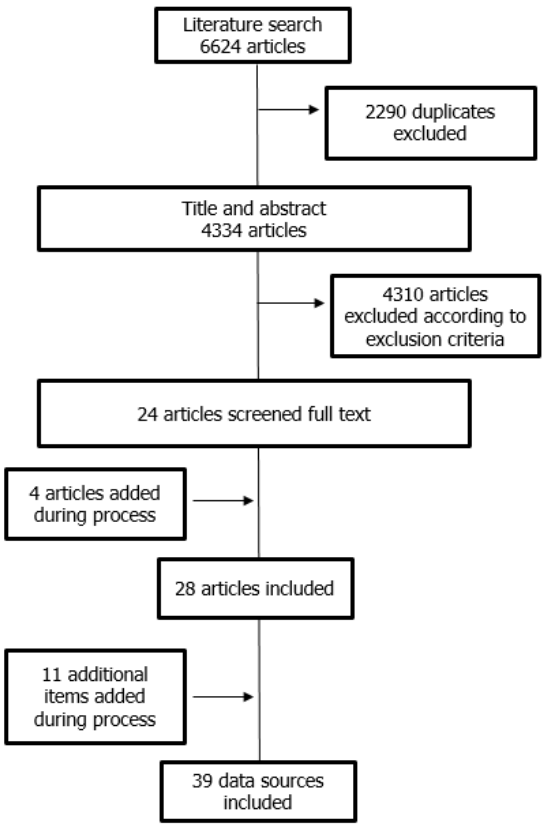
The final result of the literature search resulted in that twenty-four articles were selected and screened for full text by the research team.

[6] Libster R, Edwards KM. Re-emergence of pertussis: what are the solutions? Expert review of vaccines. 2012;11(11):1331

During the process, reference lists of included articles were scrutinized for possible additions. Experts were approached and some "grey literature" like posters and unpublished communications were included.

Altogether, four additional articles and 11 additional items were included during the process (Figure). The 11 additional items were one unpublished clinical report (n = 1), one earlier clinical report (n = 1) published electronically for a limited time period, newsletters (n = 2), data extraction from national surveillance systems in Norway and Finland (n = 2) and summary of product characteristics (SPC) (n = 5).

Figure Results of literature review



Immunogenicity and effectiveness

Data on immunogenicity for both full dose DTaP-IPV and low dose dTap-IPV vaccines revealed essentially consistent high antibody levels against tetanus and the three polio viruses, while antibody levels against diphtheria and pertussis demonstrated greater variation. All dTap-IPV vaccines contain PT in variable amounts, and in addition other pertussis antigens, which vary in numbers by vaccine. Since the only common antigen is PT, we have focused on this antigen. Previous studies indicate that anti-PT antibodies are of importance for protection and anti-PT recall responses are regarded as good markers of vaccine response not

confounded by cross-reactive bacteria[7]. It was decided to restrict comparisons between vaccines and to focus on anti-DT and anti-PT levels in the current report. Reported results on levels for the other vaccine antigens can be found in the tables on immunogenicity for each vaccine (Tables 5-7 and 9-11).

Full dose vaccines have been used for many years at school entry in both Norway and Sweden. The data on full dose vaccines was regarded as benchmark against which data from individual low dose dTap-IPV vaccines were compared.

Full dose vaccines

Vaccine specific overview for full dose DTaP3-IPV vaccine (Infanrix-Polio® /Kinrix®)

Data sources

Data in this part was based on immunogenicity studies (1-7), epidemiological studies and reviews (8-11).

Vaccine content and trade names

DTaP3-IPV is a full dose vaccine licensed as Infanrix-Polio® or Kinrix®. Each 0.5-mL dose of the vaccines is formulated to contain ≥ 30 IE (25 Lf) of diphtheria toxoid, ≥ 40 IE (10 Lf) of tetanus toxoid, 40 D-antigen Units (DU) of Type 1 poliovirus (Mahoney), 8 DU of Type 2 poliovirus (MEF-1), and 32 DU of Type 3 poliovirus (Saukett). The vaccine also contains *three* pertussis antigens with 25 mcg of inactivated pertussis toxin (PT), 25 mcg of filamentous hemagglutinin (FHA) and 8 mcg of pertactin (12).

Immunogenicity one month after booster

In an open, randomized study, Nilsson et al studied Italian and Swedish children previously vaccinated in a 2+1 primary schedule at 3, 5 and 12 months of age (1). At 4-6 years of age, they were randomized to receive dose 4 either as DTaP3-IPV (Infanrix-Polio®) or injections of DTaP3 and IPV separately. Immunogenicity for all antigens was assessed at GSK laboratories in Belgium. GMC for anti-DT was 6.2 IU/ml and anti-PT 63 EL.U/ml (Table 5).

Immunogenicity results for children with a 3+1 primary schedule were obtained from a series of open, randomized clinical studies, performed in Australia and USA using DTaP3-IPV (Infanrix-Polio®/Kinrix®) as a preschool booster, dose 5 (2-4, 6). Dose 4 had been given during the second year of life. Samples were analyzed either at GSK laboratories in Belgium or at the Pichichero lab in Rochester, NY, USA. Results for GMC for anti-DT ranged from 5.9 to 17.9 IU/ml and anti-PT from 63 to 111 EL.U/ml.

In cross-sectional studies, Schure et al and Hendrikx et al assessed immunogenicity after DTaP3-IPV (Infanrix-Polio®) had been given as a booster, dose 5, to 4-6 year

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7 Eberhardt and Siegrist Cold Spring Harb Perspect Biol 2017 Mar 13 pii: a029629. doi: 10.1101/cshperspect.a029629.

old Dutch children previously vaccinated in a 3+1 primary schedule with the first booster given at 11 months of age (5, 7). Only antibodies against pertussis antigens were reported. Analyses were performed at the RIVM laboratories in the Netherlands. GMC for anti-PT were 187 and 192 EL.U/ml respectively, and were markedly higher compared to the studies mentioned above (Table 5).

Duration of immunity

Schure et al also analyzed pertussis immune response in a cross sectional study in 61 children two years after the booster. Anti-PT GMC had then decreased to 26 EL.U/ml (Table 6). The authors propose that values were somewhat higher than expected due to the epidemiological situation with widespread circulation of *Bordetella pertussis* in the Dutch population and the increased incidence of pertussis in the entire decade before 2009 (5).

Furthermore, Dutch researchers at RIVM have also conducted a series of cell-mediated immunity studies (7, 13). According to personal communication with RIVM, a more complete report summarizing data from all of these studies is in progress and preliminary results are confidential until publication.

Vaccine effectiveness

We have not identified any published studies regarding vaccine effectiveness against pertussis after introduction of DTaP3-IPV at school entry or preschool age. However, Dutch researchers recently published some limited age-specific incidence data on cohorts that had received DTaP3-IPV (Infanrix-Polio®) as preschool booster at 4 years of age. A series of changes were instituted into the Dutch NIP during the years 2001 to 2011. After using low dose dTap5-IPV (Triaxis-Polio) for a short period, a switch was made to DTaP3-IPV (Infanrix-Polio®) in February 2008 for children born on or after February 2004. For the yearly cohorts vaccine effectiveness has been estimated by the "screening" method. The Dutch investigators emphasize that the estimate should not be interpreted as "true" absolute efficacy or effectiveness, but might be used to study trends. For the 2004 cohort the effectiveness estimates were 84 %, 89 %, 67 %, 72 % and 69 % at respectively 5, 6, 7, 8 and 9 years of age (14). According to the report, there were indications that vaccine induced protection against pertussis is of limited duration, about five years (14).

Vaccine specific overview for full dose DTaP2-IPV vaccine (Tetravac®/Tetraxim®)

Data sources

Data in this part was based on immunogenicity studies (15-18) and epidemiological data from Norway and Finland (19-21).

Vaccine content and trade names

DTaP2-IPV is a full dose vaccine licensed as Tetravac® or Tetraxim®. Each 0.5-mL dose of the vaccines is formulated to contain ≥ 30 IE (25 Lf) of diphtheria toxoid, ≥ 40 IE (10 Lf) of tetanus toxoid, 40 D-antigen Units (DU) of Type 1 poliovirus (Mahoney), 8 DU of Type 2 poliovirus (MEF-1), and 32 DU of Type 3 poliovirus (Saukett). The vaccine also contains *two* pertussis antigens with 25 mcg

of inactivated pertussis toxin (PT) and 25 mcg of filamentous hemagglutinin (FHA) (22).

