Anhang zur wissenschaftlichen Begründung der STIKO-Empfehlung der 6-fach-Impfung (DTaP-IPV-Hib-Hep B) im Säuglingsalter nach dem 2+1-Schema im Epid Bull 26/2020 vom 25.06.2020

Inhaltsverzeichnis

1. PICO-Fragestellung

Tab. 1: PICO-Kriterien für den systematischen Review zur Effektivität der Pertussis-Impfung mit 2 Impfstoffdosen im Vergleich zu 3 Impfstoffdosen im Alter von 5-11 Monaten

Population	Säuglinge im Alter <12 Monaten
Intervention	Impfung mit azellulärem Pertussis-Impfstoff; 2 und 3 Impfstoffdosen im Alter von 5-11 Monaten
Comparator (Vergleichsintervention)	keine Impfung, Placebo oder Impfung gegen einen anderen Erreger als Pertussis
Outcome	Pertussis jeglicher Form, Pertussis-Hospitalisierung, ambulant behandelte Pertussis

2. Suchstrategie und Flussdiagramm des systematischen Reviews zur Effektivität der Pertussis-Impfung mit 2 Impfstoffdosen im Vergleich zu 3 Impfstoffdosen im Alter von 5-11 Monaten

Suchstrategie:
Suche in EMBASE (Datum der Suche: 01.08.2019)

('pertussis'/exp OR 'pertussis' OR 'pertussis vaccine'/exp OR 'pertussis vaccine') AND (effectiveness OR 'efficacy'/exp OR efficacy) AND ('infant'/exp OR infant OR 'child'/exp OR 'child')

