TUM Fakultät für Medizin

Institut für Medizinische Statistik und Epidemiologie

Economic Evaluation of Universal Varicella Zoster Immunization Programs in Developed Countries - A Meta Analysis

Christoph Paul Klapproth

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Abstract

Universal varicella zoster virus (VZV) vaccination programs have been adopted by several countries during the last decades. Policy makers were hoping this would turn out to be cost saving to both public health providers and society. Several studies and systematic reviews addressing this matter have been conducted, not yet though a meta analysis.

The aim of this paper is to quantitatively assess the degree of economic effectiveness of universal VZV vaccination programs in a meta analysis. This is done by introducing a standardized measure ER (Effectiveness Ratio) in order to compare strategy "vaccination program" to strategy "no vaccination program" from both payer's and society's perspective. The ER is then used to perform a meta analysis.

In a first step, 7 studies were analyzed separately in a core meta analysis. From payer's perspective, strategy "vaccination program" did not turn out to be significantly superior to strategy "no vaccination program" (ER = 0.85, 95% CI 0.63-1.15). From society's perspective, strategy "vaccination program" did turn out to be significantly superior (ER = 3.03, 95% CI 1.48-6.19). In a second step, 13 studies were added to perform a complete meta analysis. Again, from payer's perspective, strategy "vaccination program" does not prove to be significantly superior (ER = 0.67, 95% CI 0.51-0.88) whereas from society's perspective, the results favor strategy "vaccination program" (ER = 3.57, 95% CI 2.29-5.55). The sensitivity analysis shows that these results are robust against changes in vaccine prices of +/- 10%.

According to this model, universal VZV vaccination programs should be introduced if cost saving to society is prioritized over cost saving to public health care providers. However, three issues have a negative impact on the calculation: 1. significant rises in vaccine prices, 2. waning vaccine efficacy, which would make a second dose necessary, 3. a rise in cases of herpes zoster due to missing booster effect after introduction of the vaccine; or all three combined.

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München, August 2015

Christoph Paul Klapproth

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List of abbreviations

add.	addition
AGV	Arbeitsgemeinschaft Varizellen
ANB	Actualized Net Benefit
ANC	Annual Net Costs
BCR	Benefit Cost Ratio
CA	Case Averted
CDC	Center for Disease Control and Prevention
CI	Confidence Interval
ECB	European Central Bank
ER	Effectiveness Ratio
FDA	Food and Drug Administration
GP	General Practitioner
HZ	Herpes Zoster
LCU	Local Currency Unit
LYS	Life Years Saved
NPV	Net Present Value
MMR	Measles, Mumps, Rubella
MMRV	Measles, Mumps, Rubella, Varicella
OECD	Organization for Economic Co-operation and Development
O.T.C.	Over The Counter
p.a.	per annum
PHN	Postherpetic Neuralgia
RKI	Robert Koch-Institut
SD	Standard Deviation
SE	Standard Error
SEM	Standard Error of the Mean
STIKO	Ständige Impfkommission
VZV	Varicella Zoster Virus
WHO	World Health Organization

ISO 3166 Codes for Countries

AUS	Australia
BEL	Belgium
BRA	Brazil
CAN	Canada
CHE	Switzerland
COL	Colombia
ESP	Spain
FRA	France
GBR	Great Britain
GER	Germany
ISR	Israel
ITA	Italy
NZL	New Zealand
SGP	Singapore
SVK	Slovakia
TWN	Taiwan
USA	United States of America

ISO 4217 Codes for Currencies

AUD	Australian Dollar
CAD	Canadian Dollar
DEM	German Mark
ESP	Spanish Peseta
EUR	Euro
FRF	French Franc
GBP	British Pound Sterling
NZD	New Zealand Dollar
SKK	Slovak Koruna
USD	United States Dollar

List of Symbols

C	Cohort
CI_0	lower bound of the Confidence Interval
CI_1	upper bound of the Confidence Interval
d_C	reduction rate
e_V	vaccine effectiveness
i_0	incidence rate before immunization program
i_1	incidence rate after immunization program
n_0	number of cases per year without vaccination program
n_1	number of cases per year with vaccination program
p_T	average price per treatment of one varicella case
p_V	vaccine price per dose
r_V	vaccination rate per birth cohort

1 Introduction

In 1995, the U.S. Food and Drug Administration (FDA) licensed a varicella vaccine (Goldman/King, 2013). In the following years, seven European countries, including Germany, have added the varicella zoster vaccination to their immunization schedules, thereby following the recommendation by the Word Health Organization (WHO) (Bilcke et al., 2013, WHO, 2015). However, there is still an ongoing debate about whether this strategy is in fact cost saving to both payers and society.

While there is largely a consensus that a universal varicella zoster vaccination program is not cost effective from the payer's perspective, there is a dispute about whether it is also cost effective to society as a whole.

Some authors argue for the cost effectiveness of a universal varicella vaccination program to society (e.g. Coudeville et al., 1999, 2004, 2005), others have doubts (e.g. Brisson/Edmunds, 2002, 2003) or even strongly oppose its introduction for economic reasons (e.g. Goldman, 2005, Goldman/King, 2013).

Investigating this issue, numerous individual studies in different countries and a number of systematic reviews have been conducted since 1985. Not yet provided though has been a quantitative meta analysis. This is the aim of the present thesis at hand.

The remainder of this paper structures as follows: in chapter 2, selection criteria, methods and assumptions are introduced. Based on these, chapter 3 presents the results of the meta analysis and the sensitivity analysis. Also, heterogeneity and publication bias are discussed. Chapter 4 discusses the impact of possible changes in the model's variables. In a brief conclusion, chapter 5 finally summarizes the major results of this paper.

2 Methods

2.1 Search methods and selection criteria

In order to give a broad and comprehensive picture of the status quo, the online database PubMed was used on a regular basis between July 2012 and July 2014 to identify relevant studies. The search for "cost effectiveness varicella vaccination" on PubMed was the most comprehensive and brought 143 results. A total of 33 studies between 1985 and 2013 comparing varicella vaccination versus non-vaccination strategies were identified. 13 of those 33 identified studies were excluded. To be included, the following three eligibility criteria had to be met:

- Developed Countries: this criterion ensures a certain amount of homogeneity among countries as far as health standards, health system standards and standard of living are concerned. Therefore, only OECD members were included.
- Vaccination strategy: only those studies comparing a one-dose vaccination strategy of toddlers versus a non-vaccination strategy were included.
- Herpes zoster and booster effect: varicella cases only were included. Due to the ongoing and not yet resolved debate, the booster effect was disregarded.

This left a total of 20 studies included in this meta analysis. Please note that one study, Coudeville et al. (2005), examined two countries (France and Germany) and is therefore counted and treated as two studies. Brisson/Edmunds (2003) examined England and Wales. For simplicity reasons, England and Wales will here be referred to as GBR. Figure 1 shows the study flow diagram. Table 1 provides an overview of the 33 studies included on the basis of title and abstract.

#	**Author Year**	**Country**	**Strategy months**	**Doses**	**HZ?**
1	Banz 2003	GER	15	1	No
2	Banz 2009	CHE	18	*2*	No
3	Beutels 1996	GER	15	1	No
4	Bilcke 2013	BEL	various	*2*	*Yes*
5	Bonanni 2004	ITA	*132*	1	No
6	Bonanni 2008	ITA	15	*2*	No
7	Brisson/Edmunds 2002	CAN	12	1	Possible
8	Brisson/Edmunds 2003	GBR	15	1	Possible
9	Coudeville 1999	FRA	<72	1	No
10	Coudeville 2004	ITA	18	1	No
11	Coudeville 2005	FRA	19	1	No
12	Coudeville 2005	GER	19	1	No
13	Diez-Domingo 1999	ESP	15	1	No
14	Getsios 2002	CAN	12	1	No
15	Gialloreti 2005	ITA	*Children&Catch-up*	1	Possible
16	Ginsberg/Somekh 2004	ISR	12	1	No
17	Goldman 2005	USA	*Not specified*	1	*Yes*
18	Hammerschmidt 2007	GER	17	*2*	No
19	Hudeckova 2000	SVK	12	1	No
20	Huse 1994	USA	15	1	No
21	Hsu 2003	*TWN*	15	1	No
22	Jean-Jasmin 2004	*SGP*	15	1	No
23	Lenne 2006	ESP	18	1	No
24	Lieu 1994	USA	<72	1	No
25	Paternina-Caicedo 2013	*COL*	<24	1	No
26	Perez-Rubio 2008	ESP	15	1	No
27	Preblud 1985	USA	15	1	No
28	Scuffham 1999	NZL	15	1	No
29	Scuffham 2000	AUS	12	1	No
30	Tseng 2005	*TWN*	15	1	No
31	Valentim 2008	*BRA*	12	1	No
32	van Hoek 2012	GBR	12	*2*	No
33	Zhou 2008	USA	15	1	No

Table 1: Results of PubMed research. Reasons for exclusion in cursive. Source: respective studies.

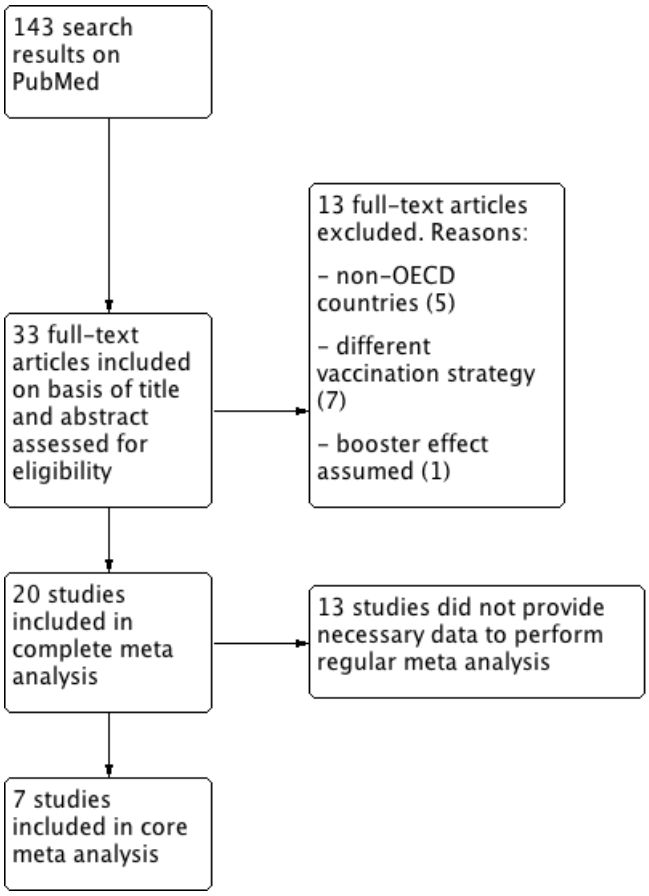

Figure 1: Study flow diagram. Source: author's calculation.

2.2 Model and assumptions

2.2.1 Model

Of those 20 studies included in this analysis, 12 used benefit-cost ratios (BCR) to quantify the economic effectiveness of the universal varicella vaccination program. The remaining 8 studies used different measures, such as costs per life year saved (per LYS), net present value (NPV), actualized net benefit (ANB), annual net costs (ANC) or costs per case averted (per CA).

In order to be able to perform a meta analysis, these different measures had to be standardized. This was done by a cost benefit analysis using the

incremental cost-effectiveness ratio, in this thesis called effectiveness ratio (ER), defined as

$$ER = \frac{p_T \cdot (n_0 - n_1)}{p_V \cdot r_V \cdot C} \quad (1)$$

where p_T is the average price per treatment of one varicella case, n_0 is the number of cases per year without vaccination program, n_1 the number of cases per year with vaccination program, p_V is the vaccine price per dose, r_V is the vaccination rate per birth cohort, and C is the size of the annual birth cohort.

All these variables are mean estimates associated with uncertainty. 13 of 20 studies did not provide standard deviations (SD) or standard errors (SE) to any of their variables. 6 studies provided confidence intervals (CI) only to the variable price per treatment p_T, while one study provided a CI in incidence rates. This will be discussed in detail in chapter 2.3.

With this model, a static comparison of the annual costs of strategy "without vaccination program" versus strategy "with vaccination program" is provided. It relates the savings in treatment costs due to the introduction of the vaccination program to its costs. Hence, for the vaccination strategy to be superior, $ER > 1$ must be fulfilled.