Immunogenicity one month, respective 1-100 days, after booster

In a phase IV open trial in Thailand, Pancharoen et al evaluated immunogenicity of booster vaccination with DTaP2-IPV (Tetraxim®) in 4-6 year olds. The Thai children were previously vaccinated with pentavalent acellular DTaP2-IPV+Hib in a 3+1 schedule with the first booster at 18-19 months of age (17). Immunogenicity data were analyzed at Sanofi Pasteur Swiftwater, PA, USA. One month after booster, anti-DT GMC was measured to 7.8 IU/ml and anti-PT GMC to 190 EL.U/ml (Table 7).

In an open multi-center study in France, Mallet et al examined serological response after a booster dose with DTaP2-IPV (Tetravac®) in 5-6 year olds. The French children were previously immunized with DTaP2-IPV+Hib in a 3+1 schedule (15). The first booster was given at 12-16 months of age. Sanofi Pasteur, France performed the assays showing anti-DT GMC of 3.7 IU/ml and anti-PT GMC of 129 EL.U/ml one month after immunization (Table 7).

Ferrera et al found similar results as Mallet in an Italian open multi-center study, where 303 children aged 4-6 years were randomized to a booster dose of either DTaP2-IPV (Tetravac®) or dTap3-IPV (Boostrix-Polio®) (16). The children were previously primed with a 2+1 immunization schedule with the first booster given at 11 months of age. Immunogenicity was assessed at GSK laboratories in Belgium. One month after booster with full dose vaccine DTaP2-IPV, anti-DT GMC was 21.3 IU/ml and anti-PT GMC 76 EL.U/ml (Table 7).

In a cross-sectional study, Aase et al analyzed anti-PT, anti-FHA and anti-Prn from a convenience sample of 498 Norwegian children who received DTaP2-IPV (Tetravac®) booster at 7-8 years of age (18). Most of the children were previously vaccinated in a 2+1 schedule with DTaP3-IPV+Hib at 3, 5 and 12 months of age. Immunogenicity data were analyzed at NIPH in Norway. Lab results, birth date and personal identification number were linked to the Norwegian Immunisation Registry (SYSVAK) to relate results to vaccination history. For 13 children the sample was obtained during the period 0-100 days, median 49 days, after the DTaP2-IPV (Tetravac®) booster. Anti-PT GMC for those 13 children was 46 EL.U/ml (Table 7).

Duration of immunity

Aase et al also analyzed anti-PT antibody levels in 24 and 79 samples, after two and 4-5 years respectively after the DTaP2-IPV (Tetravac®) booster. Anti-PT GMC was estimated to 18 and 11 EL.U/ml, respectively for the two periods (Table 6) (18).

Vaccine effectiveness

DTaP2-IPV (Tetravac®) was introduced as a booster to 7-8 year olds in Norway in 2006. According to data from MSIS the incidence of pertussis in the age group 7-11 years decreased from median 204 per 100 000 for the years 1997-2005 to

median 71 per 100 000 for the period 2008-2016 (19). Crude estimate of the intervention effectiveness was calculated to approximately 65 % for this age group (Table 8). Similar results were found in Finland where DTaP2-IPV (Tetravac®) was introduced to 4 year olds in 2005. Pertussis incidence in the age group 4-8 years fell from a median of approximately 43 per 100 000 to 13 per 100 000 from the period 1994-2004 to 2006-2016, giving a crude intervention effectiveness of 70 % (Table 8) (20, 21).

Vaccine specific overview for full dose DTaP5-IPV vaccine (Quadracel®)

Data sources

Data in this part is based on immunogenicity studies (23-26), and an epidemiological study and a review (27, 28).

Vaccine content and trade name

DTaP5-IPV is a full dose vaccine licensed as Quadracel® for use in children aged 4 to 6 years as a fifth dose for the DTaP series and as a fourth or fifth dose in the IPV series (28). Each 0.5-mL dose of the vaccine is formulated to contain 25 Lf of diphtheria toxoid, 5 Lf tetanus toxoid, 40 D-antigen Units (DU) of Type 1 poliovirus (Mahoney), 8 DU of Type 2 poliovirus (MEF-1), and 32 DU of Type 3 poliovirus (Saukett). The vaccine also contains *five* pertussis antigens with 20 mcg of inactivated pertussis toxin (PT), 20 mcg of filamentous hemagglutinin (FHA), 3 mcg of pertactin and 5 mcg fimbriae types 2 and 3 (28). The individual antigens are identical to the antigens contained in Sanofi Pasteur´s DTaP-IPV+Hib vaccine Pentacel® (27).

Immunogenicity one month after booster

DTaP5-IPV (Quadracel®) was given to 4-6-year-old children in three randomized, controlled trials in Canada (23, 25, 26). The children were previously primed with aP-containing vaccine in a 3+1 schedule where the first booster was given at 17-19 months of age. During vaccine development, an earlier variant of this full dose vaccine, with reduced amount of PT compared to DTaP5-IPV (Quadracel®), was investigated as a candidate vaccine (24). This candidate vaccine was tested in similar cohorts as described above, but is no longer in use. Immunogenicity for all four studies was assessed by Sanofi Pasteur, Toronto, Canada. Anti-DT and anti-PT GMCs ranged from 5.2 to 13.6 IU/ml and from 119 to 331 EL.U/ml, respectively, for studies with DTaP5-IPV (Quadracel®). For the candidate vaccine, corresponding GMCs were 15.4 IU/ml for anti-DT and 158 EL.U/ml for anti-PT (Table 9[8]).

Duration of immunity

We have not identified any published studies regarding duration of protection after DTaP5-IPV given as booster dose in children aged 4-8 years.

[8] A very recent publication presents similar immunogenicity data for Quadracel® as in Table 7 (Ref Smith et al Ped Infect Dis J Volume 36, Number 3, Page 319-325, 2017)

Vaccine effectiveness

We have not identified any published studies regarding vaccine effectiveness against pertussis after DTaP5-IPV given as booster dose in children aged 4-8 years.

Low dose vaccines

Vaccine specific overview for low dose dTap3-IPV vaccine (Boostrix-Polio®)

Data sources

Data in this part was based on immunogenicity studies (16, 29, 30), an epidemiological study (31) and a review (11).

Vaccine content and trade name

Low dose dTap3-IPV is licensed as Boostrix-Polio®. Each 0.5-mL dose of the vaccine contains ≥ 2 IE (2.5 Lf) of diphtheria toxoid, ≥ 20 IE (5 Lf) of tetanus toxoid, 40 D-antigen Units (DU) of Type 1 poliovirus (Mahoney), 8 DU of Type 2 poliovirus (MEF-1), and 32 DU of Type 3 poliovirus (Saukett). In addition, the vaccine contains *three* pertussis antigens with 8 mcg of inactivated pertussis toxin (PT), 8 mcg of filamentous hemagglutinin (FHA) and 2.5 mcg of pertactin (32).

Immunogenicity one month after booster

In a German randomized, controlled trial, a preschool booster with dTap3-IPV (Boostrix-Polio®) immunogenicity was assessed in 475 4-8 year old children (29). The children had been previously vaccinated with aP-containing vaccine in a 3+1 schedule with the first booster given during the second year of life. The control group received dTap and IPV vaccines as two separate injections. Immunogenicity was assessed at GSK laboratories in Belgium. After booster with dTap3-IPV (Boostrix-Polio®) anti-DT GMC was 4.5 IU/ml and anti-PT 52 EL.U/ml (Table 10).