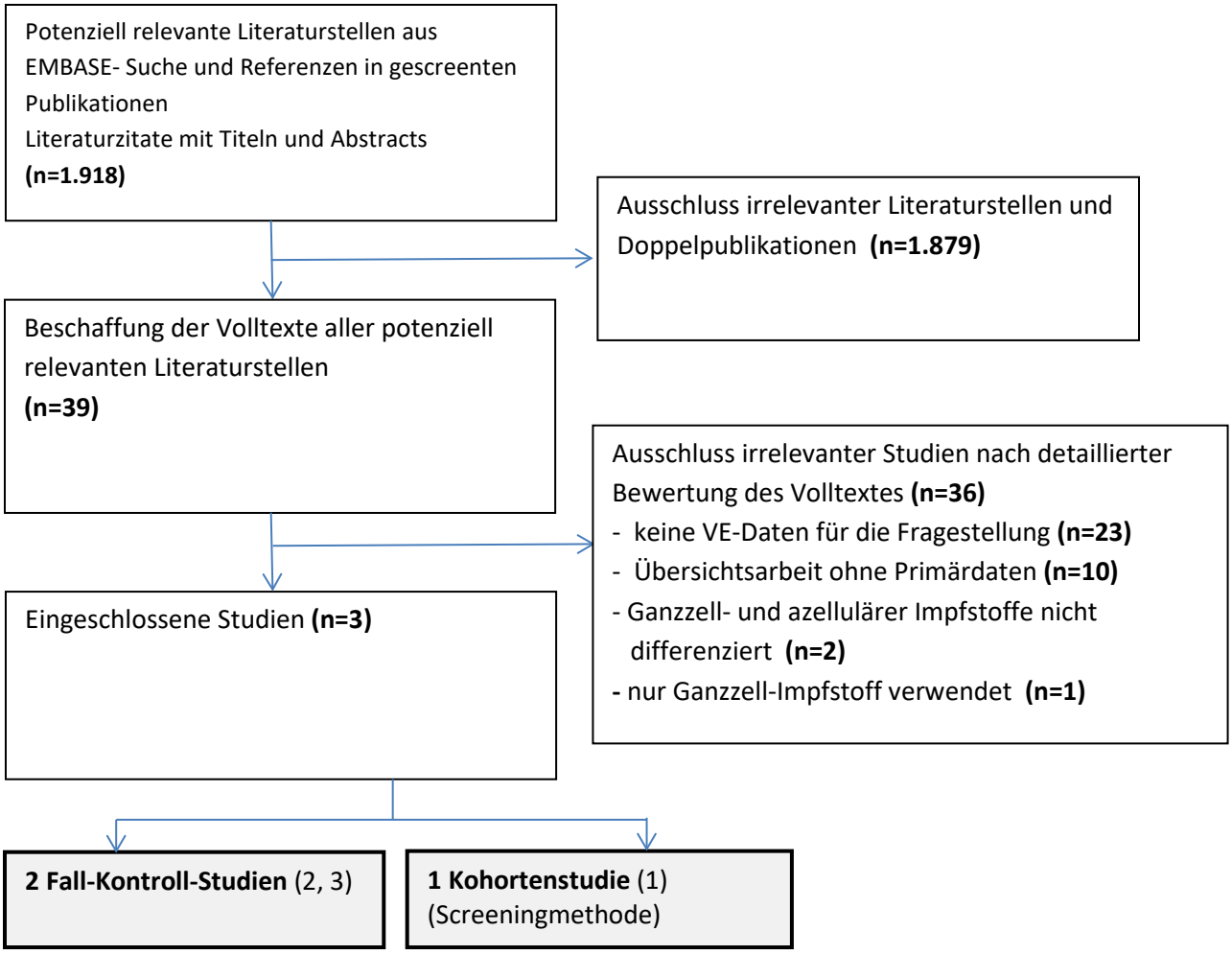

Abb. 1: Abbildung 1: Fließschema zum systematischen Review zur Effektivität der Pertussis-Impfung mit 2 Impfstoffdosen im Vergleich zu 3 Impfstoffdosen im Alter von 5-11 Monaten

3. Ein- und Ausschlusskriterien für die Identifikation von relevanten Studien für den systematischen Review zur Effektivität der Pertussis-Impfung mit 2 Impfstoffdosen im Vergleich zu 3 Impfstoffdosen im Alter von 6-11(12) Monaten

Tab. 2: Ein- und Ausschlusskriterien für die Identifikation von relevanten Studien für den systematischen Review zur Effektivität der Pertussis-Impfung mit 2 Impfstoffdosen im Vergleich zu 3 Impfstoffdosen im Alter von 6-11(12) Monaten

PICO-Kriterium	Einschluss-Kriterium	Ausschluss-Kriterium
P	Säuglinge im Alter von 6-11(12) Monaten	Andere Altersgruppen
I	-Impfung mit azellulärem Pertussis-Impfstoff (ausschließlich oder überwiegend); - 2 und 3 Impfstoffdosen im Alter von 5-11(12) Monaten	Ganzkeim-Impfstoff oder überwiegend Ganzkeimimpfstoff
C	keine Impfung, Placebo oder Impfung gegen einen anderen Erreger als Pertussis	
O	Pertussis jeglicher Form, Pertussis-Hospitalisierung, ambulant behandelte Pertussis, Pertussis-bedingter Tod	Andere outcomes, z.B. Immunogenitätsdaten
S	Beobachtungsstudien oder RCTs	
Veröffentlichungszeitraum	Keine zeitlichen Einschränkungen	

P=Population, I=Intervention, C=Comparator, O=Outcome, S=Studiencharakteristika

4. Extraktionen der eingeschlossenen Studien für den systematischen Review zur Effektivität der Pertussis-Impfung mit 2 Impfstoffdosen im Vergleich zu 3 Impfstoffdosen im Alter von 5-11 Monaten

4.1. Juretzko P., Von Kries R., Hermann M., Wirsing von König C.H., Weil J., Giani G. Effectiveness of acellular pertussis vaccine assessed by hospital-based active surveillance in Germany. Clinical Infectious Diseases (2002) 35:2 (162-167).(1)

