Immunization and Sudden Infant Death Syndrome : A meta-analysis

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= ABSTRACT =

Immunization and SIDS : meta-analysis

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Beginning with the reports of Hutcheson in 1979, a cluster of four cases of sudden infant death syndrome(SIDS) occurred among infants who had received within the previous 24h and injection of DTP, concern was raised that a recent history of DTP immunization could be associated with the occurrence of sudden infant death syndrome(SIDS). And, until now there are a lot of studies to quantitatively summarize the results of epidemiological researches on immunization and risk of SIDS. The aim of this study is to find out immunizations are risk factor for SIDS at the same time and safety based on previous studies through meta—analysis, to strengthen the statistical power of a hypothesis test of the relationship between immunization and SIDS.

Fourteen observational studies were identified using PUPMED, MEDLINE,

GOOGLE SCHOLAR, EMBASE, SCOPUS, RISS and a manual search. Summary odds ratios (ORs) for immunization and SIDS were calculated based on fixed and random effect models. The meta-regression analysis and stratified analyses were used to examine the effects of heterogeneity across the studies. Influence analysis was done to test robustness of the analysis.

The combined odds ratio indicates a reduced risk of SIDS with immunization(summary OR=0.48, 95% confidence interval(CI)=0.54-0.65). Notably, subgroup analysis with six studies which reported DTP or DTP with poliomyelitis immunization revealed a statistically significant protective effect (summary OR=0.60, 95% CI=0.41-0.88).

Immunization appears to play a protective role in the occur of SIDS. The result also implies that no increase between immunization and risk of SIDS, focusing in high incidence of SIDS which most frequently occurs in infants between two and five months of age , a period when many immunization are given. The result of this study, however, might be carefully interpreted. Considering the limited method of meta analysis and the possibility of diverse biases.

Key words : Immunization, Sudden Infant Death Syndrome(SIDS), Meta-analysis

1. Introduction

SIDS Family International(SIDSI) report that the incidence of SIDS in 2000 was less than 0.5 in 1,000 live births(SIDS Family International, 2000). According to an epidemiological data on SIDS for 2 years from 1997 to 1998 in Korea, the estimated incidence of SIDS cases was 0.56 per 1000 live births for a year(Ha and Yoon., 2004). The number of Sudden Infant Death Syndrome(SIDS) cases had been increased by from 116 cases in 1996 to 137 cases in 1999 according to the Ministry of Health & Welfare of Korea(1998). However, it was decreased by 101 cases in 2002(Ministry of Health & Welfare of Korea, 2002). 3.1% infants among 2631 infants who are died before the first birthday, born in 2002, were SIDS which was ranked in the reason of the death's top ten(Ministry of Health & Welfare of Korea, 2006).

Distribution of the dead infants by SIDS, which is reported to the National Statistical office of Korea(2005), are 103 cases in 2000, 87 cases in 2001, 89 cases in 2002, 88 cases in 2003, 70 cases in 2004, 76 cases in 2005(National Statistics Office of Korea, 2005). In our country, There is no accurate number of SIDS because of the uncertain pathologic classification and avoidance of autopsy(Ministry of Health & Welfare of Korea, 2007).

Risk factors of SIDS have been reported that 1) peak 2~5months of age(Culbertson, 1998), 2) high incidence in winter (Sternberg, 1961), 3)high incidence in black and

boys(Hunt and Hauk, 2006), 4)maternal risk factors are low social-economic level and age, low level of education, single marital status, short interval between pregnancies, substance use etc. Environment risk factors are carbon monoxide, carbon dioxide, bed sharing, hypothermia, hyperthermia etc., and genetic risk factors are autonomic nervous system, infection and inflammation, cardiac ion channelopathies related genes and promoter region of the serotonin(5-HTT)(Hunt and Hauk, 2006). Major as modifiable risk factor is prone sleeping position. After that of success the 'back to the sleeping' campaign reduced incidence of SIDS, focusing to the maternal smoking. Since the early 1990s, important modifiable risk factors such as prone and side sleeping, maternal smoking during pregnancy, cosleeping with the baby on the same surface, lack of breast feeding, no pacifier used at bed time(Vennemann et al, 2007) were studied by case-control studies..

In our country followed accidents in succession gave rise to public criticism, death of 2 months aged boy after vaccination of DTaP and polio at C-Won public health center in May, 25th 1998 and death of 2 months aged girl after vaccination of DTaP and polio with HPV at S-H Child Hospital in June, 27th, 1998 and death of 2months aged boy after DTaP and polio at K-N public health center in July, 7^{th,} 1998. Therefore, the people are became to distrust Health Center and pharmaceutical company which operate vaccination of DTaP and polio. Some doctors and parents causes a bar in National Immunization Work for the mean time. The dead infants are

estimated in unknown death or SIDS because specific reason is not founded through the autopsy(Ministry of Health & Welfare of Korea, 2000).

According to Mortimer and Jones(1979), pertussis vaccine occasionally produces severe reactions with permanent sequelae or death, but death associated with reaction has not been recorded and its pathogenesis has not been determined.

Taylor and Emery(1982) reported the results of 26 SIDS cases and 52 controls during the first three years(Aprial 1, 1979, to March 31,1982) about infant deaths in Sheffered. Babes who die unexpectedly are slightly less likely to have been received any form of immunization(DTP+polio or DT+polio, $p<0.05$) than controled infants and reveal no significant relation between recent immunization and sudden unexpected death. However, most unexpected deaths have a multifactorial aetiology and cannot exclude the possibility of recent immunization being one of several contributory factors in an occasional unexpected infant death.

Hoffman et al.(1987) had been conducted a Cooperative Epidemiological Study with NICHD(National Institute of Child Health and Human Development) and suggested that DTP immunization was not a significant factor in the occurrence of SIDS.

Since the early 1990s several well-designed case-control studies had demonstrated a number of risk factors for SIDS, such as the prone and side sleeping position, smoking of the mother in pregnancy and overheating (Fleming PJ et al., 1996; Jorc

et al., 1994; Mitchell et al., 1992; Findeisen et al., 2004). None of these studies had shown that immunization was a risk factor for SIDS. But the highest incidence for SIDS was between the second and the fifth months of life. At this time the first immunization was administered. The temporal association raised the question whether immunization is a risk factor for SIDS or not, some arguing that immunization is causing SIDS(Davies et al., 2002; Scheibner et al., 2003), a few of the studies suggest that vaccination is protective against SIDS (Michell et al., 1995; Fleming et al., 2001,Vennemann et al., 2007) and immunization should be part of the SIDS prevention campaigns(Vennemann et al., 2007).