For all 20 studies included in this meta analysis, the ERs both for payer's and society's perspective were calculated, provided by table 2. From payer's perspective, in only 7 of 20 studies the vaccination strategy proved to be cost saving. In contrast, from societal perspective, all but one study found the vaccination strategy to be superior. Note that from societal perspective, only 19 studies could be examined, since Scuffham et al. (2000) only performed the payer's perspective.

#	Author Country Year	ER Payer	ER Society
1	Banz GER 2003	3.03	5.23
2	Beutels GER 1996	0.90	4.23
3	Brisson/Edmunds CAN 2002	0.56	4.15
4	Brisson/Edmunds GBR 2003	0.37	1.92
5	Coudeville FRA 1999	1.05	2.05
6	Coudeville ITA 2004	1.32	4.46
7	Coudeville FRA 2005	0.77	4.73
8	Coudeville GER 2005	1.21	6.11
9	Diez-Domingo ESP 1999	0.39	1.16
10	Getsios CAN 2002	0.65	1.71
11	Ginsberg/Somekh ISR 2004	2.59	37.82
12	Hudeckova SVK 2000	0.52	4.62
13	Huse USA 1994	0.48	3.27
14	Lenne ESP 2006	0.94	3.50
15	Lieu USA 1994	0.62	3.66
16	Perez-Rubio ESP 2008	0.75	1.31
17	Preblud USA 1985	0.28	6.59
18	Scuffham NZL 1999	0.09	0.86
19	Scuffham AUS 2000	0.20	N/A
20	Zhou USA 2008	1.33	6.13

Table 2: Cost effectiveness analyses in payer's and society's perspective. Source: author's calculation.

2.2.2 Epidemiology

Number of cases per year were all directly taken from the studies. For the size of the birth cohort C, if it was not given by the studies, it was assumed that 90% of a cohort would suffer from chickenpox. This was necessary for Brisson/Edmunds (2003) and Hudeckova et al. (2000). Brisson/Edmunds (2002) assumed 95% of a cohort to get chickenpox in their lifetime. Breakthrough cases were included if provided separately.

Since size of population in the respected countries naturally differs, the size of the annual birth cohort C as an absolute number differs as well and is therefore not suitable for comparison. What is suitable though, is the absolute difference in varicella cases relative to annual birth cohort. Reduction rate d_C can thus be defined as

$$d_C = \frac{(n_0 - n_1)}{C} = i_0 - i_1 \tag{2}$$

and is part of equation (1). An even better measure to compare the power of the vaccination program is the vaccine effectiveness which Tugwell et al. (2004) defined as

$$e_V = 1 - \frac{i_1}{i_0} \tag{3}$$

while i_0 and i_1 are the infection rates before and after vaccination, respectively, defined as

$$i_t = \frac{n_t}{C} \tag{4}$$

Table 3 shows the varicella infection rates i_t of one annual birth cohort C before and after introduction of the universal vaccination program. It also shows the reduction rate d_C due to the vaccination program and the vaccine effectiveness e_V. For d_C, a range from 0.42 (Coudeville et al., 1999) to 0.93 (Lieu et al., 1994) was found. The mean reduction rate is 0.79, while the median reduction rate is 0.745.

Table 4 shows the vaccination rates r_V, all provided directly by the studies. They have a rather narrow range from 0.8 (Coudeville et al., 1999, Scuffham et al., 1999, Scuffham et al., 2000) to 1.0 (Beutels et al., 1996, Ginsberg/Somekh, 2004, Huse et al., 1994, Perez-Rubio et al., 2008). Mean vaccination rate is 0.91, median vaccination rate 0.9.

2.2.3 Vaccine price

It was decided to only respect the pure vaccine price p_V used in the included studies. Administration costs and other indirect costs related to the vaccination process were not respected. This is realistic, since today the varicella vaccination is conducted via the MMRV vaccine and thus does not cause any other additional costs compared to the already previously common universal MMR vaccination. This assumption had already originally been made by 5 of the 20 included studies: Brisson/Edmunds (2002), Brisson/Edmunds (2003), Getsios

#	**Author Country Year**	**Birth cohort**	**Cases n_0**	**Infect. rate i_0**	**Cases n_1**	**Infect. rate i_1**	$i_0 - i_1$	**Vaccine effectiveness**
1	Banz GER 2003	800,000	738,967	0.92	127,776	0.16	0.76	0.83
2	Beutels GER 1996	800,000	674,772	0.84	290,152	0.36	0.48	0.57
3	Brisson/Edmunds CAN 2002	431,579	410,000	0.95	114,800	0.27	0.68	0.72
4	Brisson/Edmunds GBR 2003	723,333	651,000	0.90	182,500	0.25	0.65	0.72
5	Coudeville FRA 1999	700,000	691,432	0.99	400,022	0.57	0.42	0.42
6	Coudeville ITA 2004	540,000	537,097	0.99	140,040	0.26	0.73	0.74
7	Coudeville FRA 2005	775,000	767,221	0.99	71,082	0.09	0.90	0.91
8	Coudeville GER 2005	735,000	725,550	0.99	58,299	0.08	0.91	0.92
9	Diez-Domingo ESP 1999	763,726	716,375	0.94	63,389	0.08	0.86	0.91
10	Getsios CAN 2002	100,000	92,169	0.92	34,000	0.34	0.58	0.63
11	Ginsberg/Somekh ISR 2004	138,000	123,984	0.90	10,170	0.07	0.83	0.92
12	Hudeckova SVK 2000	25,211	22,690	0.90	2,269	0.09	0.81	0.90
13	Huse USA 1994	100,000	95,400	0.95	4,800	0.05	0.90	0.95
14	Lenne ESP 2006	440,000	437,070	0.99	88,857	0.20	0.79	0.80
15	Lieu USA 1994	4,000,000	3,953,000	0.99	240,000	0.06	0.93	0.94
16	Perez-Rubio ESP 2008	100,000	48,927	0.49	3,471	0.03	0.46	0.94
17	Preblud USA 1985	3,500,000	3,291,750	0.94	726,253	0.21	0.73	0.78
18	Scuffham NZL 1999	57,200	39,540	0.69	11,116	0.19	0.50	0.72
19	Scuffham AUS 2000	255,000	240,632	0.94	92,907	0.36	0.58	0.62
20	Zhou USA 2008	4,100,000	4,084,382	1.00	475,478	0.12	0.88	0.88
	MEAN			0.91		0.19	0.720	0.79
	25% QUARTILE			0.90		0.08	0.580	0.72
	MEDIAN			0.94		0.18	0.745	0.82
	75% QUARTILE			0.99		0.26	0.865	0.91

Table 3: Annual birth cohorts, infection rates, reduction rate and vaccine effectiveness. Source: respective studies, author's calculation.

#	**Author Country Year**	**Vaccination rate r_V**
1	Banz GER 2003	0.85
2	Beutels GER 1996	1.00
3	Brisson/Edmunds CAN 2002	0.90
4	Brisson/Edmunds GBR 2003	0.90
5	Coudeville FRA 1999	0.80
6	Coudeville ITA 2004	0.90
7	Coudeville FRA 2005	0.90
8	Coudeville GER 2005	0.90
9	Diez-Domingo ESP 1999	0.95
10	Getsios CAN 2002	0.85
11	Ginsberg/Somekh ISR 2004	1.00
12	Hudeckova SVK 2000	0.90
13	Huse USA 1994	1.00
14	Lenne ESP 2006	0.97
15	Lieu USA 1994	0.97
16	Perez-Rubio ESP 2008	1.00
17	Preblud USA 1985	0.90
18	Scuffham NZL 1999	0.80
19	Scuffham AUS 2000	0.80
20	Zhou USA 2008	0.95
	MEAN	0.91
	25% QUARTILE	0.89
	MEDIAN	0.90
	75% QUARTILE	0.97

Table 4: Vaccination rate r_V. Source: respective studies.

et al. (2002), Hudeckova et al. (2000), and Preblud et al. (1985).

Table 5 shows p_V for all included studies the original vaccine prices in local currency units (LCU) as well as, for the sake of comparability, in USD2013 prices. Inflation rates and exchange rates were taken from the World Bank's online database (2015) and the European Central Bank (ECB) (1998), respectively. There is a wide range of vaccine prices, from USD2013 7.79 (Ginsberg/Somekh, 2004) to USD2013 84.1 (Hudeckova et al., 2000). The mean vaccine price is USD2013 61.49, the median vaccine price USD2013 64.88.

#	Author Country Year	Price	LCU	Year of price	USD2013
1	Banz GER 2003	51.00	EUR	1999	81.27
2	Beutels GER 1996	75.00	DEM	1995	64.87
3	Brisson/Edmunds CAN 2002	60.00	CAD	1998	80.94
4	Brisson/Edmunds GBR 2003	30.00	GBP	2001	62.70
5	Coudeville FRA 1999	100.00	FRF	1995	26.11
6	Coudeville ITA 2004	37.50	EUR	2002	61.48
7	Coudeville FRA 2005	45.50	EUR	2002	70.98
8	Coudeville GER 2005	50.00	EUR	2002	76.58
9	Diez-Domingo ESP 1999	3500.00	ESP	1994	46.96
10	Getsios CAN 2002	60.00	CAD	1998	80.94
11	Ginsberg/Somekh ISR 2004	6.00	USD	2002	7.79
12	Hudeckova SVK 1999	800.00	SKK	1996	84.10
13	Huse USA 1994	35.00	USD	1993	57.35
14	Lenne ESP 2006	30.96	EUR	2004	50.38
15	Lieu USA 1994	35.00	USD	1990	64.88
16	Perez-Rubio ESP 2008	32.00	EUR	2002	55.29
17	Preblud USA 1985	15.00	USD	1984	34.66
18	Scuffham NZL 1999	62.20	NZD	1997	72.52
19	Scuffham AUS 2000	52.87	AUD	1997	83.06
20	Zhou USA 2008	56.90	USD	2006	66.95
	MEAN				61.49
	25% QUARTILE				54.06
	MEDIAN				64.88
	75% QUARTILE				77.67

Table 5: Vaccine prices in LCU and USD2013. Source: author's calculation.

2.2.4 Treatment costs

It was assumed that the average price per treatment of one varicella case, p_T, remains constant in both strategies. This is a legitimate assumption since the share of cases suffering from complications should not change under vaccination conditions. If, as in some of the original studies, the treatment costs per case differed depending on the vaccination strategy, those treatment costs per case that were assumed under the no vaccination strategy were used. Only varicella cases were considered. Impacts of the vaccination program on related maladies, such as herpes zoster (HZ) or postherpetic neuralgia (PHN), were not taken into account.

By definition, the average price per treatment of one varicella case, p_T, is smaller from payer's perspective than from society's perspective. The health

care provider only covers direct medical costs, such as doctor's consultations and examinations, pharmaceutical prescriptions, hospitalizations and O.T.C. medications. Costs that additionally fall on the country's economy as a whole and thus on society are indirect costs of lost work days due to sickness or sickness of a child and costs of child day care arrangements.

Treatment costs per case have rarely been reported directly in the included studies as did Brisson/Edmunds (2002) and Ginsberg/Somekh (2004). To assess the actual costs per case, total costs per year were divided by number of cases per year: Brisson/Edmunds (2003), Diez-Domingo et al. (1999), Getsios et al. (2002), Hudeckova et al. (2000), Huse et al. (1994), Lieu et al. (1994), Perez-Rubio et al. (2008), Preblud et al. (1985), Scuffham et al. (1999), and Zhou et al. (2008).

In other studies, probabilities of costs, i.e. GP consultations or hospitalizations, and their average costs were multiplied. This was done for Banz et al. (2003) and Scuffham et al. (2000).

In some studies, authors did not clearly state the frequency of varicella cases in certain age groups. If necessary, it was assumed that 90% of all varicella cases were younger than 14 years of age, as it was done for Beutels et al. (1996) and had originally been assumed by Lenne et al. (2006). For Coudeville et al. (1999), Coudeville et al. (2004), and Coudeville et al. (2005) for the case of France, 90% of all cases to be younger than 18 years of age was assumed. For the case of Germany in Coudeville et al. (2005), 80% of all cases to be younger than 12 years of age was assumed.

Table 6 shows the payer's treatment costs per case and indirect treatment costs per case adding up to treatment costs per case to society. Again, for the sake of comparability, USD2013 prices were used.

