

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



LSHTM Research Online

Carabin, H; Edmunds, WJ; Kou, U; van Den Hof, S; Nguyen, VH; (2002) The average cost of measles cases and adverse events following vaccination in industrialised countries. BMC public health, 2. p. 22. ISSN 1471-2458 DOI: <https://doi.org/10.1186/1471-2458-2-22>

Downloaded from: <http://researchonline.lshtm.ac.uk/6787/>

DOI: <https://doi.org/10.1186/1471-2458-2-22>

Usage Guidelines:

Please refer to usage guidelines at <https://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: <http://creativecommons.org/licenses/by-nc-nd/2.5/>

<https://researchonline.lshtm.ac.uk>

Research article

The average cost of measles cases and adverse events following vaccination in industrialised countries

Hélène Carabin*^{1,6}, W John Edmunds², Ulla Kou³, Susan van den Hof⁴ and Van Hung Nguyen⁵

Address: ¹Department of Infectious Disease Epidemiology, Imperial College Faculty of Medicine, London, UK, ²Department of Economics, City University, London, UK, ³Vaccines and Biologicals, World Health Organisation, Geneva, Switzerland, ⁴National Institute of Public Health and the Environment, Department of Infectious Diseases Epidemiology, Bilthoven, The Netherlands, ⁵Agence d'évaluation des technologies et des modes d'intervention en santé, Montréal, Canada and ⁶Department of Biostatistics and Epidemiology College of Public Health Oklahoma University Health Sciences Center 801 NE 13th Street, Oklahoma City 73116, USA

E-mail: Hélène Carabin* - helene-carabin@ouhsc.edu; W John Edmunds - JEdmunds@phls.org.uk; Ulla Kou - kouu@who.int; Susan van den Hof - Susan.van.den.Hof@rivm.nl; Van Hung Nguyen - Van.Hung.Nguyen@aetmis.gouv.qc.ca

*Corresponding author

Published: 19 September 2002

Received: 25 July 2002

BMC Public Health 2002, **2**:22

Accepted: 19 September 2002

This article is available from: <http://www.biomedcentral.com/1471-2458/2/22>

© 2002 Carabin et al; licensee BioMed Central Ltd. This article is published in Open Access: verbatim copying and redistribution of this article are permitted in all media for any purpose, provided this notice is preserved along with the article's original URL.

Abstract

Background: Even though the annual incidence rate of measles has dramatically decreased in industrialised countries since the implementation of universal immunisation programmes, cases continue to occur in countries where endemic measles transmission has been interrupted and in countries where adequate levels of immunisation coverage have not been maintained. The objective of this study is to develop a model to estimate the average cost per measles case and per adverse event following measles immunisation using the Netherlands (NL), the United Kingdom (UK) and Canada as examples.

Methods: Parameter estimates were based on a review of the published literature. A decision tree was built to represent the complications associated with measles cases and adverse events following immunisation. Monte-Carlo Simulation techniques were used to account for uncertainty.

Results: From the perspective of society, we estimated the average cost per measles case to be US\$276, US\$307 and US\$254 for the NL, the UK and Canada, respectively, and the average cost of adverse events following immunisation per vaccinee to be US\$1.43, US\$1.93 and US\$1.51 for the NL, UK and Canada, respectively.

Conclusions: These average cost estimates could be combined with incidence estimates and costs of immunisation programmes to provide estimates of the cost of measles to industrialised countries. Such estimates could be used as a basis to estimate the potential economic gains of global measles eradication.