In a recent meta-analysis conducted in Germany, the summary odds ratio (OR) in the univariate analysis, suggested that immunization was protective as o.58 fold decrease of SIDS risk (95%CI:0.46-0.73) but the heterogeneity was present. However, multivariate ORs was 0.54(95%CI:0.39-0.76) with no evidence of heterogeneity(Vennemann et al., 2007). These protective effects are supposed to be related to the healthy vaccine effect(Virtanen et al., 2000; Ehreth, 2003).

As recent rapid decrease in motality, SIDS is being given a great deal of weight on the reason of dead infant(National Statistical office, 2005). Yet research have not enoughly mentioned about risk factors and specific character of the disease.(Ministry of Health & Welfare of Korea, 2007). Moreover our country has no reasonal standard for prevention of SIDS by clarifying of risk factors and origination

of the disease and to make clear the relationship of vaccination and adverse event(Ministry of Health & Welfare of Korea, 2007). This study aims to bring case-control studies and cohort study together and perform a meta-analysis to increase the statistical power of the hypothesis test and to evidence based statement whether immunizations are risk factor for SIDS or not, and using considering immunization safety.

2. Methods

1) Literature search

Table 1 lists the 14 studies included in this meta-analysis. To search for observational studies of immunization and SIDS, we conducted a literature search using the following medical databases, PUBMED, MEDLINE, GOOGLE SCHOLAR, EMBASE, SCOPUS and RISS(to search for Korean literature), restricting to papers published from 1970 to Feburary 2008. For the search, we identified articles using such medical-subject heading terms as 'SIDS, SUDI, SUD, Sudden Infant Death Syndrome, Cot death' in combination with 'vaccination, vaccine, immunization, DTP, diphtheria, tetanus, pertussis, polio, BCG, MMR, measles, mumps, Rubella Hepatitis B, Haemophilus influencae B, epidemiology'. For Korean literature, used keywords '예방접종(immunization or vaccination, vaccine), 영아돌연사증후군 또는 영아급사증후군(SIDS)'.

2) Inclusion of the studies

SIDS is defined as the sudden, unexplained death of an infant younger than one year old : even if autopsy , the conditions and history in that time of death, and after examination(National Institute of Child Health and Human Development, 2000) but

included all case of SIDS whether no autopsy or death occurred during the 15-month time period.

All case-control and cohort studies about SIDS and immunization were considered. We only included articles that provide full information on the number of SIDS cases and controls.

There was no restriction on language, type of immunization, dose, frequency. If there were multiple publications from one study, only the publication with the most relevant information was used.

Initially twenty one papers in English(Hutcheson, 1979; Torch, 1982; Hoffman et al.,1982, Taylor and Emey,1982; Baraff et al., 1983; Hoffman et al.,1987; Walker et al.,1987; Flahault et al., 1988; Bouvier-Colle et al.1989; Jonville-Bera et al., 1995; Michell et al., 1995; Fleming et al., 1996; Alm B et al,1998; Jonville-Bera et al., 2001; Hauck et al,2003; Heininger, 2004; Eriksen, 2004; Matthews et al., 2004; Tappin et al, 2005; Vennemann et al., 2007a ;Vennemann et al., 2007b) were identified with the above-mentioned search method. Three reports(Hutcheson, 1979; Torch, 1982; Hoffman et al.,1982) were not opened because they were researched in CDC or other unknown reason. Baraff et al.(1983) was excluded because the control group was not specified. Two reports(Bouvier-Colle et al.1989; Vennemann et al., 2007b) were excluded because they were either a review article or meta-analysis of previously published works.

And the four case-control studies by Alm B et al(1998), Hauck FR et al(2003),

Matthews T et al(2004) , Tappin D et al(2005) were excluded because they have not reported the risk of SIDS with immunization and considered further.

Two more papers in English(Heininger, 2004; Eriksen, 2004) were identified from the reference list of the articles previously found. there were no papers conducted in Asia except the review article of SIDS risk factors(Ministry of Health & Welfare of Korea, 1989) and report of development of SIDS surveillance system(Ministry of Health & Welfare of Korea, 2007).

Vaccination schedules varied from country to country. In some countries it started at 6 weeks(New Zealand) but more commonly at 3 months. Sometimes the immunization schedule changed during a study period(New Zealand, Germany, USA)(Michell et al., 1995; Vennemann et al., 2007; Walker et al., 1987). Most reported immunization was the one type was diphtheria, tetanus, pertussis(DTP) except two studies(Heininger, 2004; Eriksen, 2004). And most studies was combined with oral polio and DTP, which was the common polio vaccine until the late 1990s and early 2000s when it was changed to an intramuscular inactivated polio virus vaccine in most countries. In this meta-analysis the DTP vaccine is used as a marker for immunization.

Taylor and Emery(1982) reported the results of 26 SIDS cases and 52 controls during the first three years(Aprial 1, 1979, to March 31,1982) about infant deaths in Sheffered. Babies who die unexpectedly are slightly less likely to have been received

any form of immunization(DTP+polio or DT+polio, $p<0.05$) than control infants and reveal no significant relation between recent immunization and sudden unexpected death. However, most unexpected deaths have a multifactorial aetiology and cannot exclude the possibility of recent immunization being one of several contributory factors in occasionally unexpected infant death.

Hoffman et al.(1987) has conducted a large multicenter(Chicago, California, New York City and Seattle, Upstate New York, St Louis) population based ,case-control , Cooperative Epidemiological Study with NICHD(National Institute of Child Health and Human Development). With a sample of 838 case infants(800 singleton and 38 multiple brith case infants) ascertained under a common necropsy protocol to establish SIDS during the 15-month period from October 1978 through December 1979. There were 1,600 age-matched living singleton control infants and 40 co-multiple birth control infants recruited into the study from six geographically defined study centers. The population of births included with the geographical areas of the six study centers represented approximately 10% of the total births annually in the United States. The comparison result of 757 SIDS infants, corresponding two control infants(n=1,514) and SIDS infants were less likely to have received any DTP immunization. Only 39.8% infants had been received at least one DTP and immunization compared to 55.0%, 53.2% respectively. 1.8% of SIDS infants, died within the first 24 hours following immunization with DTP immunized, were lower than the 2.2%, 5.0% of control infants. That suggested DTP immunization is not a

significant factor in the occurrence of SIDS. (1) Death occurred during the specified 15-month time period with the geographic region of a study center were included, (2)Any death of an infant younger than 14 days or older than 24 months of age were excluded.

In the report by Walker et al.(1987), the study population for the report consists of apparently health infants of birthweight greather than 2500 grams born in GHC; Group Health Cooperative of Puget Sound(GHC) is a consumer-owned health maintenance organization founded in 1945 which provides its members with full coverage for virtually all aspects of outpatient and inpatient medical care, hospitals from 1972 to 1983. who were subsequent user of GHC services. and for whom all medical records were retrievable in 1985 and 1986, the period during which this investigation was carried out. There were 35,581deliveries at GHC hospitals during the period study. All deaths occurring from 1972 through 1983 among GHC members from 30 to 365 days of age were identified by linkage of GHC membership files to State records. These deaths on the basis of death certificate diagnosis, hospital discharge data, and pharmacy taken together that could be clearly ascribed to causes not related to immunization. SIDS was defined as any death for which no cause could be discerned among infants of normal birthweight without predisposing medical conditions born at GHC hospitals from 1972 to 1983. The case series consisted of all 29 SIDS deaths.