From payer's perspective, a wide range of prices per treatment was found, starting at USD2013 10.72 (Scuffham et al., 1999) and ending at USD2013 273.87 (Banz et al., 2003). The high costs per treatment in two studies conducted in Germany, Banz et al. (2003) and Beutels et al. (1996), can partially

#	Author Country Year	Payer	Indirect	Society
1	Banz GER 2003	273.87	199.36	473.23
2	Beutels GER 1996	121.53	449.77	571.30
3	Brisson/Edmunds CAN 2002	60.16	382.21	442.37
4	Brisson/Edmunds GBR 2003	31.87	135.08	166.95
5	Coudeville FRA 1999	52.67	50.21	102.88
6	Coudeville ITA 2004	98.99	236.38	335.37
7	Coudeville FRA 2005	54.51	281.81	336.32
8	Coudeville GER 2005	91.99	372.19	464.18
9	Diez-Domingo ESP 1999	21.51	42.79	64.30
10	Getsios CAN 2002	76.77	125.26	202.03
11	Ginsberg/Somekh ISR 2004	24.47	332.70	357.17
12	Hudeckova SVK 2000	48.42	383.34	431.76
13	Huse USA 1994	30.33	176.84	207.17
14	Lenne ESP 2006	58.31	158.07	216.38
15	Lieu USA 1994	42.21	205.87	248.08
16	Perez-Rubio ESP 2008	91.75	67.41	159.16
17	Preblud USA 1985	11.85	268.53	280.39
18	Scuffham NZL 1999	10.72	90.06	100.78
19	Scuffham AUS 2000	22.37	N/A	N/A
20	Zhou USA 2008	96.04	347.12	443.16
	MEAN	66.02	226.58	294.89
	25% QUARTILE	28.87	130.17	184.49
	MEDIAN	53.59	205.87	280.39
	75% QUARTILE	91.81	339.91	437.07

Table 6: Treatment costs per varicella case in USD2013. Payer's perspective, indirect costs and society's perspective. Source: author's calculation.

be explained by the unique German institution of *Krankenpflegegeld*, which is a payment from the health care provider covering the costs of lost work days for parents having to stay home to take care of their sick child, covering 70% of these costs. This payment, which is unique for Germany, turns indirect costs into direct costs that fall on the payer's budget. The mean price per treatment to the payer is USD2013 66.02, the median price per treatment to the payer is USD2013 53.59.

From society's perspective, results range even more widely from USD2013 64.30 (Diez-Domingo et al., 1999) to USD2013 571.30 (Beutels et al., 1996). While the mean price per treatment to society is USD2013 294.89, the median price per treatment to society is USD2013 280.39.

In all but three cases, indirect costs had a higher share of society's costs than

payer's costs: only Banz et al. (2005), Coudeville et al. (1999), and Perez-Rubio et al. (2008) calculated payer's costs to be higher than indirect costs.

2.3 Meta analysis

Of all 20 studies included in the meta analysis, only 6 provided confidence intervals (CI) for the average price per treatment of one varicella case p_T, while one study provided CI of incidence rates (Perez-Rubio et al., 2008). Most of them provided 95% CIs, only Brisson/Edmunds (2003) originally provided a 90% CI. This has been transformed into a 95% CI. For each study, the CI was used to approximate the standard error of the mean (SEM) by applying

$$SEM = \frac{CI_1 - CI_0}{2 \cdot 1,96} \tag{5}$$

CI_1 and CI_0 being the upper and lower bound of the CI, respectively. Table 7 shows these 7 studies and their SEM for both payer's and society's perspective. It also shows the mean and the median SEM. Since the SEM of the remaining 13 studies is expected to be similar to those of the original 7 studies, two further analyses were performed, firstly using the mean SEM and secondly using the median SEM. In the end, three meta analyses were performed, each for both payer's and society's perspective:

1. The core analysis including all 7 fully applicable studies.
2. A first complete analysis of all 20 studies, using the core analysis' mean SEM for the remaining 13 studies.
3. A second complete analysis of all 20 studies, using the core analysis' median SEM for the remaining 13 studies.

All meta analyses were performed with The Cochrane Library's RevMan® 5.2, using a random-effects model due to significant heterogeneity in my data.

#	Author Country Year	Payer's perspective ER	Payer's perspective SEM ER	Society's perspective ER	Society's perspective SEM ER
1	Brisson/Edmunds GBR 2003	0.37	0.0390	1.92	0.3079
2	Coudeville FRA 1999	1.05	0.1061	2.05	0.2405
3	Coudeville ITA 2004	1.32	0.0955	4.46	0.1987
4	Coudeville FRA 2005	0.77	0.0716	4.73	0.0716
5	Coudeville GER 2005	1.21	0.0898	6.11	0.0898
6	Lenne ESP 2006	0.94	0.1020	3.50	0.5948
7	Perez-Rubio ESP 2008	0.75	0.0064	1.31	0.0111
	MEAN	0.92	0.0729	3.44	0.2164
	MEDIAN	0.94	0.0898	3.50	0.1987

Table 7: Mean and median SEM calculation of core analysis. Source: author's calculation.

2.4 Sensitivity analysis

The sensitivity analysis was performed to explore the sensitivity of the results to changes in vaccine prices. The base case is the calculation from chapter 2.2. The worst case scenario assumes a rise in vaccine prices of 10%. For the best case scenario, vaccine prices would fall by 10%. Table 8 shows the results from payer's perspective, table 9 the results from society's perspective.

3 Results

3.1 Meta analysis

Figures 2-5 show the results of the meta analysis. As previously stated, the meta analysis was first conducted as a so called core analysis with 7 studies and their originally provided CI and SEM. Since the remaining 13 studies did not offer CIs and SEMs, two complete analyses were then conducted, once using the mean SEM of the 7 core studies and once using the median SEM, respectively.

For payer's core analysis, it is found that the strategy of vaccination is not significantly superior (P = 0.29) in terms of costs than the alternate strategy of no vaccination program (ER = 0.85, 95% CI 0.63-1.15) with significant heterogeneity (I^2 = 99%, χ^2 = 403.57, P < 0.00001). The complete analysis for the payer's perspective using the mean SEM shows significant superiority (P =

#	Author Country Year	Worst Case	Base Case	Best Case
1	Banz GER 2003	2.75	3.03	3.37
2	Beutels GER 1996	0.82	0.90	1.00
3	Brisson/Edmunds CAN 2002	0.51	0.56	0.63
4	Brisson/Edmunds GBR 2003	0.33	0.37	0.41
5	Coudeville FRA 1999	0.95	1.05	1.17
6	Coudeville ITA 2004	1.20	1.32	1.46
7	Coudeville FRA 2005	0.70	0.77	0.85
8	Coudeville GER 2005	1.10	1.21	1.35
9	Diez-Domingo ESP 1999	0.35	0.39	0.43
10	Getsios CAN 2002	0.59	0.65	0.72
11	Ginsberg/Somekh ISR 2004	2.36	2.59	2.88
12	Hudeckova SVK 2000	0.47	0.52	0.58
13	Huse USA 1994	0.44	0.48	0.53
14	Lenne ESP 2006	0.86	0.94	1.05
15	Lieu USA 1994	0.57	0.62	0.69
16	Perez-Rubio ESP 2008	0.69	0.75	0.84
17	Preblud USA 1985	0.25	0.28	0.31
18	Scuffham NZL 1999	0.08	0.09	0.10
19	Scuffham AUS 2000	0.18	0.20	0.22
20	Zhou USA 2008	1.21	1.33	1.48

Table 8: Sensitivity analysis from payer's perspective. Source: author's calculation.

#	Author Country Year	Worst Case	Base Case	Best Case
1	Banz GER 2003	4.76	5.23	5.82
2	Beutels GER 1996	3.85	4.23	4.70
3	Brisson/Edmunds CAN 2002	3.78	4.15	4.62
4	Brisson/Edmunds GBR 2003	1.74	1.92	2.13
5	Coudeville FRA 1999	1.86	2.05	2.28
6	Coudeville ITA 2004	4.05	4.46	4.95
7	Coudeville FRA 2005	4.30	4.73	5.25
8	Coudeville GER 2005	5.56	6.11	6.79
9	Diez-Domingo ESP 1999	1.05	1.16	1.29
10	Getsios CAN 2002	1.55	1.71	1.90
11	Ginsberg/Somekh ISR 2004	34.38	37.82	42.02
12	Hudeckova SVK 2000	4.20	4.62	5.13
13	Huse USA 1994	2.98	3.27	3.64
14	Lenne ESP 2006	3.18	3.50	3.89
15	Lieu USA 1994	3.33	3.66	4.07
16	Perez-Rubio ESP 2008	1.19	1.31	1.45
17	Preblud USA 1985	5.99	6.59	7.32
18	Scuffham NZL 1999	0.78	0.86	0.96
19	Scuffham AUS 2000	N/A	N/A	N/A
20	Zhou USA 2008	5.58	6.13	6.81

Table 9: Sensitivity analysis from society's perspective. Source: author's calculation.

0.004) of the no vaccination strategy (ER = 0.67, 95% CI 0.51-0.88). Again, the analysis shows significant heterogeneity ($I^2 = 99\%$, $\chi^2 = 2630.60$, P < 0.00001). As comparison of figures 2 and 4 shows, the result of the complete analysis using mean SEM merely differs from the one using median SEM (ER = 0.67, 95% CI 0.52-0.87). A significant heterogeneity was found ($I^2 = 99\%$, $\chi^2 = 1873.60$, P < 0.00001).

To the contrary, for the core analysis from societal perspective, the strategy of vaccination did perform significantly (P = 0.002) better than the strategy of no vaccination (ER = 3.03, 95% CI 1.48-6.19), again with significant heterogeneity ($I^2 = 99\%$, $\chi^2 = 633.42$, P < 0.00001). The same significance applies (P < 0.00001) for the complete analysis using mean SEM (ER = 3.57, 95% CI 2.29-5.55). Significant heterogeneity was detected once again ($I^2 = 98\%$, $\chi^2 = 1120.62$, P < 0.00001). Also, there was only little difference in results compared to the application of the median SEM (ER = 3.57, 95% CI 2.29-5.56) with significant heterogeneity ($I^2 = 99\%$, $\chi^2 = 1209.56$, P < 0.00001), as comparison of figures 3 and 5 shows.

3.2 Sensitivity analysis

Meta analyses for both the worst and the best case were done just as they were for the base case presented in chapter 3.1. As results in the base case only differed slightly between using mean SEM and median SEM, in the sensitivity analysis, only the meta analysis using the mean SEM was performed. Figures 6 and 7 show the best case scenario for payer's and society's perspective, respectively. The same accounts for the worst case scenario in figures 8 and 9.