In an Italian randomized, controlled trial 138 children aged 4-6 years previously primed in a 2+1 schedule with aP-containing vaccine were randomized to a booster dose of either DTaP2-IPV (Tetravac®) or dTap3-IPV (Boostrix-Polio®) (16). Immunogenicity was assessed at GSK laboratories, Belgium. Low dose dTap3-IPV (Boostrix-Polio®) as booster resulted in anti-DT GMC of 9.2 IU/ml and anti-PT GMC of 60 EL.U/ml (Table 10). Results for the comparative group that received full dose DTaP2-IPV (Tetravac®) as booster have been mentioned earlier i.e. anti-DT GMC of 21.3 IU/ml and anti-PT GMC of 76 EL.U/ml (Table 7)

Thus, for dTap3-IPV (Boostrix-Polio®) there was a direct head-to-head comparison against a benchmark DTaP-IPV vaccine in a randomized, clinical trial, as described above (16), in addition to an open, randomized trial assessing immunogenicity (29). These two trials were evaluated using GRADE. No limitations were identified with regard to study quality, inconsistencies or high probability of reporting bias. The assessment resulted in a moderate confidence in the immunogenicity data when comparing dTap3-IPV to DTaP2-IPV (Tetravac®) as benchmark even though the number of studies was limited. Further head-to-head studies in other populations may result in other GMCs for anti-DT and anti-PT

antibodies, but will probably not affect the comparison between dTap3-IPV (Boostrix-Polio®) and DTaP2-IPV (Tetravac®) to a great extent.

Duration of immunity

Knuf et al followed up 351 children from the German cohort mentioned above and immunized them with a second booster (dose 6) five years after the first dTap3-IPV (Boostrix-Polio®) booster at approximately 11 years of age (30). Immunogenicity was assessed at GSK laboratories in Belgium. Pre-booster, the antibody titres were 0.51 IU/ml for anti-DT GMC of and 5 EL.U/ml for anti-PT GMC (Table 6).

Vaccine effectiveness

In Israel, a fifth dose of dTap-IPV was introduced in the NIP for 7-8 year old children in 2005 and a sixth dose of dTap to 13-14 year old children in 2008, with good coverage (31). The vaccine used in Israel for dose 5 in almost the entire period was dTap3-IPV (Boostrix-Polio®) (Stein-Zamir, personal communication). From 2006 to 2009, the incidence of pertussis declined by 62 % and 74 % in 5-9 year olds and 10-14 year old, respectively (31). This observational study was evaluated using GRADE and there were limitations for study quality, inconsistencies and high probability of reporting bias. The estimate of intervention effectiveness was therefore uncertain. Further research studies in other populations will likely have an important impact on the confidence in the estimates of intervention effectiveness, and will likely change the estimates.

Vaccine specific overview for low dose dTap5-IPV vaccine (Repevax®; Adacel-Polio; Triaxis-Polio; Covaxis-Polio®)

Data sources

Data in this part was based on a clinical study (5), a Swedish Technical Study Report (33), a Swedish long-term follow-up study (34), one review (11) and chapter 7.8 in RIVM Report 2016-0141 (14).

Vaccine content and trade names

Low dose dTap5-IPV is licensed as Repevax® or Adacel-polio®. Other names used for this vaccine in the past were Triaxis-Polio® and Covaxis-Polio. Each 0.5 mL dose of the vaccine is formulated to contain 2 IU (2 Lf) of diphtheria toxoid, 20 IU (5 Lf) of tetanus toxoid, 40 D-antigen Units (DU) of Type 1 poliovirus (Mahoney), 8 DU of Type 2 poliovirus (MEF-1), and 32 DU of Type 3 poliovirus (Saukett). The vaccine also contains *five* pertussis antigens with 2,5 mcg of inactivated pertussis toxin (PT), 5 mcg of filamentous hemagglutinin (FHA), 3 mcg of pertactin and 5 mcg of fimbriae 2 and 3 (35).

Immunogenicity one month after booster

Results on immunogenicity were obtained from a Swedish study from 1999 of 721 five-year-old children previously primed with three doses of a candidate Canadian 5-component aP-containing combination vaccine in a 2+1 schedule. The first booster was given at 12 months of age. The children were randomized in three

arms to receive boosters of either 1) dTap5-IPV (Covaxis-Polio), 2) dTap5 (Covaxis) + IPV (Imovax® Polio) or 3) DT (Duplex®) + IPV (Imovax® Polio) (33). The two last groups received IPV as a separate injection. Antigen contents were similar for the two first groups, whereas the vaccine combination for the third group lacked pertussis antigens, had higher diphtheria (7.5 Lf) and lower tetanus toxoid (1.8 Lf) content. Thus, the study group was compared to a group vaccinated with a "semi-full dose" vaccine with respect to diphtheria. This vaccine/dosage was then regarded as benchmark because it was included in the Swedish NIP for 10-year-old children at the time of the study.

According to the pre-planned primary analysis in the Technical Study Report, anti-DT and anti-PT GMCs post booster were 2.5 IU/ml and 26 EL.U/ml, respectively for the 220 sera analyzed from children receiving dTap5-IPV (Table 11) (33). For the 202 children receiving DT + IPV and analyzed, anti-DT GMC was 5.7 IU/ml. More than half of the children had very low levels of anti-diphtheria antibodies before the booster, and the anti-PT antibodies were also low. The investigators stated that booster responses to polio type 1, 2 and 3 and tetanus toxoid were satisfactory (33). The Swedish institute for infectious disease control (SMI) laboratory at that time used an in-house dissociation-enhanced lanthanide fluorescent immunoassay (DELFIA) method for diphtheria, which was reported to have a reasonably good correlation with the toxin binding inhibition (ToBI) assay, but a low correlation against the Sanofi Pasteur Vero cell neutralization assay (36). A subset of 163 of the Swedish children had samples analyzed for anti-diphtheria antibodies with a Vero cell assay in the Sanofi Pasteur laboratory in Toronto, Canada. Results showed anti-DT GMC of 3.6 IU/ml in analyzed samples from 163 of the children receiving dTap5-IPV (Covaxis-Polio) (Table 11), while corresponding GMC for the samples analyzed from 150 of the children vaccinated with DT + IPV was 7.4 IU/ml.

Immunogenicity is also available from a small cross-sectional Dutch study using the dTap5-IPV (Triaxis-Polio®) as a booster. This trial has been mentioned earlier. Children had received 3+1 doses of DTaP5-IPV-Hib as infants. Only pertussis antigens were analyzed and anti-PT GMC was 45 EL.U/ml (Table 11) (5).

For the dTap5-IPV vaccine, there was thus no direct head-to-head comparison against a benchmark DTaP-IPV vaccine, but there was a randomized, clinical trial evaluating immunogenicity and safety of dTap5-IPV (Covaxis-Polio) (33). The technical report from this study was evaluated using GRADE and there were limitations with respect to study quality, imprecise data, and important inconsistencies. Further research studies in this and other populations will very likely have important impact on the confidence in the estimates of immunogenicity.

Duration of immunity

The duration of immunity in the Swedish cohort mentioned above was investigated in 2009 when the children had reached adolescence, at 14-15 years of age (34). Analyses revealed a pre-vaccination GMC titer for anti-DT of 0.12 IU/ml and anti-PT of 2.9 EL.U/ml (Table 6).

Vaccine effectiveness

We have not identified any published studies regarding vaccine effectiveness against pertussis after dTap5-IPV given as a preschool booster dose to children 4-8 years of age, but Dutch researchers recently published some effectiveness data in chapter 7.8 in RIVM Report 2016-0141 (14). As mentioned previously, a series of changes were instituted into the Dutch NIP during the years 2001 to 2011. In July 2006 low dose dTap5-IPV (Triaxis-Polio®) vaccine was introduced as a preschool booster for 4-6 year old children born on or after July 2002. This vaccine was replaced with full dose DTaP3-IPV (Infanrix-Polio®) in February 2008 for children born on or after February 2004. For the yearly cohorts effectiveness has been estimated by the screening method. The Dutch investigators emphasize that these estimates should not be interpreted as "true" absolute efficacy, but might be used to study trends. The authors calculated vaccine effectiveness for the 2002 cohort (when dTap5-IPV (Triaxis-polio®) was used as a booster) of 86 %, 71 %, 51 %, 35 % and 34 % at respectively 5, 6, 7, 8 and 9 years of age (14).

The Dutch data presented above did not represent "pure" cohorts vaccinated with dTap5-IPV (Triaxis-polio®). It was therefore not correct to interpret the percentages above as estimates of vaccine effectiveness for dTap5-IPV (Triaxis-polio®). Using GRADE there were also limitations with respect to study quality, inconsistencies and high probability of reporting bias. Further research including other populations will likely have an important impact on the confidence in the estimates of intervention effectiveness, and will likely change the estimates.