Background

In many industrialized countries, high levels of immunisation over a number of years have led to a dramatic re-

duction in measles incidence. However, measles cases continue to occur in i) countries, such as the United States or Canada, where endemic measles transmission have

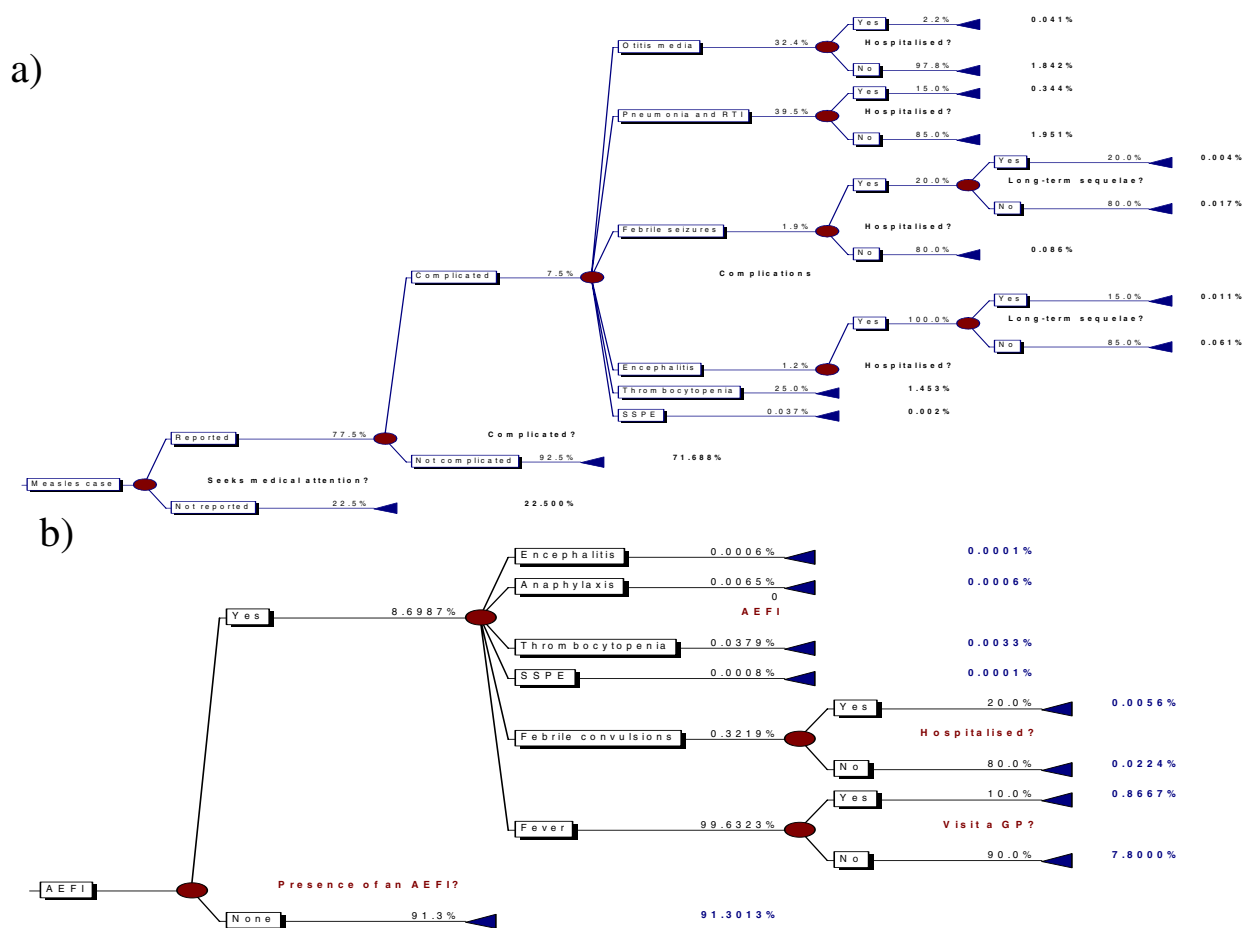


Figure 1
Decision trees. a) measles cases and b) Adverse Event Following Immunisation (AEFI) with measles vaccines. Legend: This graph shows the proportion of cases with each symptom, complication, sequelae or hospitalisation. A circle corresponds to a chance node (defined by the probability of the event occurring), a triangle represents an end node. The number at the top of each branch shows the proportion of each event occurring at that point in the tree. The total proportion of cases in each group per measles case is written at the right of each branch.