Flahault et al.(1988) studied all cases that were notified as SIDS at the National

Register of Causes of Deaths, whose death had occurred between Jan 1, 1986, and March 31, 1986, and who were aged between 3 months and 1 year. Thus 228 cases were selected. The immunization history of 135 cases (59.2%) was obtained from the physician who had notified the death. These cases were matched for sex and age with 3 living controls with an available immunization history, selected from Protection Maternelle et Infantile(PMI) services, who hold the 8th-day-of-life certificates. The immunization history of the controls was obtained by a PMI nurse or physician who visited the children's parents. 401 controls were selected (in 4 cases could not match the third control). The closing data was the data of death for each case, and for the controls the date of reaching the matched case-age at death. Controls with an available immunization history were selected from the 8th-day-of-life certificates. Recall bias was possible, while a large proportion of children are notified to the PMI services, because children who are not notified are probably in the lowest socioeconomic classes, among which mortality rates are high and immunization status is low. A real association between DTP+polio(DTCP) immunization and SIDS could exist but was not detected in this study because of a lack of power. Under this hypothesis the relative risk associated with DTP+polio(DTCP) immunization would be less than 1.51.

Jonville-Bera et al.(1995) matched the controls of SIDS cases achieved epidemiological characteristics of SIDS: the predominance of males(Hoffman et al.1987), age(Nicholl and O'Cathan, 1989) and seasonal factor(Milner, 1987;. Nicholl

and O'Cathan, 1989), Thus each child who died from SIDS was matched with 2 or 3 living children of the sex born within the same month and year and seen by a medical practitioner within two weeks before or after of the victim. Children were examined by the same practitioner from general Practitioners and Hospital Departments within six contiguous counties referred the patients and took account only those children who were born between 1 Jan 1983 and 31 Dec 1987 and whose deaths were labeled SIDS in 132 children. This study defined SIDS as sudden death not explained by the infant's medical status. Fourteen cases were eliminated because of lack of data. The final study included 118 SIDS cases and the 332 control children were matched. In this study DTP+polio(DTCP) vaccination was not a risk factor SIDS, although more of the SIDS infants less than 3 months of age had been vaccinated.

Michell et al.(1995) had studied a large nationwide case-control study that covered 78% of all live births in New Zealand over a three year study period(1 Nov 1987 to 31 Oct 1990). There were 716 postneonatal deaths, Necropsies were carried out in 474 of the 485 SIDS cases(97.7%). The cases were compared with 1800 control infants, which were randomly selected from all births in the study regions except home births. The control infants were randomly allocated a nominated date to ensure group matching for infant age, and for a nominated time of day so that the distribution of this time for controls was similar to the expected distribution of the time of death for cases. And the records written by parents were used to measure immunization status. In this study, infants were at the increasing risk of SIDS if they had not

received the 6 weeks, 3 months, and 5 months immunizations and concluded that Immunization does not increase the risk of SIDS and may even lower the risk. Even though, controlling of potential confounding variables, including those which measured health care use and infant illness, the relative risk of SIDS for infants not being immunized at 6 weeks was 2.1(95% CI=1.2,3.5).

Fleming et al.(1996) set five region in England with a combined population of over 17 million which population based case-control study, from Feb 1993 to Mar 1996. Parental interviews were conducted for each death and for four controls matched for age, locality, and time of sleep. And immunization status was taken from records held by the parents. Immunization details were available for 93%(303/325) of infants whose deaths were attributed to the sudden infant death syndrome(SIDS); 90%(65/72) of infants with explained sudden deaths; and 95%(1515/1588) of controls. This study concluded that immunization does not lead to sudden unexpected death in infancy, and the direction of the relation is towards protection rather than risk.

Jonville-Bera et al.(2001) has conducted a multicentre case-control study in the 28 French ‘SIDS Centers’. Case selection was based on death labeled SIDS of an infant aged between 30 and 90 days. Identified 114 cases of Sudden Unexpected Death(SUD) and 341 live controls; these three living controls were selected, matched for sex, gestational age and born immediately after the victim in the same maternity unit as the case. DTTP ± Hib immunization is not a risk factor for early SUD.

Heininger U et al.(2004) had studied a prospective, controlled, multicenter study to investigate the relationship between Bordetella pertussis infections and sudden unexpected deaths among German infants between 1995 and 1997. All infants who died at 7 to 365 days of age and for whom autopsies were performed in 1 of 8 participating institutes of legal medicine were enrolled. Enrolled were 254 with sudden unexpected deaths and 441 matched control subjects. Autopsies were performed for 234 of the case subjects(92%), a diagnosis of SIDS was made for 76%. In conclusion, proportion of Pertussis immunizations was 8.5%(8/94)case, and 20%(79/405)controls(OR=0.38, 95%=0.18,0.82), B pertussis infection was found for 12 of 234 infants with unexpected deaths, and the infections might have contributed to the deaths.

The Vaccine Safety Datalink(VSD) Project is the largest and only population-based surveillance system for vaccine-associated adverse events in the United States, Eriksen et al.(2004) defined a birth cohort at Southern(SCK) and Northern(NCK) California Kaiser Permanente Health Plans of 361,696 living births from 1993 to 1998 and ascertained all deaths occurring under 29 days of age. And they performed detailed clinical reviews of all HBV-vaccinated neonates who died and a sample of unvaccinated neonates who died and were matched to vaccinated deaths for days of life, sex, birth year and site of care. The Mortality database is a cumulative dataset that is updated annually and comprises deaths identified by linkage of the health

maintenance organization(HMO) databases and the annual California Death Registry database(State of California Department of Health Services, Vital Statistics Branch). There were 1,363 neonatal deaths during the study period. Though only 72 of the 1,363 neonates that died received HBV and the rate of HBV immunization at birth for the birth cohort who survived at least was 66%(239,354 of 361,696) In this study, a relationship between HBV and neonatal death was not identified.

Vennemann et al.(2007a) did a large case-control study with immunization data on 307 SIDS cases and 971 controls in Germany between 1998 and 2001. Eighteen forensic pathology institutes were involved in the study and the area covered 50% Germany. Emergency doctors, police officers and forensic pathologists reported each case of sudden and unexpected death to the study centre after accepting parents agreement of the study. All cases were autopsied. For each case three controls were recruited through the local birth registration offices, matched for gender, age, region and reference sleep. And the controls had to be held by born 4-6 weeks later than the index case, so by the time the interview with control family took place the control infants had the same age as the index case. Reported that SIDS cases were immunized less frequently and later than controls Furthermore there was no evidence to suggest the recently introduced hexavalent vaccines which were associated with an increased risk of SIDS. And provided that immunizations may reduce the risk of SIDS.