In the best case scenario, a decrease in vaccine prices by 10%, the vaccination strategy does not prove to be significantly superior (P = 0.72) to the no vaccination strategy from the payer's perspective in the core analysis (ER = 0.95, 95% CI 0.70-1.28). There was found significant heterogeneity ($I^2 = 99\%$, $\chi^2 = 410.70$, P < 0.00001). Also, in the complete analysis from the payer's perspective, the no vaccination strategy turns out to be significantly (P = 0.03)

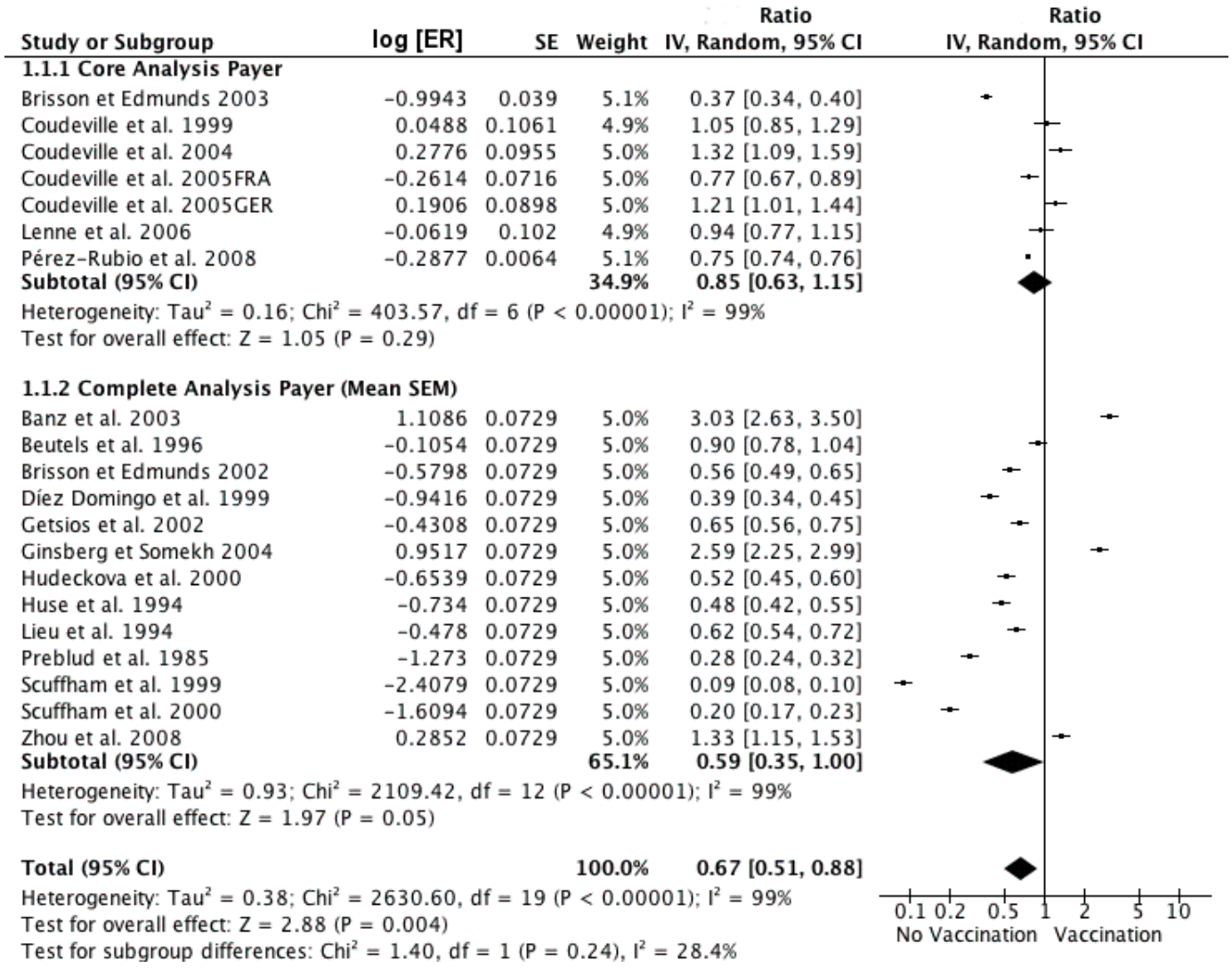

Figure 2: Meta analysis. Payer's perspective. Mean SEM. Source: author's calculation.

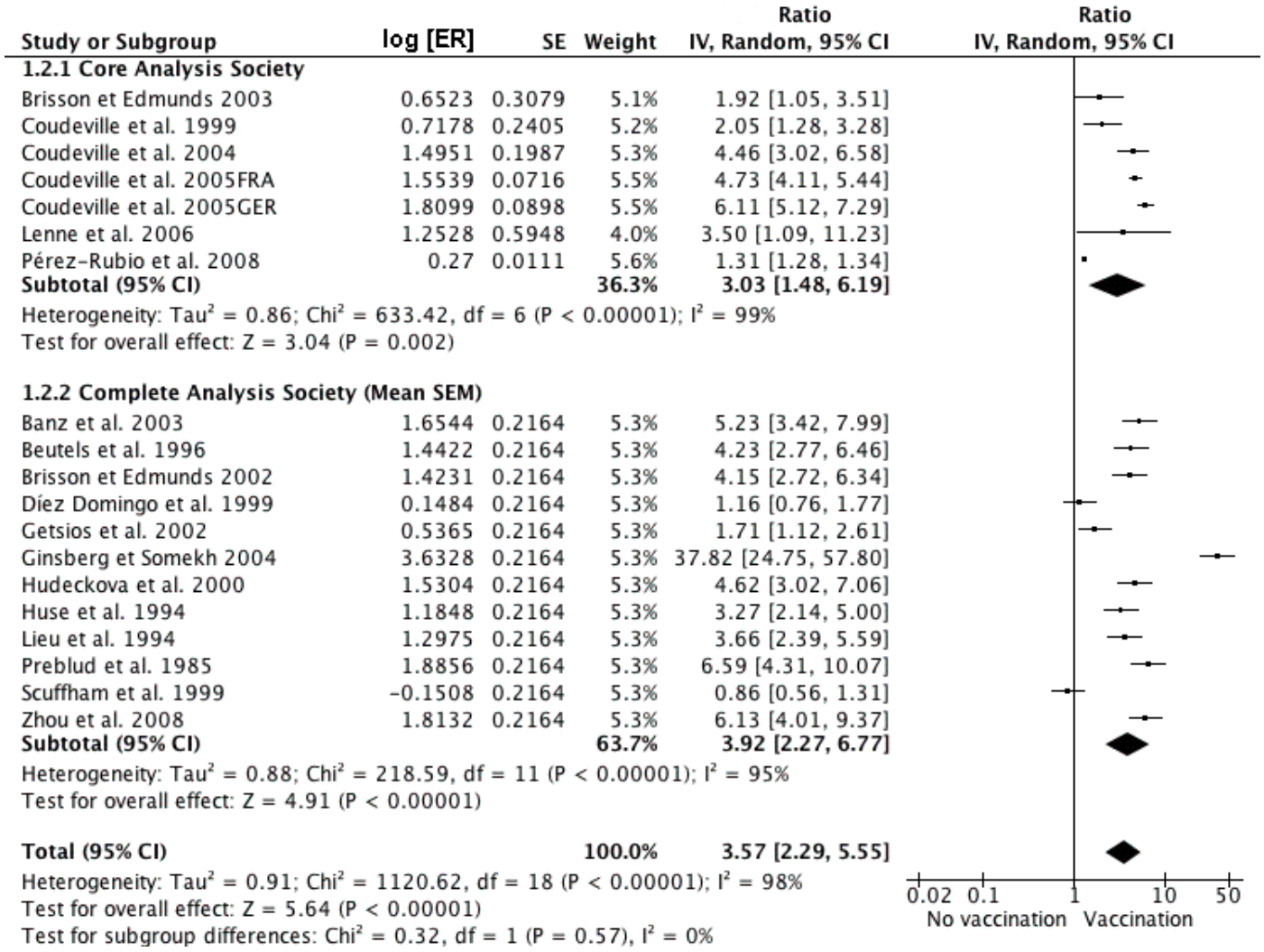

Figure 3: Meta analysis. Society's perspective. Mean SEM. Source: author's calculation.

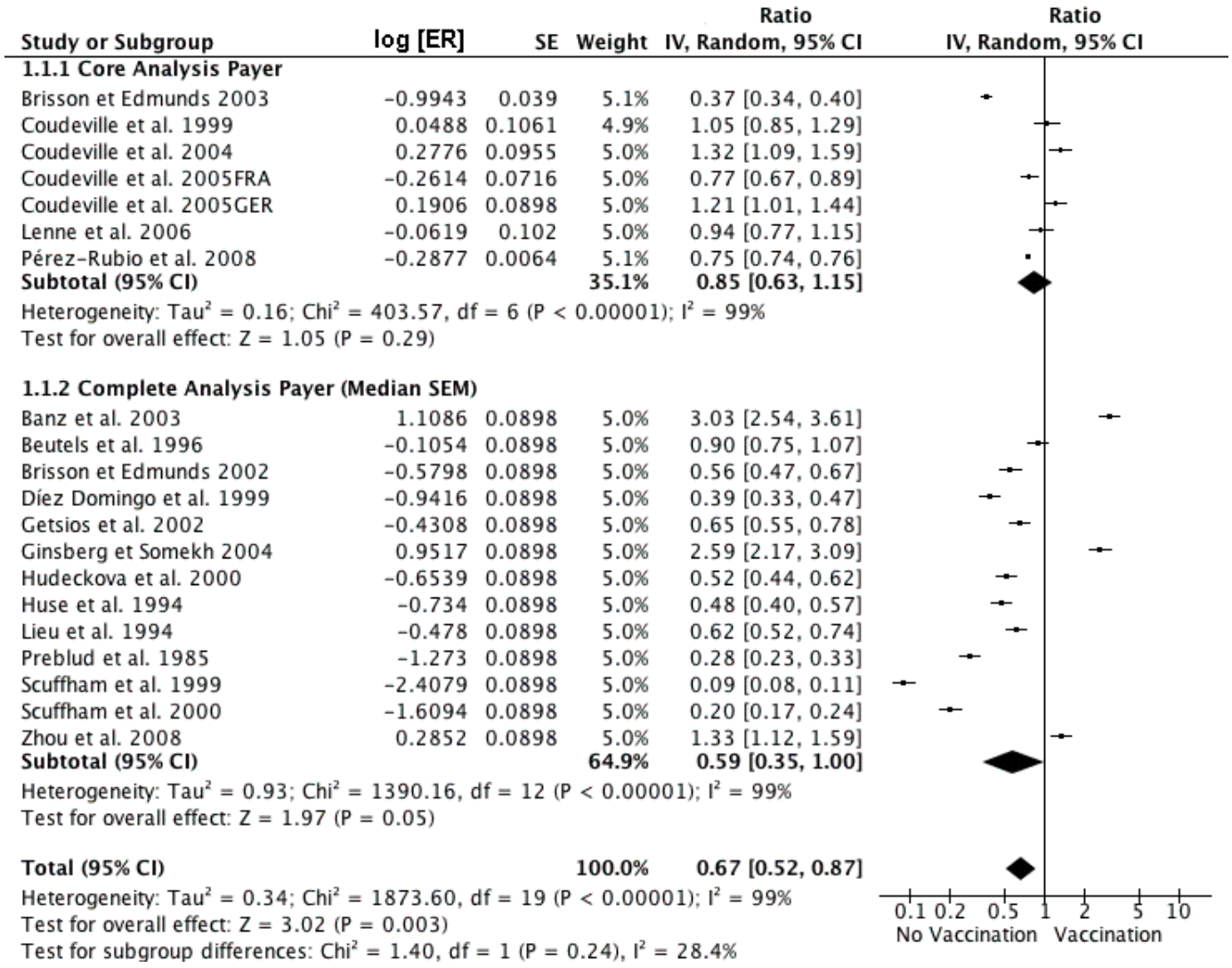

Figure 4: Meta analysis. Payer's perspective. Median SEM. Source: author's calculation.