been interrupted and cases are linked to importations [1]; and ii) countries, such as Italy and Germany, where adequate levels of immunisation coverage have not been maintained and measles continues to circulate widely. These cases of measles can lead to serious complications and deaths as recently demonstrated in outbreaks in Ireland [2], Germany [3] and the Netherlands [4,5]. In addition to the economic and public health burden that these cases represent, the maintenance of high levels of vaccine coverage imposes an additional health and economic burden. The health burden is due to the real and perceived occurrence of adverse events following immunisation (AEFI). The economic burden arises through the cost of maintaining coverage levels and surveillance programmes.

In this paper we use a simple model to estimate the average cost of measles and measles vaccine associated adverse events, using the Netherlands (NL), the United Kingdom (UK) and Canada as examples. We then compare our estimates with others available in the literature. This is the first step in what would be required to estimate the global cost of measles immunisation and cases in industrialised countries.

Methods
Estimation of the frequency of measles complications and their treatment

A decision tree with the average probabilities used for estimating the cost per average case of measles is shown in Figure 1a. Measles cases are first divided into two distinct groups, according to whether they seek medical attention

Table 1: Distributions used in the simulations to estimate the average costs per measles case.

Complication	Consequence	Distribution	Mean	Minimum	Maximum
Uncomplicated measles case					
	% cases not seeking medical attention	Triangular	22.5	0.0	45.0
Cases not seeing a GP	Number of antipyretics bought	Exponential	0.2	0.0	1.5
	Number of anti-tussives bought	Triangular	0.4	0.0	1.0
	Number of working hours missed	Uniform	12	6.0	18.0
Cases seeing a GP	Number of visits to GP	Triangular	1.5	1.0	2.0
	Number of antibiotics bought	Uniform	1.0	0.0	2.0
	Number of antipyretics bought	Triangular	1.0	0.0	3.0
	Number of anti-tussives bought	Triangular	1.3	0.0	4.0
	Number of working hours missed	Uniform	16.0	8.0	24.0
Complicated measles cases					
Hospitalised	% complicated cases	Triangular	7.5	4.0	12.5
	LoS hospital – all wards	Triangular	4.0	2.0	6.0
	LoS Intensive care Unit	Uniform	5.7	1	10.4
	% of hospital time spent in intensive care	Triangular	6.5	4.0	8.0
Specific costs for hospitalised complicated cases					
Otitis media	Frequency (per 100)	Triangular	3.5	2.0	6.0
	% hospitalised	Triangular	0.2	0.05	0.3
Pneumonia and other severe RTI	LoS hospital	Triangular	1.0	0.5	1.5
	Frequency (per 100)	Uniform	4.3	1.0	8.0
	% hospitalised	Uniform	15.0	10.0	20.0
Encephalitis	LoS hospital	Triangular	7.0	4.0	10.0
	Frequency (per 100)	Triangular	0.13	0.1	0.2
	% hospitalised	Fixed	100.0		
Thrombocytopenia	LoS hospital	Triangular	6.0	3.0	9.0
	Frequency (per 100)	Uniform	2.1	0.4	5.0
	% hospitalised	Fixed	100.0		
Convulsions	LoS hospital	Uniform	3.8	2.0	5.6
	Frequency (per 100)	Triangular	0.2	0.1	0.4
	% hospitalised	Triangular	20.0	10.0	40.0
SSPE	LoS hospital	Uniform	2.6	1.0	4.2
	Frequency (per 100,000)	Triangular	3.0	2.0	6.0
Long term sequelae following acute encephalitis					
	Proportion of cases with extra hospitalisation	Uniform	35.0	20.0	50.0
	Proportion of cases with extra consultations with a physician	Uniform	15.0	10.0	20.0

Table 1: Distributions used in the simulations to estimate the average costs per measles case. (Continued)