3) Statistical analysis

ORs were extracted from each publications. A summary OR was calculated by using the fixed effect and random effect with inverse-variance methods.(Egger M, 2001) Standard errors of natural logarithm of the ORs or RR were calculated from 95% CIs of ORs/RRs. Statistical computing was performed using the STATA statistical software(version 9.0; Cloege Station,TX).

Possible heterogeneity in results across the studies was examined using the Q statistic(DerSimonian and Laird,1986).Statistical significance for the heterogeneity test was defined as $p<0.05$, However normality; defined as $p<0.10$ rather than the conventional level of 0.05 because of the low power of this test(Hedges and Pigott,2001). When there is significant evidence for heterogeneity between studies, then the random effect model was used to calculate summary OR(Sharp.1998) The causes for heterogeneity were explored through both meta-regression and Stratified analysis. The following variables were investigated as potential contributing factors to the heterogeneity among studies: country where the study was conducted (Europe, USA and New Zealand),year of publication(before 2000 versus on and after 2000), and type of immunization(DTaP±oral polio versus others).

Results of a meta-analysis may be biased if the publication of a study is dependent on the positive results. Generally studies that show a statistically significant effect of intervention are more likely to be published, more likely to be published in English,

more likely to be cited by other authors, and more likely to be produce multiple publications than other studies(Sterne et al.,2001). To detect a possible publication bias, Begg's funnel plot was visually explored for any asymmetry. Funnel plots are simple scatter plots of the effects estimated from individual studies on the horizontal axis against some measure of study size, which is believed to reflect the precision in the estimation, on the vertical axis(Sterne et al,2001) in the absence of a publication bias, the funnel plot should be symmetrical with estimates. The funnel plots would be skewed in the presence of a publication bias. To formally test a publication bias, Egger's un-weighted regression asymmetry test(Egger et al.,1997) was done. The funnel plot was considered to be asymmetrical if the intercept of Egger's regression line deviated from zero with a p value of less than 1.0. Caution has to be paid, however, as the capacity to detect bias will be limited when meta-analysis are based on a limited number for small trials(Egger et al.,1997), which is the case in this view.

To test the robustness of the meta-analysis, influence analysis was performed. Influence of each study was estimated by deleting each in turn from the analysis and noting the degree to which the size and significance of the intervention effect change(Deeks et al. ,2001).

3. Results

Fourteen studies(Taylor and Emey,1982; Hoffman et al.,1987; Walker et al.,1987; Flahault et al., 1988; Jonville-Bera et al., 1988; Michell et al., 1995; ;Fleming et al., 1996; Heininger, 2004; Jonville-Bera et al.,2001 Eriksen, 2004; Vennemann et al., 2007) were included in the meta-analysis on immunization and SIDS. There were one cohort study(Eriksen, 2004), thirteen case-control studies. Nine studies were conducted among European population in Europe(Taylor and Emey., 1982; Flahault et al., 1988; Jonville-Bera et al., 2001; Fleming et al., 1996; Michell et al., 1995, three studies were conducted among American population in USA. No korean or Asia study in inclusion criteria.

Table 1 presents the characteristics of the studies used in the analysis.

Table 2 shows the first author, type of immunization, the number of cases and controls immunised and the total number of subjects in each study and the univariate odd ratio (OR) and 95% confidence intervals(95% CI) for the risk of SIDS if immunised.

The summarized odds ratio for the studies was 0.48(95% CI=0.54-0.65)(Fig.1), indicating that immunization is associated with a significant reduction in the risk of

SIDS. However, heterogeneity was present (Q=91.079, p<0.001).

Table 3 presents the results of the subgroup analysis according to country(Europe, USA and New Zealand), year to publication, type of immunization(DTaP or DTaP + oral polio, BCG, HepB[b,], Combined DTaP, oral polio), study design. Results among nine Europe studies were heterogeneous. (p=0.003) with significant risk reduction of 51%(Summory OR=0.49, 95% CI=0.31-0.79). USA and New Zealand studies was divergent(p=0.006, 0.009 respectively) however (Summary OR=0.64 and 0.98, 95% CI=0.47-0.89 and 0.85-1.12 respectively).

When stratified by the type of immunization(DTaP or DTaP + oral polio, BCG, HepB[b,], Combined DTaP, oral polio) all subgroup except BCG immunization have shown significant risk reduction(Summory OR=0.44, 95% CI=0.07-2.6), but still remined the heterogeneity in each subgroup., (DTaP or DTaP + oral polio , p<0.004)**(Fig.2).**

Statistically significant inverse association between immunization and SIDS was observed in ten case-control studies (Summary OR=0.82, 95% CI=0.74-0.94), year of publication (before 2000 versus on and after 2000 ; Summary OR=0.89 and 0.58,

95% CI=0.79-1.0 and 0.43-0.77 respectively). And their results were consistent to each other($p<0.001$ respectively).

Table 1. Characteristics of observational studies on immunization and SIDS

Ref. number	Reference	Publication year	Country	Design	Type of immunization	SIDS Group		Control Group	
						No. of immunised / No. of cases		No. of immunised / No. of controls	
1	Taylor and Emery,	1982	Sheffield, UK	Case-control	DTaP[a], polio	8	26	27	52
2	Hoffmann et al.	1987	NICHD, USA	Case-control	DTaP[a], oral polio	285	716	818	1,514
3	Walker et al.	1987	GHC, USA	Case-control	DTaP[a]	23	29	213	225
4	Flahault et al.	1988	France	Case-control	DTaP[a], oral polio	54	135	189	401
5	Jonville-Bera et al.	1995	France	Case-control	DTaP[a]	38	118	90	332
6	Michell et al.	1995[1)]	New Zealand	Case-control	BCG	219	317	1,000	1,524
7	Michell et al.	1995[2)]			DTaP[a], oral polio, HepB[b]	233	279	1,256	1,373
8	Jonville-Bera et al.	2001[1)]	France	Case-control	DTaP[a], HIB[c]	14	114	47	341
9	Jonville-Bera et al.	2001[2)]			BCG	6	37	117	123
10	Jonville-Bera et al.	2001[3)]			HepB[b]	3	114	10	341
11	Fleming et al.	2001	UK	Case-control	DTaP[a], oral polio, HepB[b]	149	303	822	1,234
12	Heininger U. et al	2004	Germany	Case-control	Pertussis	8	94	79	405
13	Vennemann et al.	2007	Germany	Case-control	DTaP[a], oral polio, HepB[b], HIB[c]	154	307	585	971
14	Eriksen. et al	2004	UCLA, USA	Cohort	HepB[b]	22	90	239,354	361,606