Study	**Juretzko, 2002 (1)**
Reference	Effectiveness of acellular pertussis vaccine assessed by hospital-based active surveillance in Germany. Juretzko P., Von Kries R., Hermann M., Wirsing von König C.H., Weil J., Giani G. Clinical Infectious Diseases (2002) 35:2 (162-167).
Country	Germany
Study period	Vaccine coverage: June 1996 - December 1998; Data from hospitalized children with pertussis: 1997–1998; data from patients with pertussis complications: 1997–2000
Study design	Modified screening method; cases: ESPED; controls: telephone survey// Vaccination status in children who had been hospitalized as a result of pertussis was compared with the vaccination status of a random sample of the German population of the same birth cohort. //[VE = (PPV PCV)/[(1 PCV) PPV]
Study objective	To assess the efficacy of pertussis vaccine after partial and completed primary vaccination series for preventing hospitalizations due to pertussis under field conditions in Germany, where an acellular vaccine program was established in 1995.
Vaccine name (manufacturer)	not reported, probably a mix // Currently, acellular vaccines are used for 90% of primary vaccinations
Vaccine composition	not reported
Vaccination schedule	2, 3, and 4 months of age, with a booster administered between the 12th and 15th month of life
Comparator	no vaccination
Funding	German Research Association and SmithKline Beecham Pharmaceuticals
Conflict of interest	no information
Inclusion criteria (cases) PCV	cases of pertussis requiring hospitalization reported by ESPED; controls: age matched to cases For the estimation of vaccine effectiveness, only children who were eligible for 1 vaccination (2 months of age) were included.
Exclusion criteria (cases) PCV	no vaccination status available
Inclusion criteria (population) PPV	To ensure that subjects from the general population were similar to hospitalized patients with regard to vaccine coverage, only those persons born during the period of June 1996 through December 1998 were included.
Participants (study groups)	
Infant age at enrollment	>2 months - < 16years
Sex (% male) infants (if relevant)	
Initial no. of participants included	cases: 895
Final no. of participants analyzed for each endpoint	cases: 529 (35 with no questionnaire data); total of 371 children were eligible for at least 1 dose of vaccine; vaccination status was available for **349** children. for vaccination coverage: data were available for 667 children with known vaccination status and who were born during the period of June 1996 through December 1998.

Study	Juretzko, 2002 (1)
ascertainment of vaccination status	Telephone survey: read from vaccination booklet; If no vaccination booklet was available, the parents were asked whether the child had been vaccinated. If the child had been vaccinated, parental consent was sought to approach the pediatrician for the vaccination information. cases: questionnaire was sent to the pediatric department;
Differences between cases and controls	age distribution was comparable to that of the hospitalized children; To ensure that subjects from the general population were similar to hospitalized patients with regard to vaccine coverage, only those persons born during the period of June 1996 through December 1998 were included.
Confounders adjusted for	age-adjusted
Outcome Definitions	
Definition of pertussis disease	≥1 of the following, on the basis of information from the questionnaire: typical clinical symptoms (cough lasting for 14 days or a paroxysmal cough with whoops lasting for 4 days. When the patient had been exposed to a patient with a confirmed case of pertussis, a cough of 7 days' duration or a paroxysmal cough with whoops of any duration was accepted as typical. In children aged <6 months: apnea), positive results of serologic tests, and positive results of culture, PCR, or a direct immunofluorescence test.
Definition of hospitalization due to pertussis disease	
Outcomes	
VE for prevention of pertussis	
VE after 2 Doses; all (2-32 months)	91.8% (84.7–95.7)
VE after 3 Doses; all (2-32 months)	99.8% (98.9–100.0)
VE after 2 Doses; Patients with defined complications	95.9 (89.1–98.8)
VE after 3 Doses; Patients with defined complications	100 (99.2–100.0)
	selbst berechnet nach Orenstein et al.
VE after 2 Doses; 4-5 months	85,30%
VE after 3 Doses; 4-5 months	keine Angabe
VE after 2 Doses; 6-11 months	35,40%
VE after 3 Doses; 6-11 months	99,40%
VE after 2 Doses; 4-11 months	64,00%
VE after 3 Doses; 4-11 months	99,56%
VE for prevention of pertussis related hospitalization	not reported
VE after 2 Doses; all (>2 months)	
VE after 3 Doses; all (>2 months)	
Robins-I bias assessment tool	
Bias due to confounding	screening method, only age adjustment possible; Reporting bias by severity of disease—only the most severe cases are reported—cannot be excluded, because pertussis has been described as being milder in vaccinated children than it is in unvaccinated children; this would account for an overestimation of vaccine effectiveness **-> serious**.
Bias in selection of participants into the study/analysis	random-digit dialing method; Participants did not differ significantly from nonparticipants with regard to sociodemographic criteria **-> low**