Proportion of cases with chronic treatment for epilepsy	Uniform	20.0	10.0	30.0
Proportion of cases missing school from = week to < 1 month	Uniform	12.5	5.0	20.0
Proportion of cases missing school = 1 month	Uniform	6.0	1.0	11.0
Number of school days missed between 1 week and 1 month	Triangular	11.7	5.0	20.0
Number of school days missed during = 1 month	Triangular	37.0	21.0	60.0
Proportion of cases needing residential care	Uniform	5.0	1.0	9.0
Long term sequelae following acute febrile convulsions				
Proportion of cases with extra hospitalisation	Uniform	35.0	25.0	45.0
Proportion of cases with extra consultations with a physician	Uniform	20.0	10.0	30.0
Proportion of cases with chronic treatment for epilepsy	Uniform	12.5	8.0	17.0
Variables common to long term sequelae				
Average number of extra hospitalisation per year	Triangular	0.33	0.1	0.6
Average number of extra physician visits per year	Triangular	3.0	1.0	6.0

or not. The minimum value for the proportion of cases seeking medical attention is largely based on estimates of the maximal efficiency of reporting systems. It has been estimated that in the UK [6], US [7,8] and Australia [9], between 50% and 65% of measles cases are reported to the authorities in the population [6] or during outbreaks [8,9] or are medically attended [7]. The UK study, based on a simple model, comes to the conclusion that an average of 56% of measles cases was reported between 1957 and 1977. All reported cases must first see a physician to be reported and thus we can assume that a strict minimum of between 50% and 65% of all measles cases do seek medical attention. This corresponds to a maximum proportion of patients not seeking medical attention ranging between 35% and 50%. We choose 45% as the maximum value for the proportion of patients not seeking

medical attention to take account of the fact that some cases may seek medical attention but may not be reported to the authorities as measles. We set the minimum proportion of patients not seeking medical attention to 0%. Hence, we assume that 22.5% (range 0% to 45%) of measles cases do not seek medical attention (Figure 1a).

Those that seek medical attention are divided into complicated and non-complicated cases. Based on the weighted average of five community-based studies, we estimate that 7.5% of cases are complicated [10–14]. Complicated cases are further divided according to the type of complications with proportions based on the literature [10–19]. A specific proportion of measles cases with each complication are assumed to be hospitalised: an average of 12.5% of severe respiratory tract infection (RTI), 2.2% of otitis media

(OM), 20% of febrile convulsion and 100% of all other complications are assumed hospitalised (Table 1). The average length of stay for all hospitalised cases is estimated at 4 days with 5.7% of the hospitalisation time spent in intensive care [18–20]. The literature used to estimate the range of values for all parameters is presented in the Appendix (see Additional file 1). The distribution effectively used for all parameters are presented in Table 1. Among severe complicated cases a small proportion develops long-term sequelae (Figure 1a). The estimate of the proportion of cases developing Sub-acute Sclerosing PanEncephalitis (SSPE) is taken from a large population-based study from the UK [21]. An average period from diagnosis to death for SSPE cases of 2.5 years is used, based on the same study. Estimates of the incidence of measles associated encephalitis are based on three studies of passive surveillance data [10,13,16]. Resource use estimates of long-term neurological sequelae are based on a 12-years follow-up study of 1452 acute encephalopathy, severe febrile convulsion and control cases [22]. We use the extra frequency of sequelae in the cases compared to the control group (Table 1a). We assume a life expectancy of 75 years and an average age for encephalitis and febrile convulsion cases of 8 years and used a 3% discount rate. The duration of treatment for epilepsy (recurrent convulsions) is based on a cross-sectional study of 1,628 epileptic patients taking medication [23].