[a] Diphtheria ,tetanus, and pertussis vaccine

[b] Hepatitis B

[c] Haemophilus influencae B

[1)2) 1)2)3)] Same Study

Table 2. Meta-analysis of immunization and SIDS

Reference	Type of immunization	SIDS Group No. of immunised /No. of cases(%)		Control Group No. of immunised /No. of controls(%)		Odds Ratio (RR)/(95%CI)	Weight%
Taylor and Emery, 1982	DTaP[a], polio	8/26	(30.8)	27/52	(51.9)	0.41(0.15-1.11)	1.7
Hoffmann et al.1987	DTaP[a], oral polio	285/716	(39.8)	818/1,514	(54)	0.56(0.47-0.67)	3.1
Walker et al. 1987	DTaP[a]	23/29	(79.3)	213/225	(94.7)	0.22(0.07-0.63)	1.6
Flahault et al. 1988	DTaP[a], oral polio	54/135	(40)	189/401	(47.1)	0,75(0.50-1.11)	2.8
Jonville-Bera et al. 1995	DTaP[a]	38/118	(32.2)	90/332	(27.1)	1.28(0.81-2.01)	2.7
Michell et al. 1995[1)]	BCG	219/317	(69.1)	1,000/1,524	(65.6)	1.17(0.90-1.52)	3.0
Michell et al. 1995[2)]	DTaP[a], oral polio, HepB[b]	233/279	(83.5)	1,256/1,373	(91.5)	0.47(0.33-0.68)	2.8
Jonville-Bera et al. 2001[1)]	DTaP[a], HIB[c]	14/114	(12.3)	47/341	(13.8)	0.88(0.46-1.66)	2.4
Jonville-Bera et al. 2001[2)]	BCG,	6/37	(16.2)	117/123	(95.1)	0.01(0.00-0.03)	1.5
Jonville-Bera et al. 2001[3)]	HepB[b,]	3/114	(2.6)	10/341	(2.9)	0.89(0.24-3.31)	1.3
Fleming et al. 2001	DTaP[a], oral polio, HepB[b]	149/303	(49.2)	822/1,234	(66.6)	0.48(0.38-0.63)	3.0
Heininger U et al. 2004	DTaP[a]	8/94	(8.5)	79/405	(19.5)	0.38(0.18-0.82)	2.1
Vennemann et al. 2007	DTaP[a], oral polio, HepB[b], HIB[c]	154/307	(50.2)	585/971	(60.2)	0.66(0.51-0.86)	3.0
Eriksen et al. 2004	HepB[b]	22/90	(24.4)	239,354/361,606	(66.2)	0.17(0.10-0.27)	2.7
Overall Odds Ratio						**0.48(0.34-0.67)**	

[a] Diphtheria, tetanus, and pertussis vaccine

[b] Hepatitis B

[c] Haemophilus influencae B

[1)2) 1)2)3)] Same Study

* Estimates of the summary ORs and 95%CIs were based on random effect model

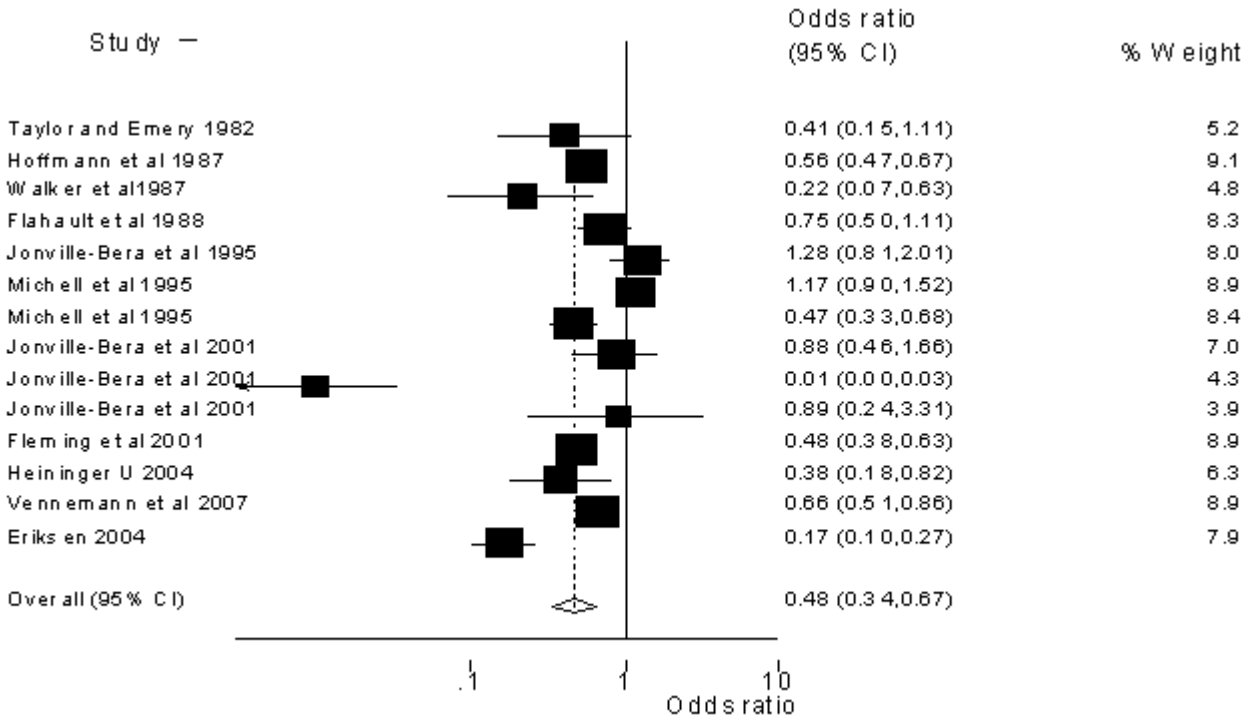

Figure1. Forest plot of odds ratio from fourteen observational studies on immunization and SIDS

The black squre and horizen line correspond to the odds ratio and 95% confidence interval. The area of the black squares reflects the weight each trial contributes to the meta-analysis. The diamond at the graph represents the combined odds ratio and its 95% confidence interval, indicating 52% reduction in the risk of sids. The solid vertical line corresponds to no effect of immunization. (odds ratio,1.0), the dotted vertical line to the combined odds ratio(0.48(0.34-0.67)). The graph was produced in STATA.