Study	Juretzko, 2002 (1)
Bias in classification of interventions	screening method was modified, parents were asked to use vaccination booklets -> good acertainment of vaccination status **-> low**
Bias due to deviations from intended interventions	not applicable **-> low**
Bias due to missing data	good data completeness **-> low**
Bias in measurement of outcomes	not all cases were lab confirmed **-> moderate**
Bias in selection of reported result	no indication **-> low**
Summary:	**Serious risk of bias**
Comments:	

4.2. Quinn HE, Snelling TL, Macartney KK, McIntyre PB. Duration of Protection after First Dose of Acellular Pertussis Vaccine in Infants. Pediatrics. 2014;133(3). (3)

Study	**Quinn_2014 (3)**
Reference	Duration of protection after first dose of acellular pertussis vaccine in infants; Quinn H.E., Snelling T.L., McCartney K.K., McIntyre P.B. Pediatrics (2014) 133:3 (e513-e519). Date of Publication: 2014
Country	Australia
Study period	January 2005 to December 2009
Study design	matched case–control study; VE by number of doses and age group was calculated as (1 – odds ratio) * 100%.
Study aim	Assessing vaccine effectiveness of 1 and 2 doses of DTaP before 6 months of age and the effectiveness of 3 doses from 6 months to 4 years of age
Vaccine name (manufacturer)	DTaP combination vaccines from 1 manufacturer (Glaxo-SmithKline)//Infanrix
Vaccine composition	
Vaccination schedule	2+1 (3+0) schedule (2,4 and >6 months)
Comparator	no vaccination
Funding	This article presents independent research commissioned by the Commonwealth Department of Health and Ageing as part of a funding agreement with the National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases to conduct disease surveillance for vaccine-preventable diseases.
Conflict of interest	Professor McIntyre has received in-kind support from GlaxoSmithKline (GSK) in the form of vaccine supply and performance of serologic tests for a National Health and Medical Research Council–funded clinical trial of pertussis vaccine in newborns and a Foundation for Children–funded pilot study that preceded it. Dr Snelling was an investigator on a study of rotavirus vaccines funded in part by GSK Australia. The other authors have indicated they have no potential conflicts of interest to disclose.
Inclusion criteria	All pertussis cases in Australia with disease onset from January 1, 2005 (from January 1, 2006 only for Western Australia and from January 1, 2007 only for Tasmania) until December 31, 2009 were included. Eligible cases were patients aged 2 months to 4 years.
Exclusion criteria	Cases where immunization status was not recorded in the notification data set supplied by states and territories were excluded.
Participants (study groups)	**Cases:** pertussis cases in Australia with disease onset from January 1, 2005 (from January 1, 2006 only for Western Australia and from January 1, 2007 only for Tasmania) until December 31, 2009 **Controls** were randomly sampled from the ACIR (Australian Childhood Immunization Register). They were matched to cases by date of birth and state or territory of residence. **Because the analysis relies on discordance in vaccination status between cases and matched control**s, and given the high vaccine coverage for 3 or more doses of DTaP-containing vaccines (92% at 12 months and 95% at 24 months) and the ready availability of controls from the ACIR, we sampled 20 age-matched controls for each case to maximize precision. We selected eligible controls born on the day before or the day after the birth date of the index case to ensure that cases were not matched to themselves. The vaccination status of controls was ascertained using the ACIR. Any doses received by a control after the date of disease onset in their matched case were not included in the total.
Infant age at enrollment	Eligible cases were patients aged 2 months to 4 years
Sex (% male) infants (if relevant)	