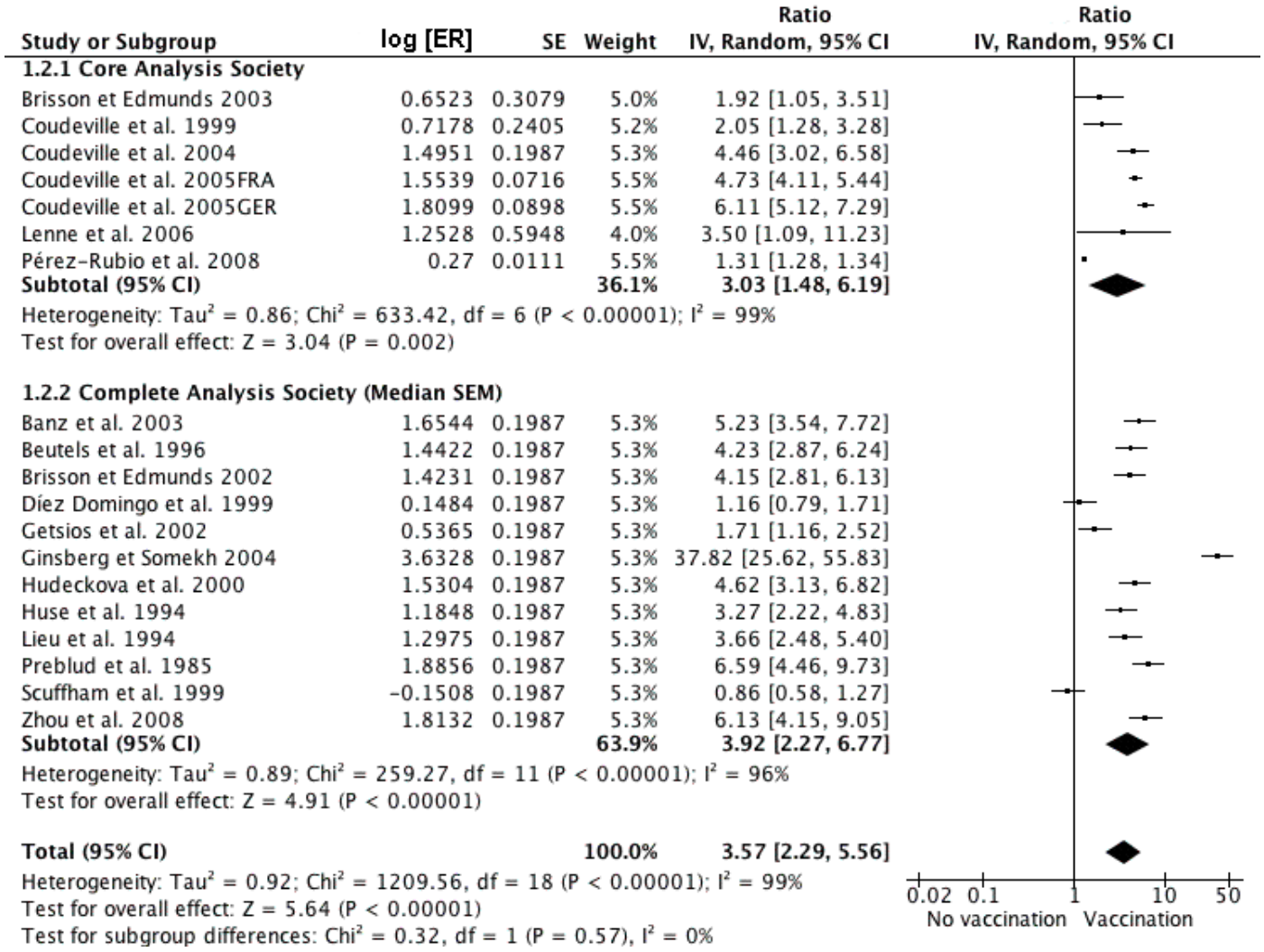

Figure 5: Meta analysis. Society's perspective. Median SEM. Source: author's calculation.

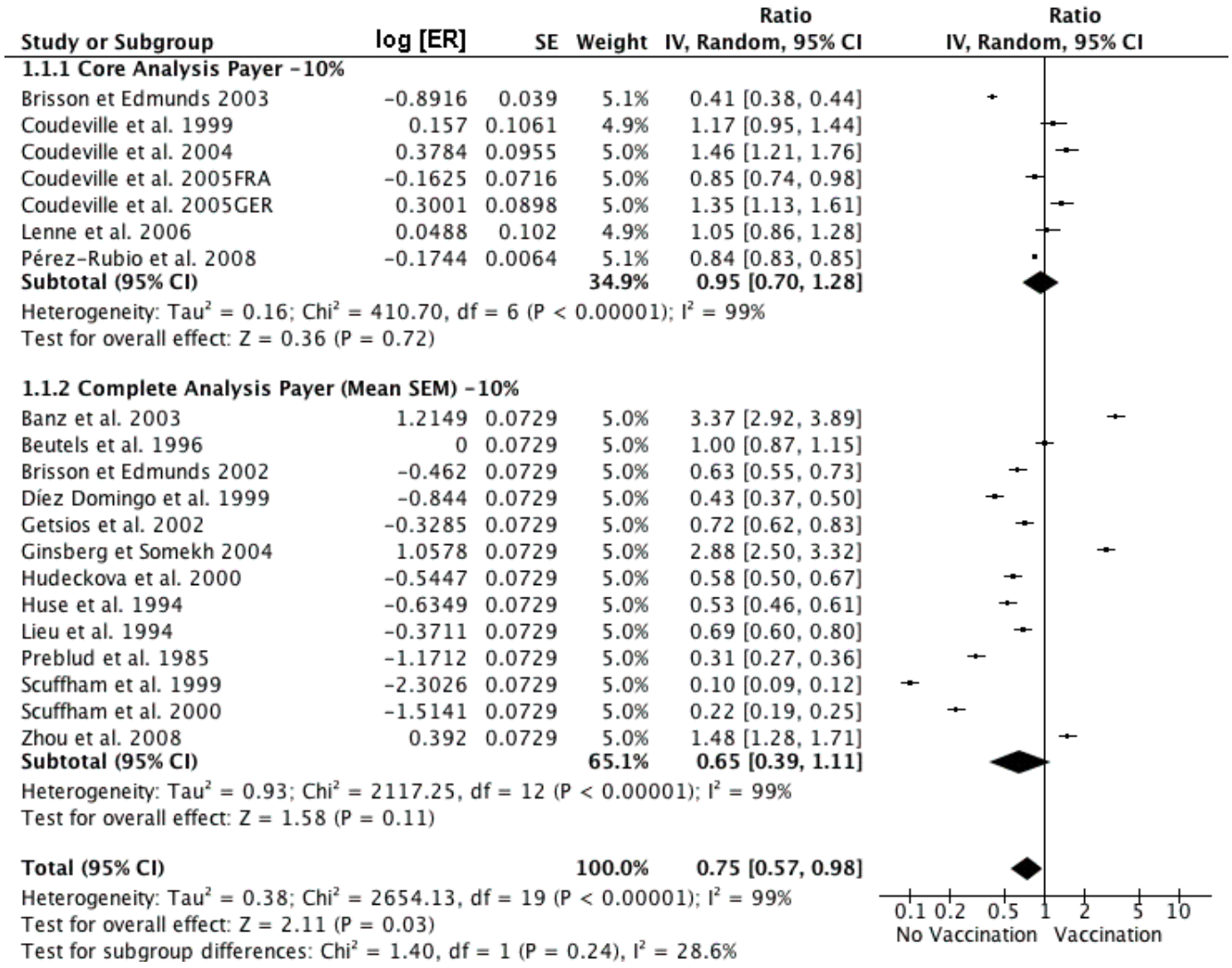

Figure 6: Sensitivity analysis. Payer's perspective. Best case. Source: author's calculation.

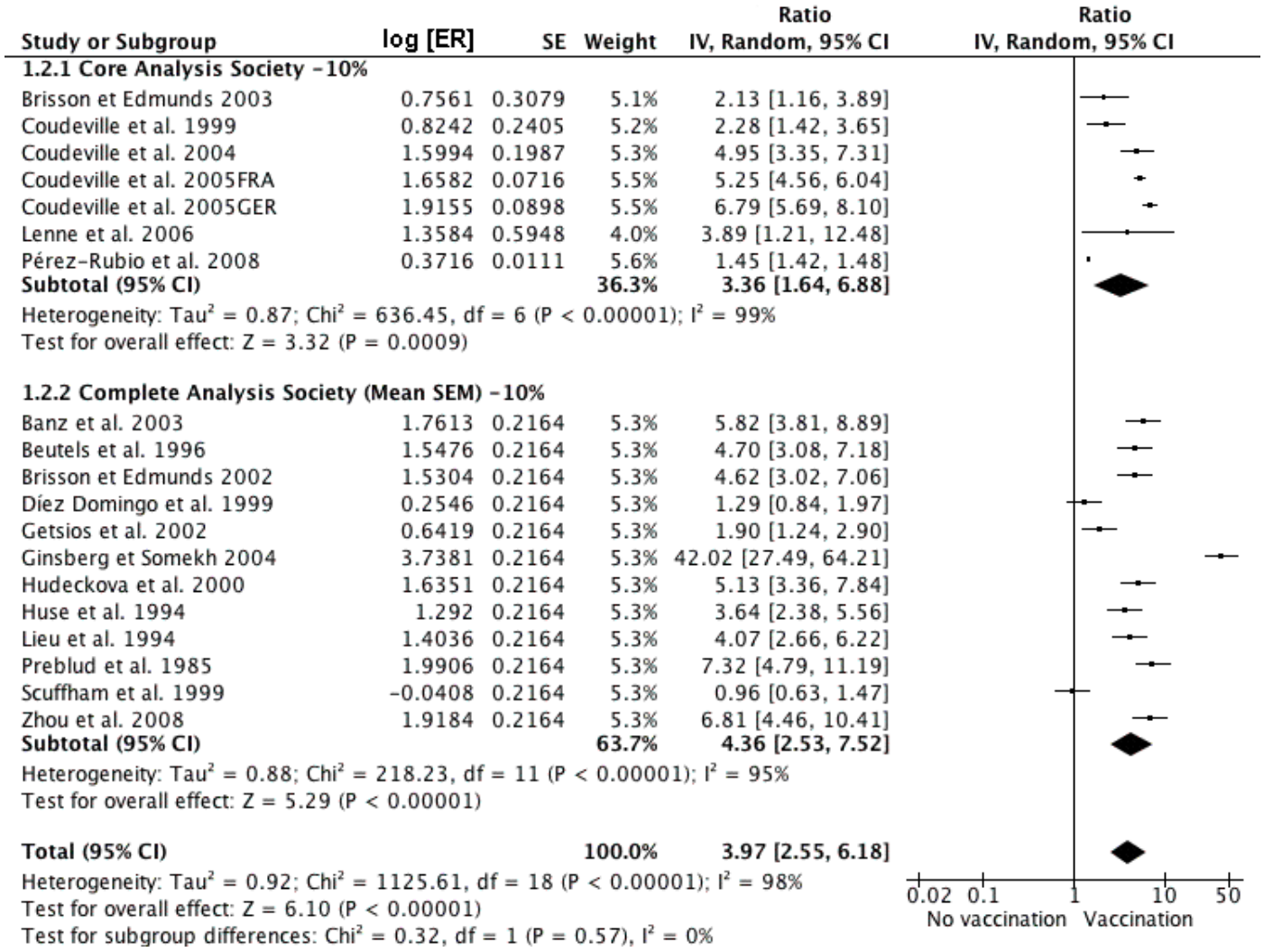

Figure 7: Sensitivity analysis. Society's perspective. Best case. Source: author's calculation.

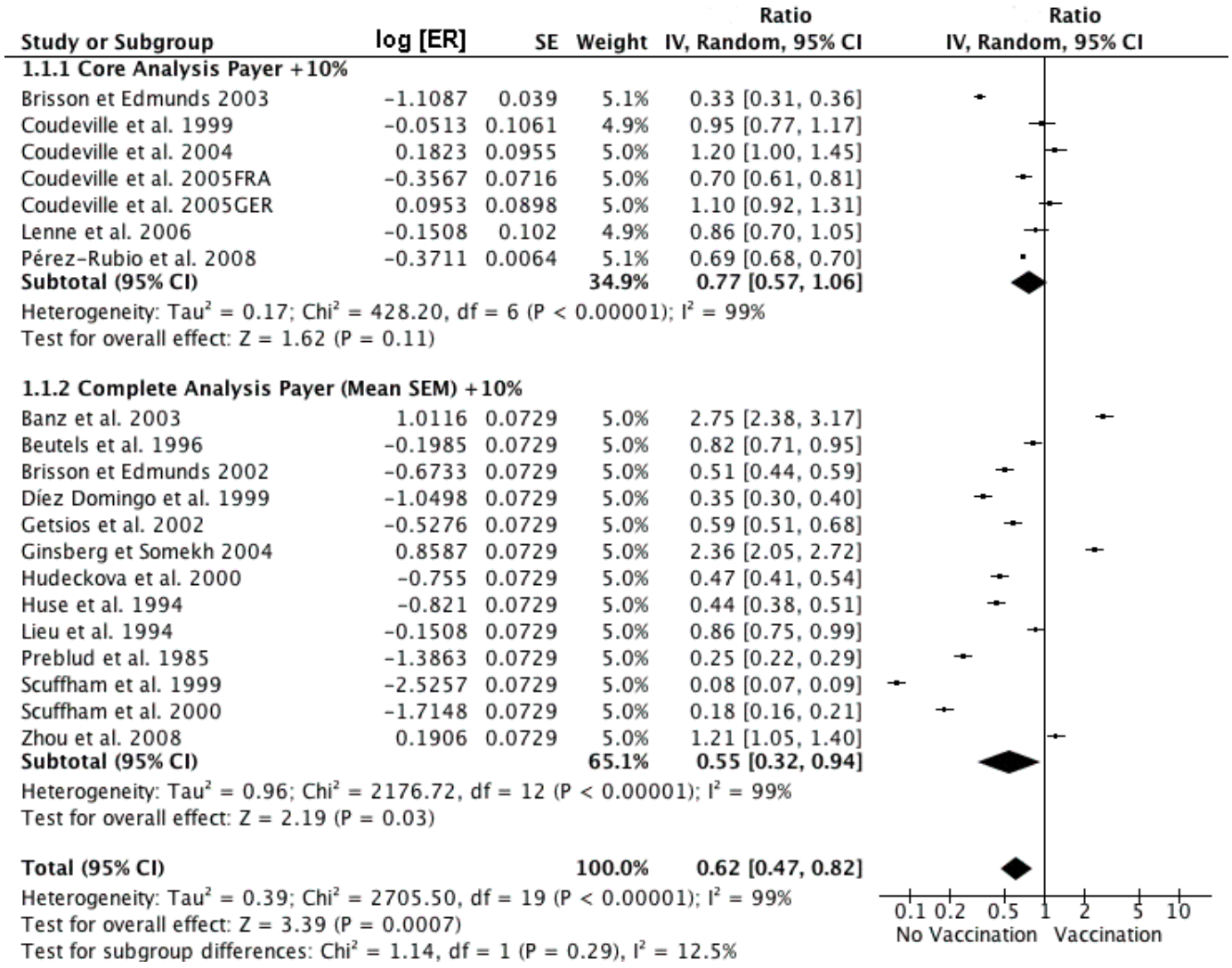

Figure 8: Sensitivity analysis. Payer's perspective. Worst case. Source: author's calculation.