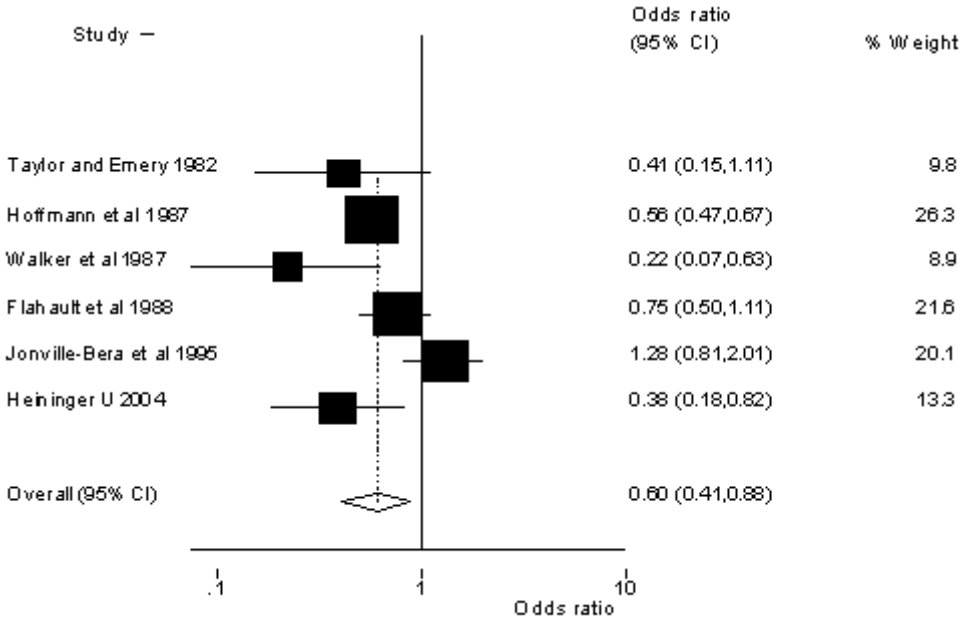

Figure 2. Forest plot odds ratio of SIDS from six studies whose type of immunization was the DTaP oral polio.

SIDS was observed thirteen case-control studies and one cohort study(Summary OR=0.82 and 0.37, 95% CI=0.74-0.94 and 0.26-0.53 respectively) and their results were consistent to each other.($p<0.000$, respectively) to support the association

Table 3. Meta-analysis of Subgroup on immunization and SIDS

Category of Studies	Subgroup	No.of Studies	Summary OR (95%CI)*	P for heterogeneity
All studies	NA	14	**0.48(0.34-0.67)**	<0.000
Country	Europe (UK, France, Germany)	9	0.49(0.31-0.79)	0.003
	USA	3	0.64(0.47-0.89)	0.006
	New Zealand	2	0.98(0.85-1.12)	0.009
Year of publication	Published before 2000	7	0.89(0.79-1.0)	<0.000
	Published after 2000	7	0.58(0.43-0.77)	<0.000
Type of immunization	DTaP ± oral polio†	6	0.60(0.41-0.88)	0.004
	BCG	2	0.44(0.07-2.6)	<0.000
	HepB[b,]	2	0.46(0.22-0.99)	0.046
	Combined DTaP, oral polio‡	4	0.84(0.74-0.94)	0.015
Study design	Case-control	13	0.82(0.74-0.94)	<0.000
	Cohort	1	0.37(0.26-0.53)	_

† DTaP or DTaP + oral polio(one case is the polio)

‡ DTaP + oral polio with BCG, Hepatitis B(HepB) , Haemophilus influencae B(HIB)

[+] BCG or Hepatitis B(HepB)

* Estimates of the summary ORs and 95%CIs were based on random effect model if the studies included are heterogeneous(i.e.p for heterogeneneity is less then 0.05)

Figure 3 presents Begg's funnel plot. Visual exploration of the plot revealed apparent asymmetry, smaller studies tended to reports large effect, while larger studies reported both positive and negative results. This implies a publication bias in the reporting of results on immunization and risk of SIDS. The result of Egger's test also supported the suspicion.

However, negative sign (â = -2.041(-5.436.1.354), p for bias 0.215) means that small studies are corelation with larger treatment effect. and this is not significant statistically by Eegg's linear regression test.

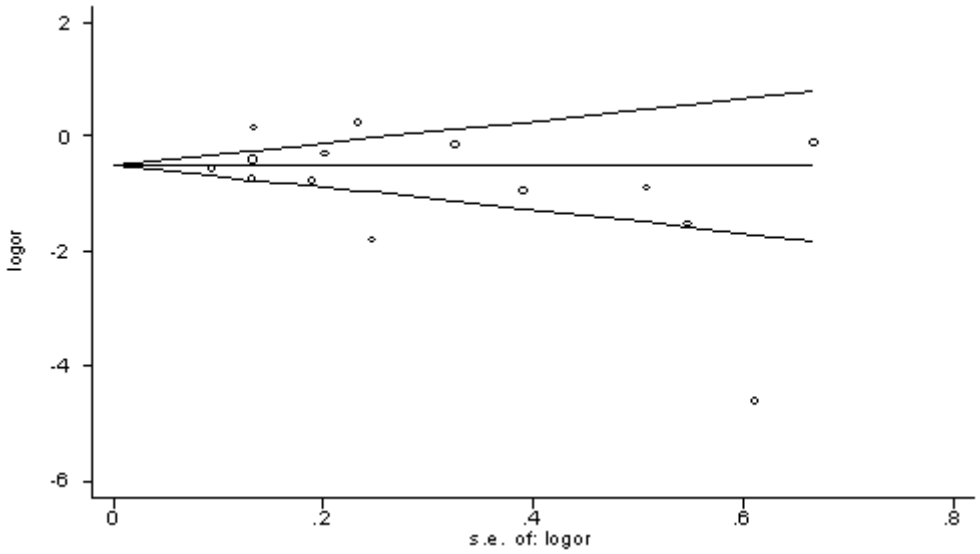

Figure3. Begg's funnel plot with 95% confidence limits on immunization and SIDS

Figure 4 presents results of the influence analysis. When combined odds ratios were computed ommiting one study at a time, no single study seemed to dominate the meta-analysis.