Vaccine specific overview for low dose dTap1-IPV vaccine (DiTeKiPol Booster ®)

Data sources

Data in this part was to a large extent based on secondary sources. A review (37) refers to a clinical study report named "Safety & immunogenicity trial in children, booster vaccination 6-years, TdaP (20&40), TdaP-IPV (20&40) SSI". This was an unpublished dose-finding study performed in Sweden in 1997-1999. We have been in contact with the Danish and Swedish investigators, but they have not been able to give us access to the data from this internal clinical report (number 007B). Epidemiological data on pertussis from Denmark have been published by Dalby et al (38) and by SSI (39).

Presentation vaccine content and trade names

Low dose dTap1-IPV is licensed as DiTeKiPol Booster®. Each 0.5-mL dose of the vaccine is formulated to contain 6,25 Lf of diphtheria toxoid (≥2 IU), 6,25 Lf tetanus toxoid (≥20 IU), (40 D-antigen Units (DU) of Type 1 poliovirus (Brunhilde), 8 DU of Type 2 poliovirus (MEF-1), and 32 DU of Type 3 poliovirus (Saukett). The vaccine also contains *one* pertussis antigen with 20 mcg of inactivated pertussis toxin (PT) (40).

Immunogenicity one month after booster

Taranger et al investigated this vaccine in preschool children in a randomized, controlled dose-finding study in Sweden in 1997-99. The immunogenicity results

from this study have not been published except for anti-PT GMC of 222 EL.U/ml (37).

Duration of immunity

We have not retrieved any published studies regarding duration of protection after dTap1-IPV given as booster dose in preschool children, but such studies are in progress (Personal communication Peter Andersen, SSI).

Vaccine effectiveness

Nationwide age-specific incidence data for pertussis in the age-group 5-9 years have been published and allow crude effectiveness data to be generated in the Danish population (Table 8). The median incidence for the years 1995-2002 for this age group was 88 per 100 000. Compared to median 19 per 100 000 for the years 2004-2013 this would translate into an intervention effectiveness of approximately 75% (38). There was an increase of the pertussis incidence in Denmark in 2016 and according to the method used, see Methods page 19, this estimate may now be somewhat reduced (39, 41).

Using GRADE there are limitations with regards to study quality, inconsistencies and high probability of reporting bias. Further research from this and other populations is likely to have an important impact on the confidence in the estimates of intervention effectiveness, and is likely to change the estimates.

Evaluation of laboratory methods used (Secondary aim b)[9]

The comparability of immunogenicity results used was assessed based on data given in the section of Material and Methods of each paper.

The DT immunogenicity was measured by three different methods in the referred studies (Enzyme-linked immunosorbent assay (ELISA), toxin neutralization test (NT), and dissociation-enhanced lanthanide fluorescent immunoassay (DELFIA)) and was performed at different laboratories.

The NT has a much greater "sensitivity" so that the limit of 0.01 IU/ml for short-term protection could be used. When using ELISA the short-term protection limit had to be raised to approximately 0.1 IU/ml, the same as the long-term protection limit. ELISA also measures antibody responses to epitopes that are not neutralizing the toxin and are thus considered not to be protective.

In most cases, when calculating GMC values below cut-off are given a numeric values corresponding to half of the lower limit of detection. A more than 10-fold difference in sensitivity in the lower range of anti-DT titres can then inflate GMC if the method used is an ELISA or ELISA-like assay compared to NT.

[9] Input to this section was provided by Audun Aase (Immunologist at NIPH, Norway), and Marta Granström (Professor of Clinical Microbiology at Karolinska Institutet, Sweden). Aase and Granström were asked to concentrate on the evaluation of the lab methods used for anti-DT and anti-PT antibodies.

Although all DT results were given in IU/ml, care must be taken when comparing results from different laboratories. This was demonstrated in a recent External Quality Assessment (EQA) study for diphtheria serology organized by the European Diphtheria Surveillance Network[10].

The PT immunogenicity was measured by ELISA in most studies, and by multiplex immune assay in two of the studies from the Netherlands. The results were reported as ELISA units/ml (EL.U/ml or EU/ml), some of the studies explicitly point out that the PT assay was calibrated against international standard, usually a Food and Drug Administration (FDA) standard.

In principle, anti-PT GMC should be more comparable between laboratories than anti-DT since they all use ELISA and express titres against an international standard. However, seroepidemiological studies have shown substantial variability between laboratories (personal communication, Lena Wehlin, FOHM).

In addition, although not known to the general public but known to authorities, several vaccine manufacturers have had problems with some of their serological assays that resulted in either overestimated (anti-PT) or underestimated (anti-polio) GMCs.

As a conclusion, the immunogenicity data from the different laboratories should be interpreted with caution. Comparisons are difficult and in this respect, head-to-head comparisons between vaccines are highly advantageous.

[10] Evaluation and assessment of serological immunity methods and external quality assessment scheme of diphtheria, ECDC. http://ecdc.europa.eu/en/publications/Publications/diptheria-serological-methods-eqa.pdf

Discussion

Background and method

During the last years the demand for combination vaccines used in NIPs have increased globally and there has been a shortage of particularly aP-containing combination vaccines for primary and booster immunization estimated to last until at least 2018. During periods of vaccine shortage, temporary changes in recommendations for the use of vaccines may be needed. It has been proposed that low dose dTap-IPV vaccines might replace booster dose in 4-8 year old children during a period of limited access to full dose DTaP-IPV vaccines. The main aim of this report was to review available data on this topic. The report was based on a rapid review of literature on this topic published between 1990 and September 2016.

The review revealed studies on three different full dose DTaP-IPV vaccines, of which only two are marketed in Europe. Full dose vaccines represents today's "standard of care" as a booster dose at school entry in the Norwegian and Swedish NIPs. It was not deemed meaningful to evaluate data using GRADE for full dose vaccines. These vaccines are already licensed for use as booster dose in 4-8 year old children.

We found data on three different low dose dTap-IPV vaccines. All of them are marketed in Europe, but one is only used in Denmark.

The importance of differences in priming schedules influencing dose-response

Primary vaccine schedules in Norway and Sweden (2+1) differ from those in countries like USA and Germany (3+1). Low dose dTap-IPV/dTap vaccines were first introduced in Germany because of side effects after the second booster dose given at 4 years of age, 2 ½ years after the first booster dose.

In Germany there is no routine school health care. The short period between the two first booster doses in the German NIP was not motivated by a medical need for a second booster dose at early age, but by logistic reasons. The number of doses given for priming may be less important than the distance between the first and the second booster with respect to antibody responses and reactogenicity. The short interval between booster doses reduces the chance of finding differences in immune responses after low dose dTap-IPV compared to full dose DTaP-IPV.

As shown in Table 2 and 3, there are four and seven years between the first and second boosters in the Swedish and Norwegian NIPs, respectively. The differences in schedules should be taken into account when evaluating vaccine responses from different countries.

Previous reviews on the use of low dose dTap-IPV vaccines as preschool booster

Two similar reviews have been published recently.

In 2014 Gabutti et al published a review where the aim was to assess if there was enough scientific evidence to support the use of low dose dTap-IPV booster in preschoolers. The authors emphasized that the probably lower reactogenicity of low dose vaccines would be important for high vaccine coverage in this age group. A total of 41 publications were selected. Results on immunogenicity for different low dose vaccines were presented separately, but the evaluations were performed for low dose vaccines as a group. The authors concluded that a number of recent papers confirmed the safety and immunogenicity profile of using low dose vaccines for boosters in 4-6 year old children with both 2+1 and 3+1 primary schedules (11). In our view, grouping vaccines together like this creates a risk that vaccines with limited data may be introduced in NIPs prematurely before there is sufficient vaccine specific data.