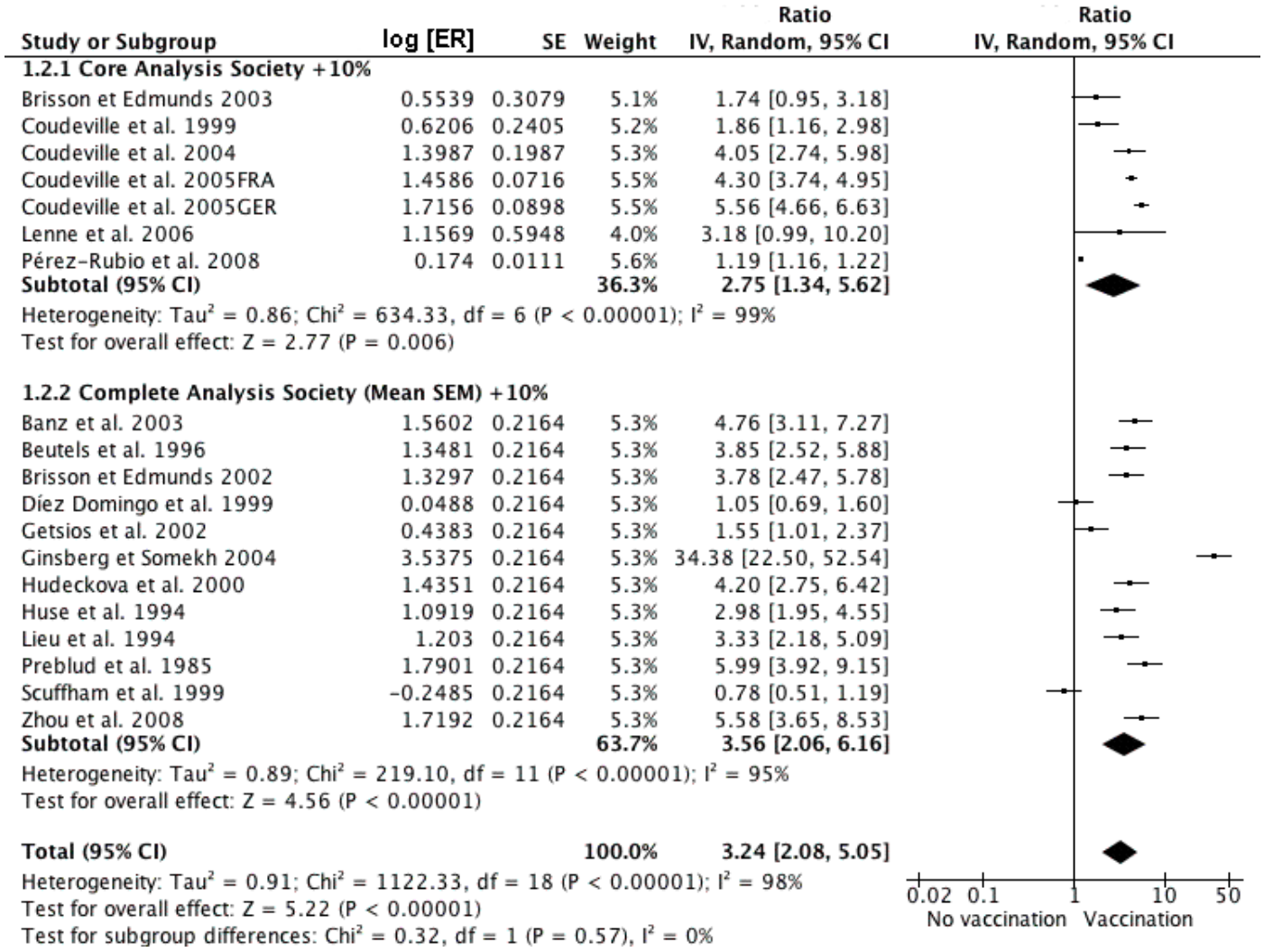

Figure 9: Sensitivity analysis. Society's perspective. Worst case. Source: author's calculation.

superior (ER = 0.75, 95% CI 0.57-0.98), also with significant heterogeneity (I^2 = 99%, χ^2 = 2654.13, P < 0.00001). The societal perspective shows a different picture, where the vaccination strategy is significantly superior, both in the core analysis (ER = 3.36, 95% CI 1.64-6.88, P = 0.0009) and in the complete analysis (ER = 3.97, 95% CI 2.55-6.18, P < 0.00001). Heterogeneity again is significant for core (I^2 = 99%, χ^2 = 636.45, P < 0.00001) and complete analysis (I^2 = 98%, χ^2 = 1125.61, P < 0.00001).

For the worst case scenario, a 10% increase in vaccine prices, the vaccination strategy is not significantly (P = 0.11) superior to the no vaccination strategy from the payer's perspective. This applies to the core analysis (ER = 0.77, 95% CI 0.57-1.06). In the complete analysis, a significant (P = 0.0007) superiority of the no vaccination strategy (ER = 0.62 95% CI 0.47-0.82) was found. The results of the core analysis once again prove to be significantly heterogeneous (I^2 = 99%, χ^2 = 428.20, P < 0.00001) as do the results of the complete analysis (I^2 = 99%, χ^2 = 2705.50, P < 0.00001). From the societal perspective, the results show significant superiority of the vaccination strategy, in the core analysis (ER = 2.75, 95% CI 1.34-5.62, P = 0.006) and in the complete analysis (ER = 3.24, 95% CI 2.08-5.05, P < 0.00001). Heterogeneity is significant for both core (I^2 = 99%, χ^2 = 634.33, P < 0.00001) and complete analysis (I^2 = 98%, χ^2 = 1122.33, P < 0.00001).

3.3 Heterogeneity

Results from the meta analyses in chapters 3.1 and 3.2 show a great amount of heterogeneity of $I^2 > 95\%$. This heterogeneity can be explained by the input data in the model shown in tables 3-6. Figures 10 and 11 show box plots that illustrate a significant degree of dispersion in all input factors, especially in society's treatment costs per case, payer's treatment costs per case, vaccine prices, and reduction rates.

The great amount of dispersion in society's treatment costs is remarkable. In the eligibility criteria, it was decided to only include industrialized countries

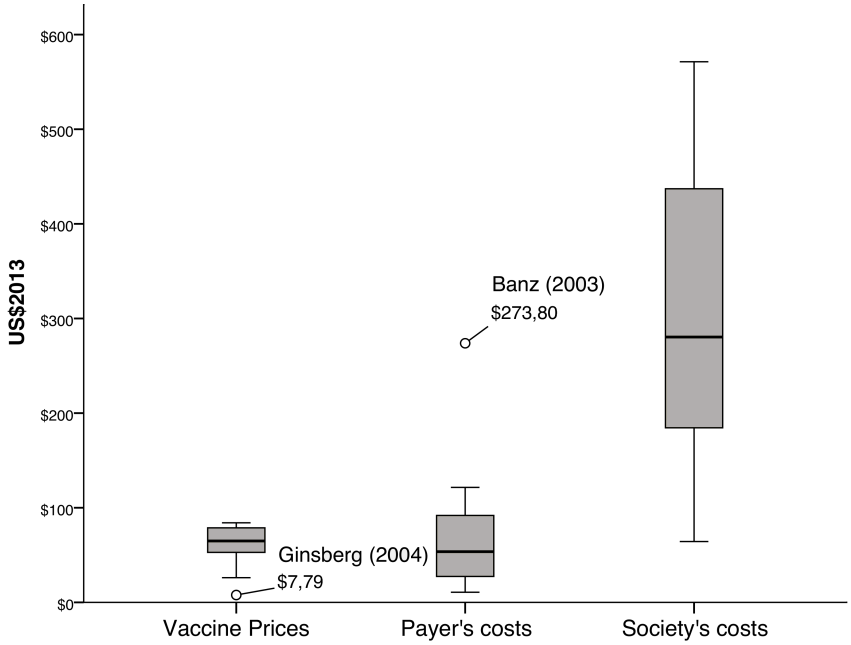

Figure 10: Box plots vaccine prices, payer's and society's treatment costs, in USD2013. Source: author's calculation.

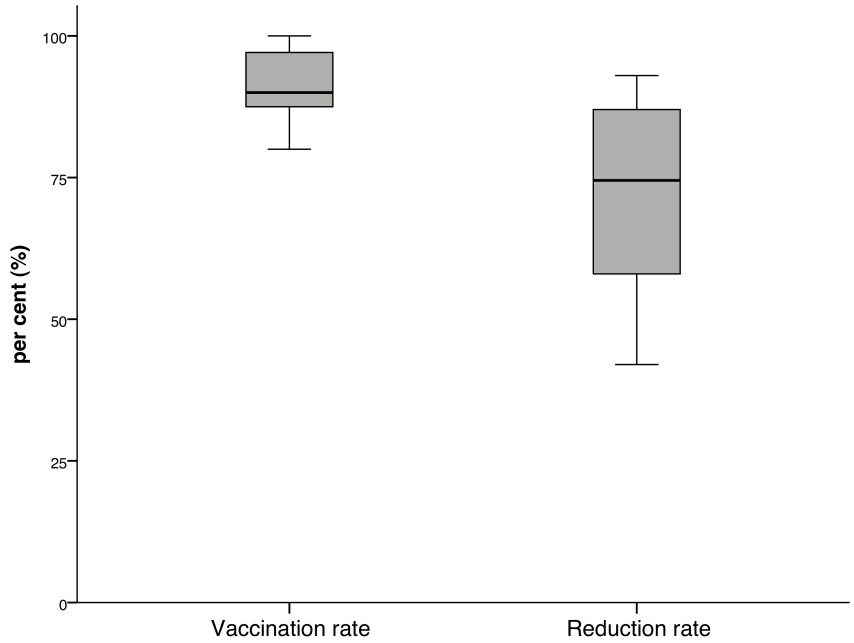

Figure 11: Box plots vaccination rate and reduction rate of the vaccination program, in per cent (%). Source: author's calculation.

which enjoy a similar standard of living, in order to avoid great heterogeneity in results. So even among countries with similar economic strength, price and wage levels, big differences when it comes to costs of missed workdays are to be observed. Possible reasons for differences in society's treatment costs, such as macroeconomic factors, employment rates, and women's labor participation are discussed in chapter 4.3.

Payer's treatment costs also spread widely. One reason, for instance, could be different prices per treatment national health systems are able or willing to pay doctors. It is known that there is a difference in payment to doctors for example between Germany and Switzerland. Prices for O.T.C. medications differ among countries as well as the willingness to subscribe and take them.

Dispersion in vaccine prices is a result of the fact that vaccine prices may differ from country to country. Also, when some of the studies were written, a vaccine had not yet been released. Thus, prices had to be estimated.