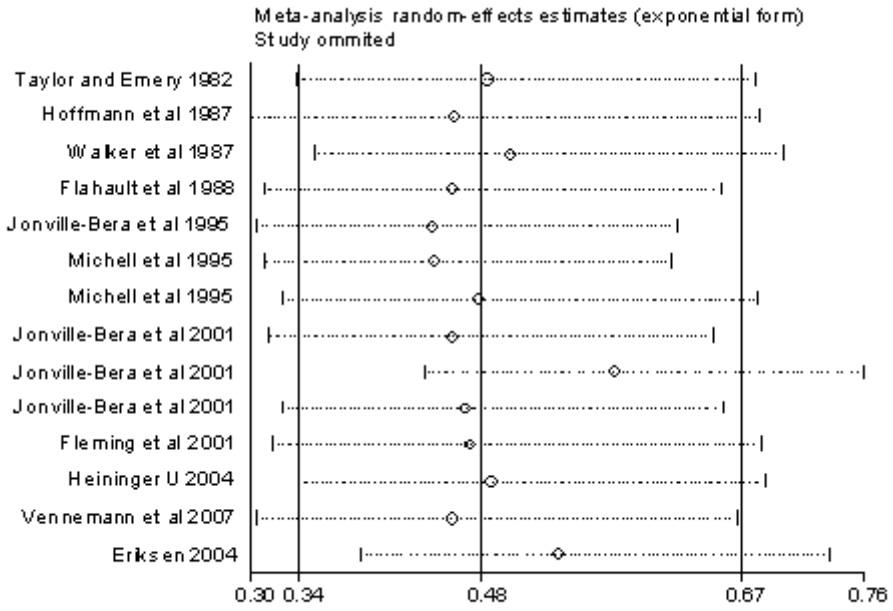

Figure4. Influence analysis of studies on immunization and SIDS. open circles indicate estimates of combined odds ratio when a study was omitted. The graph was produced in STATA.

4. Discussion

This meta-analysis has shown immunization is associated with a significantly lower risk of SIDS based on previously published researches.

The overall summary OR immunization and SIDS risk, based on fourteen observational studies, indicated a statistically significant 52% risk reduction in the case group. Substantial heterogeneity across the studies, mainly derived from the small numbers of cases and studies, was also noted.

However, before discussing the possible reason for this finding the potential limitations must be considered. First of all, selection and information bias cannot be ruled out in this study combined results from observational studies. The selection and confounding will often distort the results of a meta-analysis(Pocock and Elbourne, 2000). This results can be more prominent for preventive intervention studies like this, because the controls are more likely to be chosen and socioeconomically advantaged infants by parents with health concerns. These can be more likely to immunize their child(Egger et al., 2001), though, the control infants were randomly matched for sex

and age, or gender, time of death or sleep with 2 or 3 living controls with an available immunization history. Reported that SIDS cases were immunized less frequently. Controlling for socioeconomic status and other factors should be adjusted for this, but this study investigated only univariate analysis, so some residual confounding cannot be excluded.

Secondly , protective effects shown by case-control studies may have been also biased. Generally, case-control studies are subject to be influenced by a recall bias, which is a form of information bias, and it could lead to a spurious association(Egger et al., 2001). Recall bias was possible while a large proportion of children are notified to the hospital services, because children who are not notified are probably in the lowest socioeconomic classes, which mortality rates are high and immunization status is low. And the immunization history of the controls was obtained by a nurse or physician who visited the children’s parents or medical record s and the case infants was taken from records held by the parents and medical records.

Thirdly, publication bias could have distorted the result. Tweedie et al. reported that 45% of an observed association could be due to publication bias(Tweedie et al., 1996). As published data may be systematically different from unpublished ones, reviews or

meta-analyses based on published data may only reach a misleading conclusion(Thornton and Lee, 2000). Because of the asymmetric funnel plot, publication bias cannot be ruled out in this study.

Fourthly, there is considerable clinical diversity in the studies. The studies include different immunization schedules. The studies were undertaken both before and after the "back to sleep" campaigns, which have resulted in changes in the epidemiology of SIDS(Blair PS, 2006; Michell EA, 1997).

Lastly, there is methodological diversity. The quality of the studies varied n differences in the percentage of SIDS case autopsied, participation rates, and ascertainment of immunization status based on clinical records or parental interview. In the univariate analysis there was statistical heterogeneity, Which indicates that the summary OR must be treated with caution. Controlling for socioeconomic status and other factors should be adjusted for this, but this study investigated only univariate analysis, so some residual confounding cannot be excluded. However, multivariate analysis was absent in this study, Confidence in the summary OR which shows that the risk of SIDS was more than half by immunization.

There are a number of possible explanations for this finding. The seasonal distribution

in the occurrence of SIDS(Michell EA et al, 1997) and the high prevalence of respiratory tract symptoms suggests infection is a factor in SIDS(Gilbert RE et al,1990). A number of different viruses and bacteria have been implicated that this is a risk factor of SIDS(Rambaud C et al., 1999).

In the past much attention has been focused on pertusis immunization, because of concerns about encephalopathy with this vaccine(Cherry JD, 1984). Bordetella pertussis, especially important as an association between epidemic pertussis and sudden unexpected death in infants, has been observed(Lindgren C et al, 1997) and B. pertussis infection in infants frequently causes apnea(Southall DP et al, 1988). B. pertussis infection might have contributed to the deaths. If apnea leads to the death of the infant the cause of death may inappropriately be labeled as SIDS. The immunization schedules in the studies reported here all included immunization with B. pertussis. Immunization may reduce the incidence of reported SIDS by reducing unrecognized B. pertussis infection. Immunization may also cause non-specific enhancement of immunological activity and reduce infection from other viruses and bacteria not directly covered by the vaccines given(Aaby P et al.,1995; Otto S et al., 2000).

The immediate effect of immunization is similar to that of a mild infection. In view of the often reported association of SIDS with minor infection the ECAS study

specifically examined whether risk of SIDS was associated with immunization in the last 7 days. They reported that univariatly the OR was quite insignificant(OR=1.27 with 95% CI=0.89-1.81).Immunizations may be indirectly associated with a reduction in SIDS. Vaccination the so-called healthy vaccine effect may be avoided during illness and infections(Virtanen M et al, 2000).Thus the reduction in SIDS with immunizations may be a marker of the well being of the infant, though directly related to the immunization.

Children born in poor socio-economic circumstances are less likely to be immunized(Samad L et al, 2006; Hambidge SJ et al ,2006) In one risk factors for lack of immunization include low socio-economic status, maternal smoking and intention not to breastfeed(Hambidge SJ et al ,2006), all of which are known risk factors for SIDS. This illustrates the importance of confounding(Fine PE et al,1992). However the multivariate analysis of the studies controlled for these factor was not conducted in this study.

The benefits of immunization are well established(Ereth J,2003) if a country changes their immunization schedule to a different age. This provides an opportunity to examine changes in the SIDS mortality rate for the age group covered by the change in immunization. If there is a causal relationship between immunization and reduction

in SIDS, then SIDS mortality may be reduced further by achieving high immunization rates at the scheduled times in early infancy.

Negative effects shown by three reports(Hutcheson, 1979; Torch, 1982; Hoffman et al.,1982) was not opened because of unknown reason. However, most of studies in this investigation, lead to protective effect of immunization or no relationship between immunization and SIDS.

5. Conclusion

In summary, the result of this meta-analysis suggests a protective role of immunization on SIDS. Caution has to be paid, however, because this result might have been biased by limitations of the research design and data collection.

The combined result indicates a reduced risk of SIDS with immunization(summary OR=0.48, 95% confidence interval(CI)=0.54-0.65). Notably, subgroup analysis with six studies which reported DTP or DTP with poliomyelitis immunization revealed a statistically significant protective effect (summary OR=0.60, 95% CI=0.41-0.88).