Study	**Quinn_2014 (3)**
Initial no. of participants included	Of **5226** notified cases in the available data sets for the VE analysis, 642 (12%) were excluded because vaccination status was not recorded
Final no. of participants analyzed for each endpoint	**4584 case**s for the matched analysis
ascertainment of vaccination status	The vaccination status of notified cases was almost always derived from the Australian Childhood Immunization Register 4584 cases for the matched analysis. Cases for whom no record of vaccination status was available were significantly older (10% aged < 12 months versus 13% aged >=12 months; P<0.001) and more likely to be from the state of New South Wales (15% versus 6% elsewhere; P , .001).
Differences between cases and controls	Lack of gender and socioeconomic data for cases and controls, which may have been confounders in the analysis, although the large numbers of controls used should have minimized this effect.
Confounders adjusted for	Adjustment not possible due to lack of information
Outcome Definitions	
Definition of pertussis disease	A confirmed case requires either definitive laboratory evidence (detection by polymerase chain reaction [PCR] test or isolation by culture) or suggestive laboratory evidence (single point serology) together with a compatible clinical illness (coughing illness lasting 2 weeks and either coughing paroxysms, inspiratory whoop, or posttussive vomiting). During the period of the VE analysis, detection of B pertussis by PCR, using the IS481 target, accounted for the great majority of notifications. The majority of cases (92%) were diagnosed by PCR, with another 6% diagnosed by serology.
Definition of hospitalization due to pertussis disease	
Outcomes	
VE for prevention of all reported pertussis	
VE after 1 Dose; all (<4 months)	53.7% (95%CI 43.8; 61.9)
VE after 2 Doses; all (<6 months)	75.3% (95% CI 65.7; 82.3)
VE after 2 Doses; all (6-11 months)	80.8% (95% CI 73.5; 86.1)
VE after 3 Doses; all (6-11 months)	83.5% (95% CI, 79.1; 87.0)
VE for prevention of pertussis related hospitalization	
VE after 1 Dose; all (<4 months)	55.3% (95%CI 42.7; 65.1)
VE after 2 Doses; all (<6 months)	83.0% (95% CI 70.2,90.3)
VE after 2 Doses; all (6-11 months)	81.3% (95% CI 63,4,90.5)
VE after 3 Doses; all (6-11 months)	85.0% (95% CI, 75.0;91.0)
	Sensitivity analyses were conducted to evaluate the potential impact of differential immunization status among excluded cases with unrecorded vaccination status, where such cases were reclassified under the alternate extreme assumptions that they were all unvaccinated or all fully vaccinated for age. The relative VE of 1, 2, and 3 doses in infants, 12 months of age remained unchanged under both extreme assumptions.
Robins-I bias assessment tool	
Bias due to confounding	Controls were randomly sampled from the ACIR. They were matched to cases by date of birth and state or territory of residence. Comparisons of demographic characteristics between cases and controls were performed but not reported; no adjustment **-> serious risk of bias**

Study	Quinn_2014 (3)
Bias in selection of participants into the study/analysis	randomly sampled by date of birth and territory **-> low risk of bias**
Bias in classification of interventions	Australian Childhood Immunization Register; Sensitivity analyses were conducted to evaluate the potential impact of differential immunization status among excluded cases with unrecorded vaccination status, where such cases were reclassified under the alternate extreme assumptions that they were all unvaccinated or all fully vaccinated for age. **-> low risk of bias**
Bias due to deviations from intended interventions	not applicable **-> low risk of bias**
Bias due to missing data	no indication **-> low risk of bias**
Bias in measurement of outcomes	lab confirmation, PCR for majority **-> low risk of bias**
Bias in selection of reported result	no indication **-> low risk of bias**
Summary:	**serious risk of bias**
Comments:	There was a major increment in estimated VE to approximately 80% after the second dose but no detectable increase in VE after the third dose among children aged 6 to 11 months, despite large case numbers. This finding supports the approach of a delayed third dose, as practiced in many Scandinavian countries and recently adopted by France.