In the reduction rate, too, dispersion is found. The main reason is probably the single dose vaccination schedule all included studies follow. A two dose vaccination schedule introduced in many countries, as discussed in chapter 4.2., is expected to reduce this dispersion.

Finally, it is known that individuals tend to react very differently to an infection with the varicella zoster virus. While some suffer from heavy sickness, others merely take note of the infection. This is another factor that explains heterogeneity in incidence rates, treatments, treatment costs and number of missed work days.

3.4 Publication bias

Publication bias was analyzed by using The Cochrane Library's RevMan® 5.2. Figures 12 and 13 show the funnel plots for both the analyses of the payer's and society's perspective. Each are divided into its subgroups "Core Analysis" and "Complete Analysis (Mean SEM)". The complete analysis using the median SEM is not examined for publication bias because, as mentioned in chapter 3.1,

its ERs differed only very little if not at all from the complete analysis using the mean SEM.

A look at figures 12 and 13 reveals that there is no symmetry, neither for payer's nor for society's complete analysis. For the latter, is caused by the estimation of 13 SEMs using the mean SEM of the remaining 7 studies (see chapter 2.3). The SE(logER) of all these 13 studies is consequently the same which makes symmetry in the funnel plot impossible.

Also, both payer's and society's core analyses show asymmetry in their funnel plots. According to Egger et al. (1997), an explanation for asymmetry other than publication bias is heterogeneity. In chapters 3.1 and 3.2, heterogeneity in the meta analyses of $I^2 > 95\%$ was found, which was further discussed in chapter 3.3. Hence, for both core analysis and complete analysis, there is no proof of publication bias.

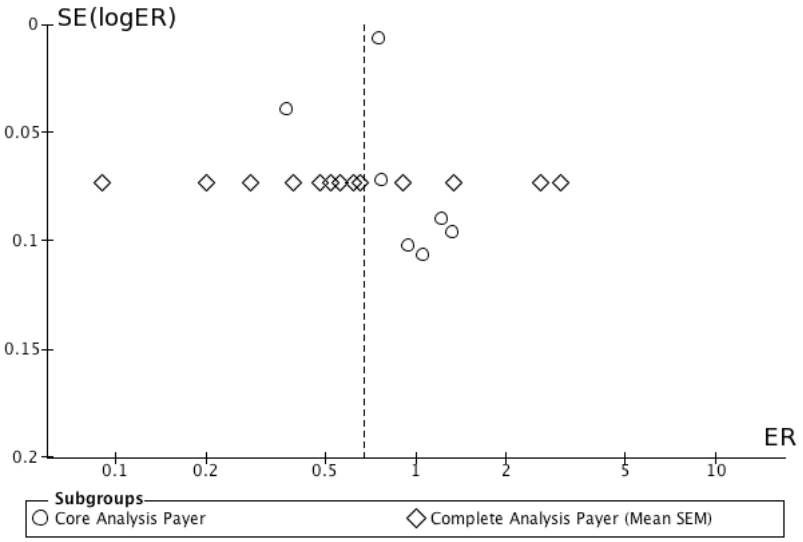

Figure 12: Funnel plot payer's perspective. Source: author's calculation.

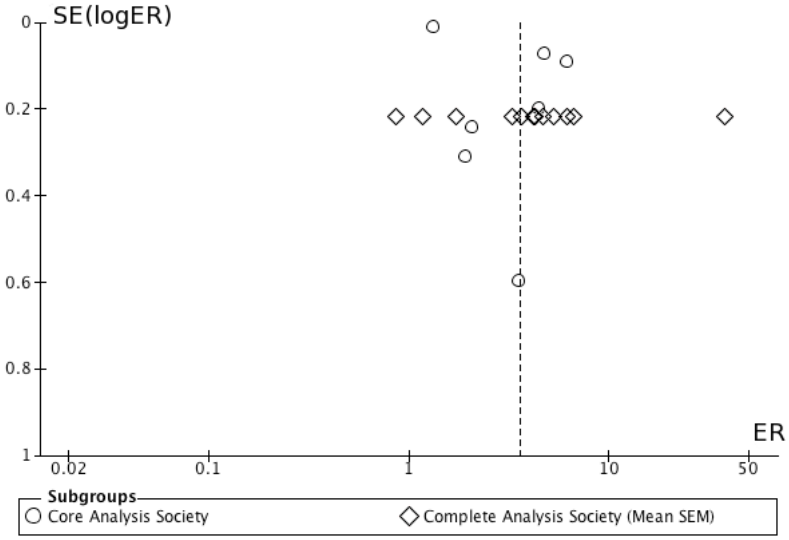

Figure 13: Funnel plot society's perspective. Source: author's calculation.

4 Discussion

As discussed above, the meta analysis shows that universal varicella vaccination programs for children are cost-effective from the societal perspective but not from the payer's perspective. However, changes in one or several variables of the model have an impact on the results. In the following, these variables are discussed. Also, the probability of changes in these variables and their impact on the results of the meta analysis are assessed.

4.1 Vaccine price

The price of the varicella vaccine dose p_V is crucial to the cost-effectiveness of a universal varicella vaccination program. According to the Center for Disease Control and Prevention (CDC) (2015), the current CDC vaccine price (June 2015) for one dose MMRV, ProQuad® by Merck, is USD 109.01. For one dose of MMR, M-M-R®II by Merck, the CDC vaccine price is USD 19.90. So the price for the addition of the varicella vaccine was USD 89.11. On September 30th, 2013, the price had still been at USD 75.36 (CDC Archive, 2015). This is

an increase of 9.12% per annum between 2013 and 2015.

Taking into account average annual inflation of 1.9% in the USA between 2008 and 2014 according to the World Bank (2015), all included studies underestimated the 2015 vaccine price, some of them grossly: Ginsberg/Somekh (2004) by factor 11, Coudeville et al. (1999) by factor 3.3 and Preblud et al. (1985) by factor 2.5. The mean vaccine price in USD2013 is 61.49, thus the current CDC price is 39.5% higher, inflation-adjusted (2013-2015). The median vaccine price in USD2013 is 64.88. The current CDC price is 32.3% higher, inflation-adjusted (2013-2015).

Table 10 shows the development of the prices per dose of MMR and MMRV vaccines from 2008 to 2015 according to the CDC. While the growth of the MMR vaccine price per dose is below inflation, the growth of the MMRV vaccine price per dose is mainly driven by the VZV addition. If, as since 2008, the vaccine price per dose continues to grow at an annual rate of more than 6% while treatment costs and costs per lost work days go along with annual inflation of roughly 2%, the vaccination strategy loses ground every year compared to the no vaccination strategy.

The results of the sensitivity analysis from chapter 3.2 show that a 10% increase in vaccine prices would not change the general result of the meta analysis. CDC prices are now about 40% higher than the originally assumed mean vaccine price. Even though prices may differ from country to country, CDC prices can serve as a gross estimate of how prices have developed compared to expectations in earlier years. For example, in Germany the O.T.C. price for the MMRV vaccine by GlaxoSmithKline, Priorix-Tetra®, was EUR 103.28 in August 2015 (medpex Versandapotheke, 2015). This is USD 114.95 at the exchange rate of August 12th, 2015, and thus even above the current CDC price. Of course, vaccine prices may decrease in the future. But for now, a significant markup is to be observed.

	2008	2009	2010	2011	2012	2013	2014	2015	% p.a.
MMR	18.26	18.30	18.64	18.99	19.33	19.76	19.91	19.90	1.28
MMRV	80.75	82.67	85.72	N/A	91.82	95.12	103.16	109.01	5.00
VZV add.	62.49	64.37	67.08	N/A	72.49	75.36	83.25	89.11	6.09

Table 10: Vaccine prices per dose in USD 2008-2015. Source: CDC Archive (2015)

4.2 Vaccine efficacy

Vaccine efficacy determines whether or not the vaccine works. The higher the vaccine efficacy, the smaller the number of cases after introduction of the varicella program (n_1) and thus the greater ER and vice versa. A poor efficacy causes breakthrough cases and would consequently make a second vaccine dose necessary. The studies included in my model all assumed a single dose vaccination to be sufficient. But some authors argue that the vaccine efficacy has been overestimated.

For example, Brisson et al. (2010) compared the incidence of varicella and zoster under a single dose regimen to the incidence of varicella and zoster under a double dose regimen. According to their model, under a single dose regimen, varicella cases can only be reduced by 64% over 80 years, while a second dose would reduce varicella cases by 86%. Figures 14 and 15 show the development of natural varicella cases and breakthrough cases, respectively, under the single dose and double dose regimens in his estimation. It is clear that in both cases, the two dose schedule performs significantly better. Michalik et al. (2008) found seroconversion after a first dose of varicella in only 76% of all cases and therefore recommends a second dose to improve vaccine effectiveness.

Going back to table 1, it is obvious that studies since 2007 observed the cost effectiveness of a two dose schedule and did therefore not meet the eligibility criteria (Banz et al., 2009, Bilcke et al., 2013, Bonanni et al., 2008, Hammerschmidt et al., 2007, van Hoeck et al., 2012). This is due to the fact that many countries switched from a one-dose schedule to a two-dose schedule, as for instance Germany in 2009. The *Ständige Impfkommission* (STIKO) of the

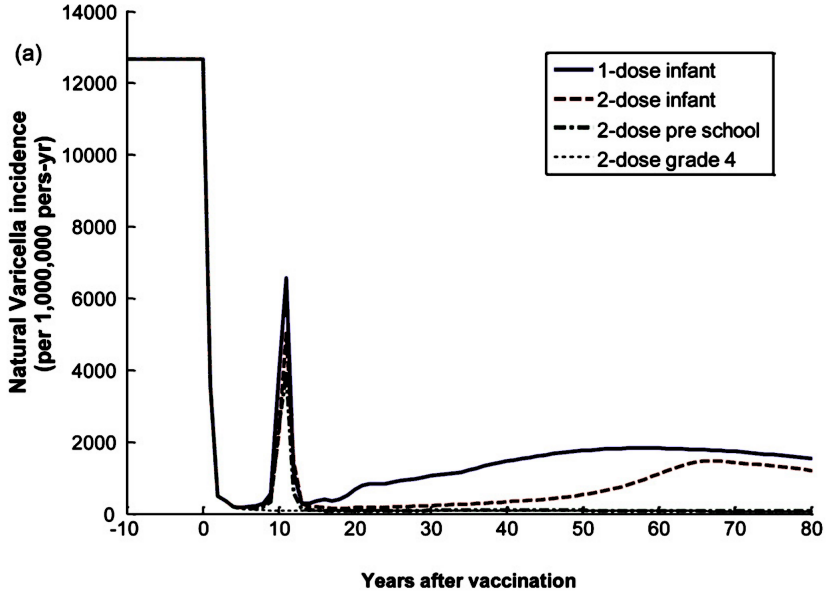

Figure 14: Natural varicella cases in a single dose versus a double dose schedule. Source: Brisson et al. (2010)

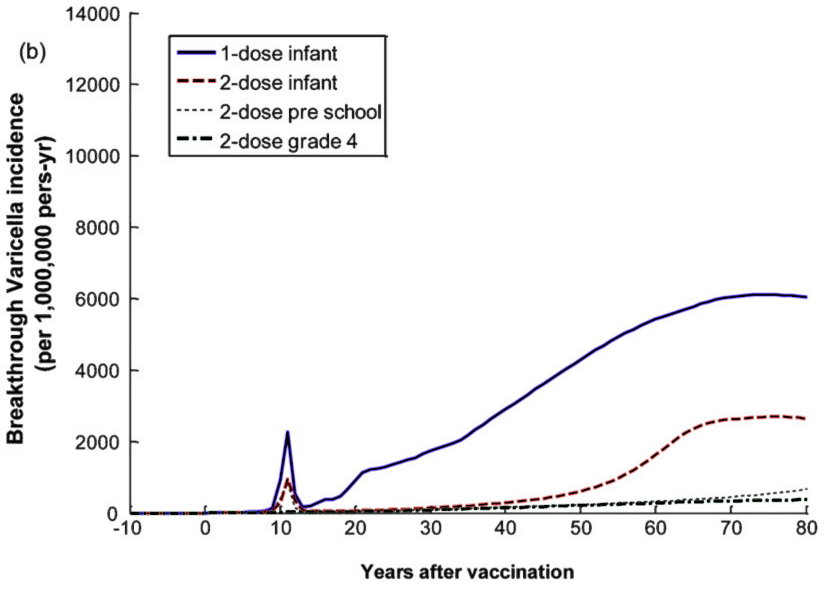

Figure 15: Breakthrough cases in a single dose versus a double dose schedule. Source: Brisson et al. (2010)

Robert Koch-Institut (RKI), who is responsible for vaccination schedule recommendations, argues this was necessary to avoid breakthrough cases. With this decision, the RKI follows the example of the USA, where a second dose had already been introduced. Despite high vaccination rates of more than 90%, there has been a significant number of breakthrough infections in the USA (Robert Koch-Institut, 2009).