Subgroup analyses revealed that the difference among the types of immunization, DTaP ± oral polio and, Combined DTaP ± oral polio, BCG, HepB[b], was found to be the most prominent factor affecting the heterogeneity of the meta-analysis. But this is not implies that the types of immunization might be a single most important factor in determining the preventive effect of immunization on SIDS.

Immunization appears to play a protective role in the occur of SIDS. And revealed that there were different types of immunization. The result also implies that no

relationship between immunization and SIDS, focusing in high incidence of SIDS which most frequently occurs in infants between two and five months of age, a period when many immunization are given. The result of this study, however, might be carefully interpreted. Considering the limited method of meta analysis and the possibility of diverse biases.

Further research focusing on temporal relationship immunization and SIDS, that is enormously in the detail of data acquisition and in the thoroughness of analysis, is needed to clarify the association.

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APPENDIX

Appendex. Table 1. Odds Ratio/RR of SIDS in the days following

Reference	Type of immunisation	Days since last vaccine			Odds Ratio (RR)/(95%CI)
		Definition	Duration	Case	
Taylor and Emery.	DTaP[a], oral polio	3< days	2.5	1	2.8(0.41-20)
		3-7 days	5	0	0(0-5.4)
		8-28 days	21	5(3)	1.0
		>28 days		2	
		total		8	
Hoffmann et al.	DTaP[a], oral polio	24h< days	1	5	
		<14 days	14	93	
		>14 days		187	
		total		285	
Walker et al.	DTaP[a]	3< days	3.5	4	3.5(1.2-9.9)
		4-7 days	4	2	1.4(0.33-5.7)
		8-29 days	22	8	1.0
		>30 days		9	
		total		23	
Flahault et al.	DTaP[a], oral polio	24h< days		6	RR(1.81)
		3< days		8	RR(2.59)
		3-7 days		17	RR(3.01)
		total		31/54	
Michell et al.	BCG,DTaP[a], oral polio,HepB[b]			P-value	OR(95%CI)
		24h<		0.6	0.7(0.2-2.8)

		days		
		24h	0.8	0.9 (0.2-2.4)
		2day	0.14	0.5(0.2-1.2)
		3day	0.06	0.5(0.2-1.0)
		4day	0.03	0.5 (0.2-0.9)
		5day	0.06	0.6 (0.2-1.0)
		6day	0.13	0.7(0.2-1.1)
		7day	0.07	0.6 (0.2-1.0)
		8day	0.06	0.6 (0.2-1.0)
		9day	0.2	0.8(0.5-1.2)
Vennemann et al.	DTaP[a], oral polio, HepB[b], HIB[c]		Case	Control OR(95%CI)
		1day	1(2.4%)	5(2.4%) 0.56(0.07-4.79)
		2day	6(14.6)	31(2.4%) 0.63(0.26-1.53)
		3day	9(22.0)	45(24.6) 0.63(0.30-1.32)
		4day	11(26.8)	61(24.6) 0.55(0.29-1.08)
		5day	18(43.9)	74(40.4) 0.74(0.43-1.26)
		6day	21(51.2)	83(45.4) 0.76(0.46-1.26)
		7day	24(58.5)	96(52.5) 0.74(0.46-1.19)
		8day	28(68.3)	114(62.3) 0.72(0.46-1.12)
		9day	28(68.3)	127(69.4) 0.63(0.40-0.97)
		10day	31(75.6)	143(78.1) 0.60(0.40-0.92)
		11day	34(82.9)	151(82.5) 0.63(0.42-0.95)
		12day	36(87.8)	159(86.9) 0.63(0.42-0.94)
		13day	39(95.1)	171(93.4) 0.64(0.43-0.93)
		14day	41	183 0.63(0.43-0.92)

[a] Diphtheria,tetanus,and pertussis vaccine

[b] Hepatitis B

[c] Haemophilus influencae B

국문 요약

예방접종과 영아급사증후군 : 메타 분석

예방접종과 영아급사증후군과의 관계에 대한 연구는 1979 년 Hutcheson 이 디티피 백신을 접종 받고 24 시간 이내에 영아급사증후군으로 사망한 4 명을 보고한 후 디티피 백신 접종에 의한 영아돌연사 증후군 발생 가능성이 대두되었다. 그리고 예방접종과 영아급사증후군의 관계에 대한 다양한 역학적 연구 결과를 병합하려는 시도는 현재까지 이루어지고 있다. 이 연구의 목적은 기존에 발표된 연구 결과를 토대로 메타 분석을 통하여 예방접종과 영아급사증후군 위험 사이의 관계에 대한 가설 검정력을 강화함과 예방접종이 영아급사증훈군의 위험요인인지 밝히고, 동시에 예방접종의 안정성을 밝히려는 것이다.

PUPMED, MEDLINE, GOOGLE SCHOLAR, EMBASE, SCOPUS, 한국학술정보원 데이터베이스와 이를 통해 찾은 자료의 참고 문헌을 조사하여 총 열 네 편의 관찰 연구를 확인하였다. 각 연구에서 예방접종과 영아급사증후군 사이의 승산비를 병합하였으며, 통합 효과 크기는 동질성 검정 결과에 따라 고정 효과 모형 혹은 확률 효과 모형을 사용하여

계산하였다. 각 연구 사이의 이질성을 설명하기 위해서 메타 회귀 분석 및 층화 분석을 실시하였고, 결과의 확고성을 확인하기 위하여 영향력 분석을 실시하였다.

예방접종과 영아급사증후군의 관계에 대한 통합승산비는 0.48, 95% 신뢰구간은 0.54-0.65 으로 예방접종과 영아 돌연사 증후군 사이에는 유의한 음의 상관 관계가 존재하였다. 특히 디티피와 폴리오 또는 폴리오를 예방접종한 여섯개의 연구들에서 통계적으로 유의한 보호 효과가 확인되었다(통합승산비 0.60, 95% 신뢰구간 0.41-0.88).

결론적으로 예방접종은 영아급사증후군에 대해 보호 효과를 보이는 것으로 확인되었다. 또한 이러한 효과는 예방접종의 종류별로 약간의 차이가 있었으나, 영아 돌연사가 많이 발생하는 2~5 개월 접종 스케줄에 의해 논란이 되어왔던, 디티피와 폴리오 또는 폴리오 예방접종이 영아급사증후군의 위험을 증가시키는 것은 아니다라고 확인 되었다. 그러나 관찰 연구에 대한 메타 분석의 방법론적 한계와 이 연구에서의 출판 편견의 가능성 등을 고려할 때, 이러한 결과는 조심스럽게 해석되어야 할 것이다.

중심단어 : 예방접종, 영아급사증후군, 메타분석