In the same year, another review was published by The National Advisory Committee on Immunization (NACI) in Canada with 18 articles included (42). The review focused on protection against pertussis after dose 5 of aP-containing vaccine in 4-6 year old children. The Canadian NIP uses a 3+1 primary immunization schedule with aP-containing vaccines given at 2, 4, 6 and 18 months of age, and subsequent booster doses at age 4-6 and 14-16 years. The conclusion was that both full dose DTaP-IPV and low dose dTap-IPV vaccines might be used in this age group, and NACI did not recommend one vaccine over the other. However, they also stated that full dose vaccines might elicit higher and more durable immune responses, and since the correlate of protection for pertussis is not known, vaccine choice had to be made with respect to the epidemiology. The recommendation was of "Grade C" which in the report was defined as "NACI concludes that the existing evidence is conflicting and does not allow making a recommendation for or against immunization; however other factors may influence decision-making". As firm recommendation could not be made the report listed research priorities to improve the situation and encouraged future improvements of surveillance and immunization registries.

Immunogenicity one month after booster

After the booster, most studies consistently showed rather high anti-TT and anti-polio antibody levels. GMCs were above established levels of protection for both full dose and low dose vaccines. Post booster anti-DT antibody levels were high above protective levels for licensed full dose aP combination vaccines. In general, low dose vaccines had lower levels of anti-DT antibodies and there were very limited data for the 2+1 schedule used in the Norwegian and Swedish NIPs.

Israel, Ireland and the Netherlands use low dose dTap3-IPV (Boostrix-Polio®) as preschool booster. Immunogenicity has been evaluated both in 2+1 and 3+1 schedules one month after booster. One of the studies was a head-to-head

comparison of dTap3-IPV (Boostrix-Polio®) against full dose DTaP2-IPV (Tetravac®) (16). Anti-DT and anti-PT titers one month after booster with the low dose vaccine were similar to the lower ranges obtained with full dose vaccines (Table 12) (16, 29).

Low dose dTap5-IPV (Triaxis-Polio) has been used short-term as preschool booster in some countries like the Netherlands. There were limited data available for this vaccine, both with regards to immunogenicity and effectiveness. Immunogenicity has been evaluated in 2+1 and 3+1 schedules one month after booster (Table 11 and 12). We have not identified any studies on direct head-to-head comparison of dTap5-IPV with full dose vaccines or against low dose dTap3-IPV. Results for anti-DT and anti-PT titers seemed to be lower than the lower ranges of titers reported in other studies for full dose vaccines (Table 12) (5, 33).

Low dose dTap1-IPV (DiTeKiPol Booster®) has been used as preschool booster in Denmark. Immunogenicity was evaluated in 2+1 schedule one month after booster, but there was published data only for anti-PT showing high likelihood of protection against symptomatic pertussis (Table 12).

Effectiveness

Recently, there has been an emergence of pertussis in many countries with high vaccine coverage. Full dose DTaP vaccines have been shown to have a shorter duration of protection than the efficacious wP combination vaccines, see footnote page 22. For low dose dTap vaccines, the protective ability might be even worse when used as dose 4 in Norwegian and Swedish NIPs.

Incidence data on pertussis from the Netherlands may indicate a trend towards an earlier waning of immunity against pertussis with low dose dTap5-IPV (Triaxis-Polio/Repevax®) compared to full dose DTaP3-IPV (Infanrix-Polio®) (14).

Effectiveness data from Norway and Finland, where DTaP2-IPV (Tetravac®) has been used as a booster to 4-8 year old children for many years, show that the booster led to an improved control of pertussis. Similar data are reported from Sweden where both DTaP2-IPV (Tetravac®) and DTaP3-IPV (Infanrix-Polio®) have been used (43).

Incidence data on pertussis from Israel indicate that low dose dTap3-IPV (Boostrix-Polio®) as booster in Israel has led to an improved control of pertussis (31).

Incidence data on pertussis from Denmark indicate that low dose dTap1-IPV (DiTeKiPol Booster®) as booster in Denmark has led to an improved control of pertussis (38).

Duration of seroprotection

There are very few studies on long term seroprotection against diphtheria and pertussis for both full dose and low dose DTaP-IPV / dTap-IPV vaccines. The few

studies identified underline the need for subsequent boosters, especially against pertussis and diphtheria.

Strengths

The PICO question for this rapid literature review was well defined, resulting in a limited number of studies after a thorough selection based on the predefined inclusion and exclusion criteria. The review provided vaccine specific data on immunogenicity and effectiveness of value for NIPs in Norway and Sweden.

Limits

Evaluation of vaccine safety and reactogenicity was not an aim of this report due to limited time and resources. This might be regarded as a shortcoming.

Studies with a primary immunization schedule using wP combination vaccines were excluded. This might be regarded as a shortcoming, especially since vaccines experts in some countries propose to introduce at least one wP dose in NIPs that otherwise use aP-containing combination vaccines only.

Studies reporting use of DTaP/dTap and IPV as separate injections were excluded. Therefore some important data on immunogenicity and effectiveness may be lacking in this report. This is briefly discussed in Appendix 2.

It is known from the literature that *Bordetella pertussis* is evolving and that current strains are not well matched with the antigens in neither aP nor wP vaccines. Traditionally, pertussis has demonstrated cyclic epidemiology with high incidence every 3-4 years. These factors could influence estimates of both vaccine effectiveness and long term immunogenicity, and are not taken into account in depth in this report.

Conclusion

With the limited data on immunogenicity and uncertain data for effectiveness for low dose dTap-IPV vaccines, it is questionable whether there is sufficient evidence for use of these vaccines as replacement for the full dose DTaP-IPV vaccines presently used as dose 4 in the Norwegian and Swedish vaccination schedules. The preferred option for the Norwegian and Swedish NIPs should be to continue with full dose DTaP-IPV vaccine as dose 4. In case of a temporary shortage of full dose DTaP-IPV vaccine, will be difficult to make firm conclusions regarding a switch to low dose dTap-IPV vaccine, and changes to the immunization schedules might be needed. Different scenarios are possible and are discussed in Appendix 2.

Tables

Table 1 Antigen content in different DTaP-IPV and dTap-IPV vaccines

Vaccine	Manufacturer	DT antigen (dose)	TT antigen (dose)	PT antigen (dose)	FHA antigen (dose)	Prn antigen (dose)	Fim 2/3 antigen (dose)	Polio 1 antigen (dose)	Polio 2 antigen (dose)	Polio 3 antigen (dose)	Adjuvant
Full dose vaccines											
Infanrix-Polio® / Kinrix®	GSK, Belgium	≥ 30 IU (25 Lf)	≥ 40 IU (10 Lf)	25 µg	25 µg	8 µg		40 DU	8 DU	32 DU	Al hydroxide (Al^{3+} 0,5 mg)
Tetravac® / Tetraxim®	Sanofi Pasteur, France	≥ 30 IU	≥ 40 IU	25 µg	25 µg			40 DU	8 DU	32 DU	Al hydroxide (Al^{3+} 0,3 mg)
Quadracel®	Sanofi Pasteur, Canada	≥ 30 IU 15 Lf	≥ 40 IU 5 Lf	20 µg	20 µg	3 µg	5 µg	40 DU	8 DU	32 DU	Al phosphate 1,5mg
«Classic» Canadian (No longer marketed)	Previous Aventis Pasteur, Canada	15Lf	5 Lf	10 µg	5 µg	3 µg	5 µg	40 DU	8 DU	32 DU	Al phosphate 1,5mg

Low dose vaccines											
Boostrix-Polio®	GSK, Belgium	≥ 2 IU 2.5 Lf	≥ 20 IU 5 Lf	8 µg	8 µg	2,5 µg		40 DU	8 DU	32 DU	Al phosphate (Al^{3+} 0,2 mg) Al hydroxide (Al^{3+} 0,3 mg)
Repevax® Covaxis-Polio / Adacel-Polio® / Triaxis-Polio®	Sanofi Pasteur, Canada	≥ 2 IU 2 Lf	≥ 20 IU 5 Lf	2,5 µg	5 µg	3 µg	5 µg	40 DU	8 DU	32 DU	Al phosphate 1,5mg (Al 0,33mg)
DiTeKiPol Booster®	SSI, Denmark	≥ 2 IU	≥ 20 IU	20 µg				40 DU	8 DU	32 DU	Al hydroxyhydrate 0,5mg