This shows that the assumption of a one-dose schedule made by the included studies in my meta analysis can no longer be valid due to lack of vaccine efficacy. Hammerschmidt et al. (2007) investigated whether a two-dose schedule would still be cost-saving in Germany and found that it would be, to both society and payer. Banz et al. (2009) for Switzerland and Bonanni et al. (2008) for Italy found the two-dose schedule to be cost-saving to society but associated with higher costs to public health care providers.

4.3 Treatment costs

As mentioned above, treatment costs per varicella case p_T have to be analyzed from two perspectives: payer's and society's perspective.

The costs per treatment for the health care provider depend on the costs for diagnostics and treatment in practices. Since diagnostics and treatment of children suffering from chickenpox are relatively simple, there is little reason to believe these costs would rise significantly. Political pressure on public health care providers and economic pressure on private health insurance also indicate these costs will remain stable. However, if for any reason, the number of complications and VZV-related diseases such as HZ (discussed below) and PHN rise after introduction of the vaccination program, this would make treatment per case more costly and thus have a negative effect on the ER.

The societal treatment costs per case also include indirect costs such as costs of lost work days due to varicella infections. These are, for example, subject to macroeconomic factors: In times of economic prosperity, increases in wages and high employment rates would make it more expensive for society if mothers or

fathers have to be absent from work due to child care. On the other hand, an economic recession, followed by unemployment and stagnation of wages would lower the opportunity costs of a mother or father having to stay home to take care of an ill child. The ER thus correlates positively with economic growth.

Another factor to the societal treatment costs is women's labor participation. Some countries, such as Denmark, Sweden or Finland, have a relatively high rate of women's employment. Others have a rather low women's labor participation, for example Italy, Greece and Spain (Bundesministerium für Familie, Senioren, Frauen und Jugend, 2015). Evidently, in a country with high women's labor participation, lost work days would more often occur and hence be more expensive to society than in a country with low women's labor participation.

4.4 Booster effect

This meta analysis assumed, according to its 20 included studies, there would be no such thing as an exogenous booster effect, strengthening the immune system of the elderly through contact to children with natural varicella infections. This, according to the hypothesis, would prevent cases of Herpes zoster (HZ) in the elderly (Hope-Simpson, 1965). Whether or not the booster effect actually exists, is subject to ongoing debates and shall not the focus of this thesis. Nevertheless, the potential effect on the results if the hypothesis of the booster effect turned out to be correct, need to be discussed.

A majority of studies did not take into account a booster effect. Others argued that due the booster effect, a universal varicella vaccination program would be economically costly, not only from payer's perspective, but also from society's perspective.

For example, one prominent advocate of the booster hypothesis is G.S. Goldman. In his 2005 paper, he argues that an introduction of a varicella vaccination program would cause an increase in Herpes Zoster (HZ) cases, reaching a peak 15 years after introduction of the vaccination program. According to his model, the number of annual HZ cases with vaccination program would be higher than

without vaccination program until 65 years after its introduction. He estimates annual costs of USD 280 per additional HZ case. As far as cost-benefit analysis is concerned, he estimates a break-even point after approximately 50 years of introduction (Goldman, 2005).

Similarly, Goldman/King (2013) conclude, "the proponents for universal varicella vaccination have failed to consider increased HZ-related morbidity as well as the adverse effects of both the varicella and HZ vaccines which have more than offset the limited benefits associated with reductions in varicella disease" (Goldman/King, 2013, p. 12). They argue that therefore, the vaccination program is not only more expensive, but also more harmful to patients. Figure 16 illustrates the development of varicella and HZ incidence rates they observed in the Antelope Valley community after introduction of VZV vaccination program. While varicella incidence declined, HZ incidences among 20 to 59 year-old adults and among teenagers rose after about five years.

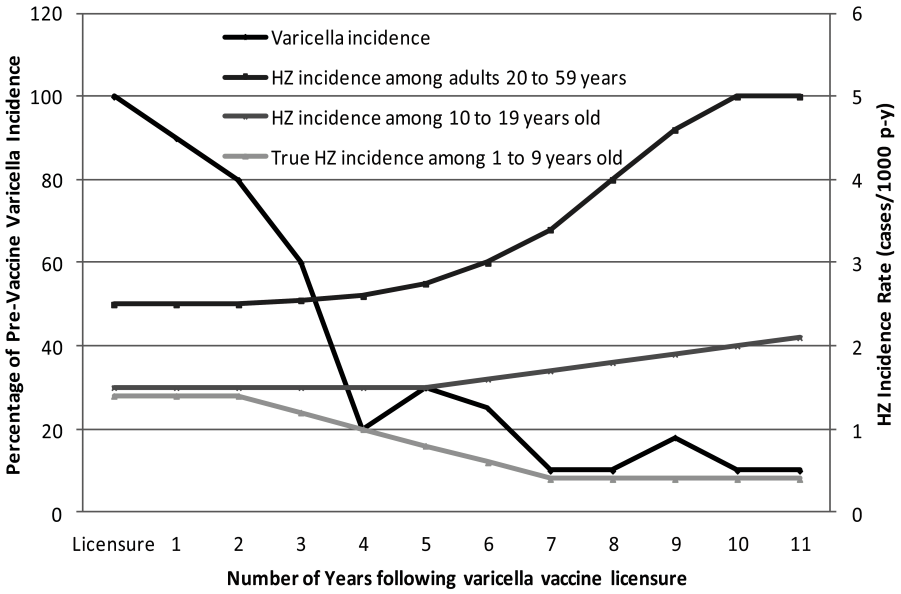

Figure 16: Post-vaccine-introduction development of Varicella and HZ incidence. Source: Goldman/King (2013)

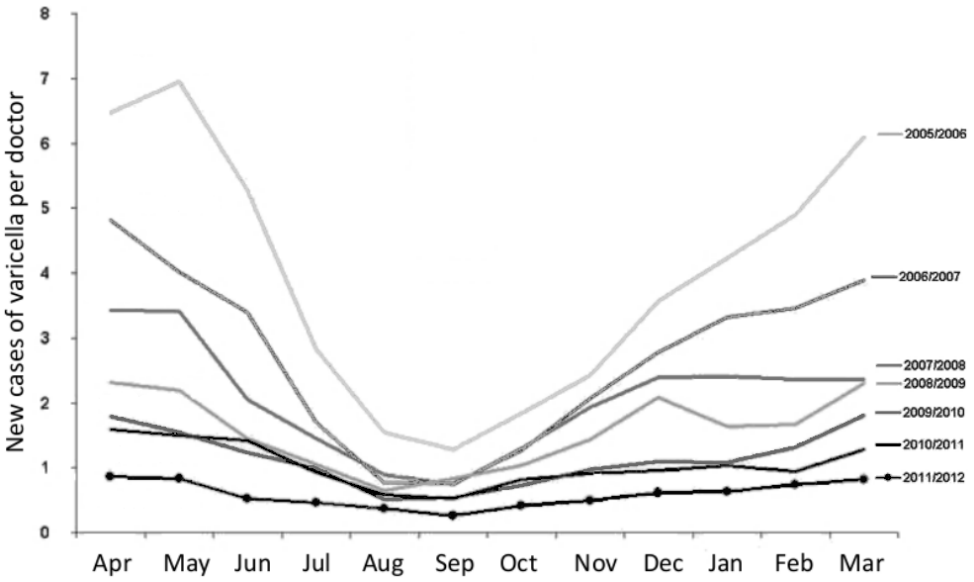

Figure 17: Development of annual varicella cases per doctor under universal vaccination regimen in Germany from 2005 to 2012. Source: Arbeitsgemeinschaft Varizellen (AGV, 2012), author's translation into English.

A decline in varicella incidence rates under vaccination program has also been found by the German *Arbeitsgemeinschaft Varizellen* (AGV, 2012). Figure 17 shows the effect of a vaccination program on the number of varicella cases per doctor in Germany: In May 2005, a doctor had about 7 varicella cases on average. In May 2012, it was less than one case per doctor.

For HZ cases though, using data from Antelope Valley as well, Civen et al. (2009) found an increase in the age group of 10-19 year-olds but they also found that HZ is less common in children having received a varicella vaccine.

In their 2002 paper, Brisson et al. found that HZ is more frequent in adults that do not or did not live with children than in adults that do or did live with children. Incorporating this in their model, they argue that 50% of the population aged 10-44 years at the time of introduction of the varicella vaccination program would suffer from HZ and consequently call this a "major epidemic" (Brisson et al., 2002, p. 1).

One of the latest papers considering this matter was written by Bilcke et al. (2013). In her paper, she finds VZV vaccination to be cost-effective to society

only if exogenous boosting does not exist or after 33 to 100 years, depending on how parameters develop.

An increase in HZ cases as result of the vaccination program is also predicted by van Hoeck et al. (2011), van Hoeck et al. (2012), and Patel et al. (2008). Finally, Ogunjimi et al.'s review (2013) concludes that exogenous boosting exists, even if not for all persons and all situations.

On the other hand, some authors also find an increase in HZ cases after introduction of a varicella vaccine program but argue there could be other reasons for that increase than the vaccination program (Yih et al., 2013), or find an increase of HZ cases possible but not inevitable (Poletti et al., 2013). Leung et al. (2011) and Hales et al. (2013) observed an increase of HZ cases even before the introduction of the varicella vaccination program and thus argue it cannot be the cause.

In summary, there has not yet been a final resolution to this debate. Some papers argue there is no exogenous boosting and some papers suggest the booster effect exists. If the booster effect does not exist, it would be in line with this paper. If it does exists, it would have a negative effect on the ER of the model. This potential effect is not yet quantifiable but likely to be strong enough to make the vaccination strategy from society's perspective not cost effective, at least for a number of decades, as mentioned results by Bilcke et al. (2013), Brisson et al. (2002), Goldman (2005) and Goldman/King (2013) suggest.

4.5 Strengths, weaknesses and limitations of the model

The strength of this model certainly is its ability to compare the two scenarios of the annual costs in a country with universal varicella vaccination program versus the annual costs in the same country without universal varicella vaccination program. Also, it is a good way to standardize all different measurements (e.g. BCR, ANB, ANC etc.) so far utilized to examine the cost effectiveness of universal varicella vaccination programs and thus make them comparable and suitable for a meta analysis.

Its weakness though is the lack of dynamic in time. A vaccination program is certainly not introduced over night. It takes time for incidence rates to adapt from one state to the other. Consequently, the ER in the first years after introduction of the vaccination program is expected to be much lower than the ER at the point in time when a high vaccination coverage assumed in the model is reached. This lower ER that falls upon health care providers and society during the years of transition from the introduction of a vaccination program to its full establishment can be interpreted as an investment that pays off after having reached a certain level of ER after a certain time. As seen in chapter 4.4, this is particularly true if it turns out that exogenous boosting exists.

5 Conclusion

According to this paper, universal VZV vaccination programs are cost-effective from societal perspective but not cost-effective from the perspective of the health care provider. These findings are in line with findings of systematic reviews by Rozenbaum et al. (2008), Skull/Wang (2001), de Soarez et al. (2009) and Thiry et al. (2003).

However, as discussed in chapter 4, three issues could have a negative impact on this calculation: 1. significant rises in vaccine prices of more than 10%, as partially already observed, 2. the introduction of a second dose due to waning efficacy, as has already taken place and 3. a rise in cases of herpes zoster due to missing booster effect after introduction of the vaccine, of which so far is no proof. Thus, further research on the booster hypothesis is necessary.

A standardized way of presenting results would make them more transparent and consequently easier to integrate in a systematic review or meta analysis. This applies especially for the great dispersion observed in input data of societal treatment costs per case and payer's treatment costs per case which caused great heterogeneity in this meta analysis.

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