4.3. Zamir CS, Dahan DB, Shoob H. Pertussis in infants under one year old: risk markers and vaccination status—a case-control study. Vaccine. 2015;33(17):2073-8.(2)

Study	**Zamir_2015 (2)**
Reference	Pertussis in infants under one year old: Risk markers and vaccination status; A case-control study. Zamir C.S., Dahan D.B., Shoob H. Vaccine (2015) 33:17 (2073-2078). Date of Publication: 21 Apr 2015
Country	Israel, Jerusalem district
Study period	1998–2011
Study design	matched case-control study; Ratio: 1:3
Vaccine name (manufacturer)	no information
Vaccine composition	combined diphtheria–tetanus–acellular pertussis–Polio–Haemophilus influenzae B (DTaP–IPV–Hib) vaccine
Vaccination schedule	3+1 (2, 4, 6 months and a 12 months booster)
Comparator	no vaccination
Funding	no information
Conflict of interest	no information
Inclusion criteria	**cases:** infant under one year of age reported with pertussis during 1998–2011. **controls:** Three controls per case were randomly selected from the newborn registry. Controls were matched by birth date and residence in the district. The controls were checked against the notifications to ensure that they were not reported as pertussis cases.
Exclusion criteria	no information
Participants (study groups)	notified pertussis cases, infants younger than one year
Infant age at enrollment	Age (months) median (interquartile range) cases: 2.9 (1.6–5.5) ; controls: 2.9 (1.6–5.5)
Sex (% male) infants (if relevant)	cases: 180 (56.8%); controls: 483 (50.8%)
Initial no. of participants included	317 cases; 951 age-matched controls
Final no. of participants analyzed for each endpoint	169 cases during 2002–2010 ('aP vaccine period') and106 cases in 2011 ('epidemic year').
ascertainment of vaccination status	Routine childhood vaccinations are provided in well-baby clinics and immunization data are recorded in computerized health records in the vaccinations registry
Differences between cases and controls	Overall, the pertussis cases showed a higher proportion of low birth weight (LBW, <2500 g), a higher birth order (born 4th and above) and overrepresentation of males, compared to the control infants. The low birth weight proportion was 12.3% among cases and 6.3% among controls. Data on the socio-economic status were available for 910 infants (197 cases and 713 controls); the proportion of low socio-economic rank was higher among the cases compared to controls (49.5% vs. 33.2%OR = 2.09 95%CI = 1.51–2.92 p = 0.0001). The vaccination status (up-to-date) differed between cases and controls.
Confounders adjusted for	no information on the confounder that were adjusted for, but stated that adjustment was undertaken and conditional log. regression model was used.
Outcome Definitions	
Definition of pertussis disease	clinical pertussis as diagnosed by a physician, with or without laboratory confirmation; The physicians refer patients for laboratory tests based on the clinical presentation(acute cough illness with cough paroxysms, inspiratory "whoop",posttussive vomiting, or apnea with/without cyanosis). Laboratory tests included real time polymerase chain reaction (PCR) test for *B. pertussis* (since 2000) and/or serologic tests for immunoglobulin IgA and IgG antibodies to *B. pertussis* by a standardized enzyme-linked immunosorbent assay (ELISA).

Study	**Zamir_2015 (2)**
Definition of hospitalization due to pertussis disease	not applicable
Outcomes	
VE for prevention of pertussis	Vaccine effectiveness was also estimated for the three time periods of the study ('wP vaccine period' 1998–2001, 'aP vaccine period' 2002–2010 and 'epidemic year' 2011) with no significant difference between the time periods.
VE after 2 Doses; all (>2 months)	76.1; 95% CI: 60.6–85.6
VE after 3 Doses; all (>2 months)	84.4; 95% CI: 72.2–91.3
VE after 2 Doses; age 6–12 months	89.2; 95% CI: 69.5–96.2
VE after 3 Doses; age 6–12 months	98.5; 95% CI: 86.1–98.2
VE after 2 Doses; age 4–6 months	85.1; 95% CI: 59–94.6
VE for prevention of pertussis related hospitalization	not reported
VE after 2 Doses; all (>2 months)	
VE after 3 Doses; all (>2 months)	
Robins-I bias assessment tool	
Bias due to confounding	controls were matched, inspite of this differences in birth weight and socio-economic status are likely due to confounding; details on adjustement not reported, but adjustment was undertaken **-> serious risk of bias**
Bias in selection of participants into the study/analysis	no exclusions reported; no indication of selection bias **-> low risk of bias**
Bias in classification of interventions	vaccinations registry with probably well documented vaccinations, if misclassification than probably not differential **-> low risk of bias**
Bias due to deviations from intended interventions	deviation from vaccination not possible
Bias due to missing data	data for all recruited infants seemed to be available for all variables -> high data completeness **-> low risk of bias**
Bias in measurement of outcomes	laboratory confirmation was not mandatory; 6.4% of hospitalized and **21.8%** of non-hospitalized infants were only clinically/epidemiologically defined/had no lab confirmation -> this should not be differential between vaccinated and non-vaccinated infants, thus should not influence outcome **-> moderate risk of bias**
Bias in selection of reported result	comprehensive reporting **-> low risk of bias**
Summary:	**Serious risk of bias**
Comments:	combination of acellular and whole cell vaccine, percentages not reported > does not correspond to study question