Table 2 Swedish NIP, per March 2017

Age	**3 months**	**5 months**	**12 months**	**18 months**	**5 years**			
Year of school						**1-2**	**5-6**	**8-9**
Diphtheria Tetanus Pertussis	Dose 1	Dose 2	Dose 3		Dose 4			Dose 5
Polio	Dose 1	Dose 2	Dose 3		Dose 4			
Hib	Dose 1	Dose 2	Dose 3					
Pneumococcal disease	Dose 1	Dose 2	Dose 3					
Measles Mumps Rubella				Dose 1		Dose 2		
HPV (girls)							Dose 1 + 2	

Table 3 Norwegian NIP, per March 2017

Age	6 weeks	3 months	5 months	12 months	15 months				
Year of school						2	6	7	10
Rotavirus	Dose 1	Dose 2							
Diphtheria Tetanus Pertussis		Dose 1	Dose 2	Dose 3		Dose 4			Dose 5
Polio		Dose 1	Dose 2	Dose 3		Dose 4			Dose 5
Hib		Dose 1	Dose 2	Dose 3					
Hepatitis B		Dose 1	Dose 2	Dose 3					
Pneumococcal disease		Dose 1	Dose 2	Dose 3					
Measles Mumps Rubella					Dose 1		Dose 2		
HPV (girls)								Dose 1 + 2	

Table 4 Quantitative correlates of protection after vaccination
(adapted from Plotkin Clin Vaccine Immunol. 2010 Jul; 17(7): 1055–1065)

Vaccine	Test	Level required for long term protection
Diphtheria	Toxin neutralization	0.1 IU/ml
Tetanus	Toxin neutralization	0.1 IU/ml
Polio	Neutralization	1/8 dilution
Pertussis	ELISA, various antigens	Not determined

Table 5 Immunogenicity one month after booster with DTaP3-IPV (Infanrix-Polio®, Kinrix®) in 4-8 year old children

GMCs from different laboratories may not be directly comparable.

Reference	N	Previous vaccines	Study vaccine	Lab ID / method	GMC DT IU/ml	GMC TT IU/ml	GMC PT (EL.U/ml)	GMC FHA (EL.U/ml)	GMC PRN (EL.U/ml)	GMC PV1 IU/ml	GMC PV2 IU/ml	GMC PV3 IU/ml
Klein 2012 (USA)	428	aP 3+1	Kinrix®	GSK Belgium DT, TT, pertussis: ELISA Polio: NT	14,3	8,7	97	969	627	1638	1573	2588
			Kinrix®		14,8	8,1	101	968	620	1790	1903	3190
Marshall 2006 (Australia)	148	aP 3+1	Infanrix-Polio®	Pichichero lab DT, TT, pertussis: ELISA GSK Belgium Polio: NT	5,9	7,9	111	372	707	3014	2883	4849
Nilsson 2005 (Italy, Sweden)	208	aP 2+1	Infanrix-Polio®	GSK Belgium TT, pertussis: ELISA Polio: NT DT: ELISA (NT)	6,2 (5,3)	10,0	63	735	996	2096	1702	2543
Black 2006 (USA)	172	aP 3+1	Infanrix-Polio®	Pichichero lab DT, TT, pertussis: ELISA Polio: NT	7,8	8,0	102	379	658	1337	1218	2090
Black 2008 (USA) Immunogenicity data listed in Weston 2008	853	aP 3+1	Infanrix-Polio®	GSK Belgium DT, TT, pertussis: ELISA Polio: NT	17,9	10,3	71	864	599	2109	2266	3563
Schure 2013 (Netherlands)	11	aP 3+1	Infanrix-Polio®	RIVM Netherlands			187	521	1253			
Hendrikx 2009 (Netherlands)	41	aP 3+1	Infanrix-Polio®	RIVM Netherlands			192	518	1274			

Table 6 Long term immunogenicity after booster with DTaP-IPV or dTap-IPV in 4-8 year old children

GMCs from different laboratories may not be directly comparable.

Vaccine	Reference	N	Previous immunization	Time post booster	GMC DT IU/ml	GMC TT IU/ml	GMC PT (EL.U/ml)	GMC FHA (EL.U/ml)	GMC PRN (EL.U/ml)	GMC FIM (EL.U/ml)
Full dose vaccines										
Infanrix-Polio®	Schure 2013 (Netherlands)	61	aP 3+1+1	2 years			26	81	110	
Tetravac®	Aase 2014 (Norway)	24	aP 2+1+1	2 years			18	228	28	
		79		4-5 years			11	164	29	
Low dose vaccines										
Boostrix-Polio®	Knuf 2010 (Germany)	330	aP 3+1 Boostrix-Polio® 4-8 year olds	5 years	0,51	1,2	5	70	47	
Repevax®	Carlsson 2015 (Sweden)	114	aP 2+1+1	10 years	0,12	0,8	2,9	14	42	27

Table 7 Immunogenicity one month, respectively 1-100 days, after booster with DTaP2-IPV (Tetravac®, Tetraxim®) in 4-8 year old children

GMCs from different laboratories may not be directly comparable.

Reference	N	Previous vaccines	Study vaccine	Lab ID / method	GMC DT IU/ml	GMC TT IU/ml	GMC PT (EL.U/ml)	GMC FHA (EL.U/ml)	GMC PRN (EL.U/ml)	GMC PV1 IU/ml	GMC PV2 IU/ml	GMC PV3 IU/ml
Pancharoen 2012 (Thailand)	123	aP 3+1	Tetraxim®	SP Swiftwater, PA USA TT, PT, FHA: ELISA DT, polio: NT	7,8	7,7	190	356		3013	3430	3837
Aase 2014* (Norway)	13	aP 2+1	Tetravac®	NIPH, Oslo, Norway PT, FHA:ELISA			46	337	24			
Mallet 2004 (France)	231	aP 3+1	Tetravac®	SP, France DT, PT, FHA: ELISA Polio: NT	3,7	10,3	129	467		3174	3051	3847
Ferrera 2012 (Italy)	144	aP 2+1	Tetravac®	GSK, Belgium TT, DT, pertussis: ELISA Polio: NT	21,4	11,0	76	614	8	948	1315	1657

* Serology analyzed 0-100 (median 49) days after booster dose

Table 8 Intervention effectiveness against pertussis after introduction of booster with DTaP-IPV or dTap-IPV vaccines in 4-8 year old children

Vaccine	Reference	Previous immunization schedule	Effectiveness
Tetravac®	MSIS data NIPH 2016 (Norway)	aP 2+1+1 aP 7-8 year olds (initiated 2006)	65% in children 7-11 years
	THL data 2017 (Finland)	aP 2+1+1	70% in children 4-8 years
Boostrix-Polio®	Stein-Zamir 2011 (Israel)	aP 3+1+1 dTap-IPV 7-8 year olds (initiated 2005) dTap 13-14 year olds (initiated 2008)	62% in children 5-9 years
DiTeKiPol booster®	Dalby 2016 (Denmark)	aP 2+1+1 aP 5 year olds (initiated 2003)	75% in children 5-9 years

Table 9 Immunogenicity one month after booster with DTaP5-IPV (Quadracel®) in 4-8 year old children

GMCs from different laboratories may not be directly comparable.

Reference	N	Previous vaccines	Study vaccine	Lab ID / method	GMC DT IU/ml	GMC TT IU/ml	GMC PT * (EL.U/ml)	GMC FHA (EL.U/ml)	GMC PRN (EL.U/ml)	GMC FIM (EL.U/ml)	GMC PV1 IU/ml	GMC PV2 IU/ml	GMC PV3 IU/ml
Halperin 1999 (Canada)	25	aP 3+1	Quadracel®	SP Toronto TT, pertussis: ELISA DT, polio: NT	5,2	6,8	137	188	247	321	11000	18000	7459
Halperin 2003 (Canada)	62	aP 3+1	Canadian candidate vaccine	SP Toronto TT: immunoassay Pertussis: ELISA DT, polio: NT	15,4	15,1	158	167	387	419	15000	39000	21000
Langley 2007 (Canada)	≈252	aP 3+1	Quadracel®	SP Toronto DT: NT TT, pertussis: ELISA	13,6	6,7	331	258	243	738			
Scheifele 2005 (Canada)	≈145	aP 3+1	Quadracel®	SP Toronto DT, TT, pertussis: ELISA	6,4	8,0	119	168	163	641			

* Specific laboratory issues with this assay

Table 10 Immunogenicity one month after booster with dTap3-IPV (Boostrix-Polio®) in 4-8 year old children
GMCs from different laboratories may not be directly comparable.