Care takers of measles cases that do not seek medical attention are assumed to buy Over-The-Counter (OTC) drugs and miss some working hours. Non-complicated cases that do seek medical attention and complicated non-hospitalised cases are assumed to consult a physician, be prescribed antibiotics and have their care takers buy OTC drugs and miss some working hours. For all non-complicated and non-hospitalised cases, information specifically on measles is supplemented by data from a large study of upper RTI in toddlers attending daycare centres [24]. The frequency of physician visits and antibiotics prescribed in this study agreed well with a smaller study conducted on measles patients.[25] As there are no recent studies of the average period of absenteeism caused by measles cases, we base our estimates on those for chickenpox. Chickenpox results in an average of 1.3 days lost per case (taking account women's employment patterns) [26]. As measles is more severe, we assume that the average period of maternal absenteeism is 2 days (ranging from 1 to 3 days), and for non-reported cases this is reduced by 25%, based on the daycare centre study [24]. For hospitalised cases, maternal absenteeism, adjusted for the proportion of working women, is assumed to equal the hospitalisation period.

Estimating the frequency of AEFI and their treatment

A similar model is used for measles AEFI (Figure 1b). That is, we determine the proportion of vaccinees that are likely to develop each possible AEFI. We include only those AEFI thought to be associated with the measles component of MMR vaccines based on a thorough review of the literature [27] and reviews conducted by national advisory committees on immunization [28,29]. Hence, we exclude possible AEFI cases of Crohns disease, Guillain Barré syndrome and autism as the evidence linking these conditions to measles vaccine is, at best, extremely weak [30–32]. Similarly, the occurrence of sequelae after encephalitis or febrile seizures is not included because they had been shown not to be related to AEFI with measles containing vaccines [34,35].

It is difficult to attribute AEFI solely to the measles component of vaccine because measles immunisation is almost always given as the triple vaccine MMR. Here we assume that any AEFI likely to be caused in part or in total by the measles component of MMR [27] are wholly attributable to the measles component. This means that our estimate is likely to be an overestimate of the frequency (and thus cost) of AEFI attributable to the measles component of the vaccine.

The frequency of AEFI per vaccinee is considerably lower than that of complications per measles case and thus is more difficult to accurately quantify. Nevertheless, for fever, rashes, encephalitis, thrombocytopenia and febrile convulsions, comparative studies do exist (see Appendix) and are used to obtain a feasible range of these estimates (Table 2). For other AEFI, such as anaphylaxis or SSPE, case reports and studies of expert opinion are used.

For more common and mild AEFI we only include outcomes found significant in a large Finnish double-blind cross-over placebo controlled trial conducted among 581 pairs of twins [35]. For all fever cases, it is estimated that 0.51 days with fever was attributable to the first dose of MMR. In addition, mild symptoms occurred 16 times less frequently in children receiving a second dose of MMR [35]. No other mild symptom was important. Rashes were also found not to increase significantly after the vaccine compared to the period before vaccination [36].

We assume that all severe outcomes (anaphylaxis, thrombocytopenia, encephalitis) would be hospitalised (see Table 2). We also assume that on average 10% of fever cases would consult a physician (Table 2) [37].

The treatment of complicated hospitalised and non-hospitalised cases is assumed to be the same as for measles cases. For fever cases, we assume the same duration of parental absenteeism as for non-reported measles case.

Table 2: Distributions used in the simulations to estimate the average costs of adverse events per vaccinee.

Complication	Consequence	Distribution	Mean	Minimum	Maximum
Adverse events (per vaccinee)					
Encephalitis	Frequency (per 100,000)	Triangular	0.05	0	0.1
	% hospitalised	Fixed	100.0		
	LoS hospital	Triangular	6.0	3.0	9.0
Convulsions	Frequency (per 100,000)	Triangular	28.0	17	34
	% hospitalised	Triangular	20.0	10.0	40.0
	LoS hospital	Uniform	2.6	1.0	4.2
	% visiting a clinic	Fixed	100.0		
	Number of antipyretics bought	Fixed	1.0		
	Number of anticonvulsivants bought	Fixed	1.0		
Anaphylaxis	Frequency (per 100,000)	Triangular	0.6	0.1	1.0
	% hospitalised	Fixed	100.0		
	LoS hospital	Uniform	1.5	1.0	2.0
Thrombocytopenia	Frequency (per 100,000)	Uniform	3.3	3.1	3.5
	% hospitalised	Fixed	100.0		
	LoS hospital	Uniform	3.8	2.0	5.6
Fever	Frequency (per 100)	Triangular	8.7	2.0	19.0
	% visiting a clinic	Uniform	10.0	0.0	20.0
	Number of antipyretics bought	Fixed	1.0		
	Number of working hours missed	Uniform	12	6.0	18.0
SSPE	Frequency (per 100,000)	Uniform	0.07	0	0.14