5. GRADE Evidenzprofil

Authors: Sabine Vygen-Bonnet, Judith Koch
Date: 09.Juni 2020
Bibliography: Effectiveness of hexavalent vaccine in a 2+1 schedule vs. 3+1 schedule for the prevention of pertussis. Systematic Review 2019/2020.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hexavalent vaccine in a 2+1 schedule	Control	Relative (95% CI)	Absolute		
Pertussis 3+1 (assessed with: clinically and lab confirmation)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20 cases 136 controls		OR 0.01 (0.00 to 0.14)	-	⊕OOO VERY LOW	CRITICAL
								0.015%		148 fewer per 1,000,000 (from 129 fewer to 150 fewer)		
								0.03%		297 fewer per 1,000,000 (from 258 fewer to 300 fewer)		
								0.06%		594 fewer per 1,000,000 (from 516 fewer to 600 fewer)		
Pertussis 2+1 (assessed with: clinically and lab confirmation)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16 cases 53 controls		OR 0.11 (0.04 to 0.3)	-	⊕OOO VERY LOW	CRITICAL
								0.015%		133 fewer per 1,000,000 (from 105 fewer to 144 fewer)		
								0.03%		267 fewer per 1,000,000 (from 210 fewer to 288 fewer)		
								0.06%		534 fewer per 1,000,000 (from 420 fewer to 576		

										fewer)		
Pertussis hospitalisation 3+1 (assessed with: lab confirmation)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59 cases 1734 controls		OR 0.15 (0.09 to 0.25)	-	⊕OOO VERY LOW	CRITICAL
								0.015%		127 fewer per 1,000,000 (from 112 fewer to 136 fewer)		
								0.03%		255 fewer per 1,000,000 (from 225 fewer to 273 fewer)		
								0.06%		510 fewer per 1,000,000 (from 450 fewer to 546 fewer)		
Pertussis hospitalisation 2+1 (assessed with: lab confirmation)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16 cases 416 controls		OR 0.19 (0.09 to 0.37)	-	⊕OOO VERY LOW	CRITICAL
								0.015%		121 fewer per 1,000,000 (from 94 fewer to 136 fewer)		
								0.03%		243 fewer per 1,000,000 (from 189 fewer to 273 fewer)		
								0.06%		486 fewer per 1,000,000 (from 378 fewer to 546 fewer)		

[1] Bias due to confounding cannot be excluded in both studies. No or little adjustment of analyses. Only the most severe cases are reported. It has been described that Pertussis is milder in vaccinated children than it is in unvaccinated children. This would lead to an overestimation of vaccine effectiveness

6. Literatur zum Anhang

1. Juretzko P, von Kries R , Hermann M, Wirsing von König CH, Weil J, Giani G. Effectiveness of Acellular Pertussis Vaccine Assessed by Hospital-Based Active Surveillance in Germany, Clinical Infectious Diseases. 2002;35,(2):Pages 162-7, .
2. Zamir CS, Dahan DB, Shoob H. Pertussis in infants under one year old: risk markers and vaccination status—a case-control study. . Vaccine. 2015;33(17):2073-8.
3. Quinn HE, Snelling TL, Macartney KK, McIntyre PB. Duration of Protection After First Dose of Acellular Pertussis Vaccine in Infants. Pediatrics. 2014;133(3):e513-e9.