Reference	N	Previous vaccines	Study vaccine	Lab ID / method	GMC DT IU/ml	GMC TT IU/ml	GMC PT (EL.U/ml)	GMC FHA (EL.U/ml)	GMC PRN (EL.U/ml)	GMC PV1 IU/ml	GMC PV2 IU/ml	GMC PV3 IU/ml
Ferrera 2012 (Italy)	138	aP 2+1	Boostrix-Polio®	GSK Belgium DT, TT, pertussis: ELISA Polio: NT	9,2	12,5	60	556	355	1146	1076	1938
Sänger 2007 (Germany)	475	aP 3+1	Boostrix-Polio®	GSK Belgium DT, TT, pertussis: ELISA Polio: NT	4,5	13,9	52	536	477	3514	3389	3772

Table 11 Immunogenicity one month after booster with dTap5-IPV (Repevax®) in 4-8 year old children
GMCs from different laboratories may not be directly comparable.

Reference	N	Previous vaccines	Study vaccine	Lab ID / method	GMC DT IU/ml	GMC TT IU/ml	GMC PT (EL.U/ml)	GMC FHA (EL.U/ml)	GMC PRN (EL.U/ml)	GMC FIM (EL.U/ml)	GMC PV1 IU/ml	GMC PV2 IU/ml	GMC PV3 IU/ml
Gustafsson 2000 (Sweden)	220/	aP 2+1	Repevax®	SMI, Sweden TT, PT, Prn, FHA, Fim 2/3: ELISA DT: DELFIA SP, Toronto, Canada Polio: NT	2,5	25	26	68	397	351	281	416	131
	163			DT: Vero cell NT	3,6								
Hendrikx 2009 (Netherlands)	16	aP 3+1	Repevax®	RIVM Netherlands			45	182	629	2,7			

Table 12 Anti-PT and anti-DT results before and one month after booster with DTaP-IPV and dTap-IPV vaccines in 4-8 year old children

Reference	Vaccine	Pertussis valency	Anti-DT IU/ml, pre booster	Anti-DT IU/ml, post booster	Anti-PT (EL.U/ml), pre booster	Anti-PT (EL.U/ml), post booster
FULL DOSE DTaP-IPV VACCINES						
Nilsson 2005	Infanrix-Polio®	aP3	0,08 (0,04)*	6,2 (5,3)*	3,6	63
Black 2006	Infanrix-Polio®	aP3	0,2	7,8	4,7	102
Jaquet 2006	Infanrix-Polio®	aP3		6,2		63
Marshall 2006	Infanrix-Polio®	aP3	0,2	5,9	5,4	111
Black 2008	Infanrix-Polio®	aP3	0,3	17,9	4,0	71
Hendrikx 2009	Infanrix-Polio®	aP3				192
Klein 2012	Kinrix®	aP3	0,2	≈ 14,5	≈ 5,0	≈ 100
Schure 2013	Infanrix-Polio®	aP3				187
Mallet 2004	Tetravac®	aP2	0,05	3,7	2,7	129
Ferrera 2012	Tetravac®	aP2		21,4		76
Pancheron 2012	Tetraxim®	aP2	0,15	7,8	11,0	190
Aase 2014* (Data 0-100 days post booster)	Tetravac®	aP2				46
Halperin 1999	Quadracel®	aP5	0,1	5,2	9,1	137
Halperin 2003	«Classic» Canadian DTaP5-IPV	aP5	0,09	15,4	7,0	158
Scheifele 2005	Quadracel®	aP5	0,13	6,4	8,9	119
Langley 2007	Quadracel®	aP5		13,6		331
LOW DOSE dTap-IPV VACCINES						
Sänger 2007	Boostrix-Polio®	ap3	0,2	4,5	4,3	52
Ferrera 2012	Boostrix-Polio®	ap3		9,2		60
Gustafsson 2000	Repevax®	ap5	0,012 (0,04)*	2,5 (3,6)*	1,2	26
Hendrikx 2009	Repevax®	ap5				45
Thierry-Carstensen 2013	DiTeKiPol Booster®	aP1				222

* Values in parenthesis were measured with neutralization test.

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Appendices

Appendix 1 - Complete search strategy

Daatabase: PubMed **Databaseproviser: NLM**		**Date: 2016-10-06**	
Search #	Field	Words used	Number of hits
1	MeSH	"Child"[Mesh]	1672134
2	Title/Abstract	child[Title/Abstract] OR children[Title/Abstract] OR preschool[Title/Abstract] OR pre-school[Title/Abstract] OR preschoolers[Title/Abstract] OR pre-schoolers[Title/Abstract] OR primary school[Title/Abstract] OR schoolchildren[Title/Abstract]	1039216
3		1 OR 2	1980208
4	MeSH	"Immunization, Secondary"[Mesh]	7278
5	Title/Abstract	booster[Title/Abstract] OR vaccine[Title/Abstract] OR vaccines[Title/Abstract] OR vaccination[Title/Abstract] OR vaccinations[Title/Abstract] OR vaccinate[Title/Abstract] OR vaccinated[Title/Abstract] OR immunization[Title/Abstract] OR immunisation[Title/Abstract] OR immunize[Title/Abstract] OR immunise[Title/Abstract] OR immunity[Title/Abstract]	408988
6		4 OR 5	410277
7	MeSH	"Diphtheria-Tetanus-acellular Pertussis Vaccines"[Mesh] OR "Diphtheria-Tetanus-Pertussis Vaccine"[Mesh] OR "Poliovirus Vaccine, Inactivated"[Mesh] OR "Pertussis Vaccine/administration and dosage"[Mesh:NoExp] OR "Pertussis Vaccine/prevention and control"[Mesh:NoExp] OR "Whooping Cough/prevention and control"[Mesh] OR "Poliomyelitis/prevention and control"[Mesh:NoExp] OR "Diphtheria/prevention and control"[Mesh] OR "Tetanus/prevention and control"[Mesh]	14295
8	Title/Abstract	Boostrix[Title/Abstract] OR Repevax[Title/Abstract] OR DTPa-IPV[Title/Abstract] OR DTaP-IPV[Title/Abstract] OR dtpa-IPV[Title/Abstract] OR dtap-IPV[Title/Abstract] OR Tdap-IPV[Title/Abstract] OR Di-Te-Ki-Pol[Title/Abstract] OR "Di Te Ki	1637

		Pol"[Title/Abstract] OR Di-Te-Per[Title/Abstract] OR "Di Te Per"[Title/Abstract] OR diphtheria-tetanus-pertussis[Title/Abstract] OR "diphtheria tetanus pertussis"[Title/Abstract] OR diphtheria-tetanus-acellular pertussis[Title/Abstract] OR "diphtheria tetanus acellular pertussis"[Title/Abstract] OR inactivated poliovirus[Title/Abstract] OR tetanus-diphtheria-pertussis[Title/Abstract] OR "tetanus diphtheria pertussis"[Title/Abstract] OR tetanus-diphtheria-acellular pertussis[Title/Abstract] OR "tetanus diphtheria acellular pertussis"[Title/Abstract]	
9		7 OR 8	14808
10		3 AND 6 AND 9	5182
11		#10. Filters activated: Publication date from 1990/01/01	**3764***

*Exported to EndNote

Database: Cochrane Library Database provider: Wiley		Date: 2016-10-06	
Search #	Field	Words used	Number of hits
1	MeSH Descriptor	MeSH descriptor: [Child] explode all trees	200
2	Title/Abstract/Key	child or children or preschool or pre-school or preschoolers or pre-schoolers or "primary school" or schoolchildren:ti,ab,kw (Word variations have been searched)	89403
3		1 OR 2	89403
4	MeSH Descriptor	MeSH descriptor: [Immunization, Secondary] explode all trees	775
5	Title/Abstract/Key	booster or vaccin* or immuni?ation or immuni?e or immunity:ti,ab,kw (Word variations have been searched)	18991
6		4 OR 5	18991
7	MeSH Descriptor	MeSH descriptor: [Diphtheria-Tetanus-acellular Pertussis Vaccines] explode all trees	175
8	MeSH Descriptor	MeSH descriptor: [Diphtheria-Tetanus-Pertussis Vaccine] explode all trees	481
9	MeSH Descriptor	MeSH descriptor: [Poliovirus Vaccine, Inactivated] explode all trees	251
10	MeSH Descriptor	MeSH descriptor: [Pertussis Vaccine] this term only and with qualifier(s): [Administration & dosage - AD]	76
11	MeSH Descriptor	MeSH descriptor: [Whooping Cough] this term only and with qualifier(s): [Prevention & control - PC]	160
12	MeSH Descriptor	MeSH descriptor: [Poliomyelitis] this term only and with qualifier(s): [Prevention & control - PC]	94
13	MeSH Descriptor	MeSH descriptor: [Diphtheria] this term only and with qualifier(s): [Prevention & control - PC]	69
14	MeSH Descriptor	MeSH descriptor: [Tetanus] this term only and with qualifier(s): [Prevention & control - PC]	93

15		7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14	823
16	Title/Abstract/Key	Boostrix or Repevax or DTPa-IPV or DTaP-IPV or dtpa-IPV or dtap-IPV or Tdap-IPV or Di-Te-Ki-Pol or "Di Te Ki Pol" or Di-Te-Per or "Di Te Per" or diphtheria-tetanus-pertussis or "diphtheria tetanus pertussis" or diphtheria-tetanus-acellular pertussis or "diphtheria tetanus acellular pertussis" or "inactivated poliovirus" or tetanus-diphtheria-pertussis or "tetanus diphtheria pertussis" or tetanus-diphtheria-acellular pertussis or "tetanus diphtheria acellular pertussis":ti,ab,kw (Word variations have been searched)	825
17		15 OR 16	1000
18		3 AND 6 AND 17	**526*** Cochrane Reviews: 7 Other Reviews: 6 Trials: 496 Technology Assessment: 1 Economic Evaluations: 16

*Exported to EndNote. Publications published before 1990 was excluded in EndNote (33 references).

Database: Scopus Databaseprovider: Elsevier		Date: 2016-10-06	
Search #	Field	Words used	Number of hits
1	Title-Abs-Key	TITLE-ABS-KEY(child OR children OR preschool OR pre-school OR preschoolers OR pre-schoolers OR "primary school" OR schoolchildren)	2652933
2	Title-Abs-Key	TITLE-ABS-KEY (booster OR vaccine OR vaccines OR vaccination OR vaccinations OR vaccinate OR vaccinated OR immunization OR immunisation OR immunize OR immunise OR immunity)	786872
3	Title-Abs-Key	TITLE-ABS-KEY (boostrix OR repevax OR {DTPa-IPV} OR {DTaP-IPV} OR {dtpa-IPV} OR {dtap-IPV} OR {Tdap-IPV} OR di-te-ki-pol OR "Di Te Ki Pol" OR di-te-per OR "Di Te Per" OR "diphtheria tetanus pertussis" OR "diphtheria tetanus acellular pertussis" OR "inactivated poliovirus" OR "tetanus diphtheria pertussis" OR "tetanus diphtheria acellular pertussis")	4483
4		1 AND 2 AND 3	2644
5		#4. Limited to: Publication year 1990-2000	819*
6		#4. Limited to: Publication year 2001-2010	936*
7		#4. Limited to: Publication year 2011-2016	612*

*Exported to EndNote

Appendix 2 – Discussion of different scenarios and consequences of possible vaccine switch (Secondary aim c)

This appendix lists different scenarios for the use of full dose DTaP-IPV or low dose dTap-IPV vaccines as booster dose 4 to 4-8 year old children in the Norwegian and Swedish NIPs. Norwegian and Swedish health authorities need to be prepared to adapt an appropriate strategy in the case of a future shortage of full dose DTaP-IPV vaccines.

The scenarios are not only based on the results of the literature review and they should not be taken as firm recommendations. In the case of a vaccine shortage, a number of other aspects including costs and logistics need to be taken into account, as already discussed during the preparation of this report with a Scandinavian expert group.

The different scenarios are as follows:

A. At least one full dose DTaP-IPV vaccine is available.

Continuance with full dose DTaP-IPV vaccine as dose 4 is feasible. Changes to the immunization schedules are not necessary.

B. Full dose DTaP-IPV vaccines are not available. At least two low dose dTap-IPV vaccines are available.

The literature review showed limited immunogenicity and effectiveness data for low dose dTap3-IPV (Boostrix-polio®). Anti-DT and anti-PT titers one month after booster with the low dose vaccine were similar to the lower ranges obtained with full dose vaccines. Similar data have not been found for dTap5-IPV (Repevax®) or dTap1-IPV (DiTeKiPol booster®).

If dTap3-IPV (Boostrix-polio®) is used as dose 4 in the Norwegian and Swedish NIPs for a shorter period of time, it may be important with follow-up serology. However, some data for dTap3-IPV (Boostrix-polio®) in a 2+1+1 schedule is already published (Ferrera et al 2012).

C. Full dose DTaP-IPV vaccines are not available. Low dose dTap3-IPV (Boostrix-polio®) is not available. Low dose dTap plus IPV as separate injections are available.

Low dose dTap1 (diTekiBooster®) is presently used in Sweden as teenage booster and one possibility could be to use dTap1 + IPV for 4-8 year olds. If **dTap1 (diTekiBooster®) + IPV** is used as dose 4 in the Norwegian and Swedish NIPs, it will probably be important with comprehensive follow-up serology. The main reason is that available data are very limited for this age group. However, diTekiBooster® was not included in our systematic literature review.

If **dTap3 (Boostrix®) + IPV** is used as dose 4 in the Norwegian and Swedish NIPs, it will also be important with comprehensive follow-up serology. There are limited available data with this vaccine in this age group. However, Boostrix® was not included in our systematic literature review.

The results of the follow-up studies may indicate that dose 5 of dTap or dTap-IPV be moved forward in time and/or may indicate the need to give full dose vaccine also to adolescents. This would then be in accordance with the French schedule of full dose vaccines at 10-12 years of age for children who are vaccinated with low dose vaccine at 5 years of age.

D. Full dose DTaP-IPV vaccines are not available. Low dose dTap3-IPV (Boostrix-polio®) is not available. Low dose dTap5-IPV (Repevax®) is available.

If low dose **dTap5-IPV (Repevax®)** is used as dose 4 in the Norwegian and Swedish NIPs, it will be important with comprehensive follow-up serology. The main reason is that available data are very limited for this age group. One study showed that anti-DT and anti-PT titers one month after booster was lower than the lower ranges of titers reported in other studies for full dose vaccines and some other low dose vaccines (Gustafsson et al 2000).

The results of the follow-up studies may indicate that dose 5 of dTap or dTap-IPV be moved forward in time and/or may indicate the need to give full dose vaccine also to adolescents. This would then be in accordance with the French schedule of full dose vaccines at 10-12 years of age for children who are vaccinated with low dose vaccine at 5 years of age.

E. Full dose DTaP-IPV vaccines are not available. Low dose dTap3-IPV (Boostrix-polio®) and dTap5-IPV (Repevax®) are not available. Low dose dTap1-IPV (DiTeKiPol booster®) is available.

During the preparation of the report, it was difficult to obtain immunogenicity data for **dTap1-IPV (DiTeKiPol booster®)**. It is unlikely that this dTap-IPV vaccine will be available for the Norwegian and Swedish NIPs, but based on the quantity of DT and PT in the vaccine it could be an option.

F. Full dose DTaP-IPV vaccines are not available. Low dose dTap-IPV vaccines (any type) are not available.

Temporary postponement of dose 4 in the NIP is logistically difficult and potentially disruptive for the immunization program. This is not a preferable option.

This rapid literature review aimed to identify and present studies for evaluating the possibility of a temporary replacement of full dose DTaP-IPV with low dose dTap-IPV for dose 4 in 4-8 year old children in the Norwegian and Swedish NIPs when facing a period of vaccine shortage. The consequences of such a vaccine switch was also evaluated. This report is intended to be used as a basis for recommendations if changes to the national immunization programs are needed in Norway and Sweden. The Public Health Agency of Sweden, Norwegian Institute of Public Health, county councils, vaccine experts and the Medical Products Agency are the primary target group for this report.

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