Estimating the cost of measles cases and AEFI

We estimate the average cost of each outcome described above. The overall average cost of a measles case is the sum of these average costs weighted by the proportion of measles cases that result in each group (shown at the far right of each branch in Figure 1).

Costs of an average measles case and of an average case of measles-associated AEFI are estimated from both the health care provider (HCP) and wider society perspectives. Costs to the HCP include physician consultations (including prescribed drugs), hospitalisations (including intensive care) and of long-term care for SSPE or other sequelae. Costs to society (including HCP costs) include the costs of OTC drugs, maternal absenteeism to care for a sick child and social costs to care for long-term sequelae. We exclude indirect costs associated with death and productivity loss and we do not attempt to put a monetary value on pain and suffering or measles associated premature death.

Unit costs for each of the outcomes for each of the study countries (NL, UK and Canada) are estimated from several sources. These sources, given in Table 3, include official statistics [38–42], health economics databases [43–45], commercial data [46] and reference from the literature [47].

All reported costs are updated to their 2001 values using the health Consumer Price Index in each country [43]. The data is then converted to US\$ 2001 values with inter-bank average exchange rates between 01/01/01 and 01/06/01 [48].

Uncertainty and sensitivity analyses

To take into account the considerable uncertainty surrounding many of the parameter estimates, distributions are defined for the input parameter values. The model is run many (10,000) times and on each occasion, a new set of parameter values for all the uncertain parameters described in Tables 123 are randomly selected according to

Table 3: Itemised cost menu (2001 US\$) used in the calculations

Item	Unit	Country	Cost	Reference (distribution)
Exchange rate (ro 2001 US\$)	Per local currency	Netherlands	0.42	48
		UK	1.45	48
		Canada	0.67	48
Hospitalisation – general ward	Per day	Netherlands	\$ 232.35	64
		UK	\$ 332.97	38
		Canada	\$ 430.23	43
Hospitalisation – intensive care unit	Per day	Netherlands	\$ 364.77	43
		UK	\$ 421.07	38
		Canada	\$ 548.76	43
Residential care	Per week	Netherlands	\$ 645.81	64
		UK	\$ 406.00	38 (Triangular(267,415,535))
		Canada	\$ 298.05	39 (Triangular (175.32, 298.05, 420.80))
Visit to the physician	Per visit	Netherlands	\$ 15.63	64
		UK	\$ 37.33	38
		Canada	\$ 19.85	39
Antipyretics	Per pack	Netherlands	\$ 0.84	64
		UK	\$ 4.06	46
		Canada	\$ 2.98	44 (uniform(1.7, 4.1))
Cough Syrup	Per bottle	Netherlands	\$ 4.22	64
		UK	\$ 4.27	46 (uniform(3.9, 4.6))
		Canada	\$ 4.13	44 (triangular(2.7, 4.1, 5.5))
Antibiotics for RTI	Per course	Netherlands	\$ 9.29	64
		UK	\$ 4.85	52 (triangular (2.9, 4.4, 7.3))
		Canada	\$ 11.69	44 (triangular (6.8, 10.9, 17.1))
Anticonvulsivant (diazepam for acute case)	Per dose	Netherlands	\$ 0.78	64 (Uniform(0.52, 1.04))
		UK	\$ 18.40	45 (Uniform (16.42, 19.41))
		Canada	\$ 3.63	44
Anticonvulsivant (for epilepsy)	Per day	Netherlands	\$ 3.53	47 (Triangular (0.6, 4.25, 5.75))
		UK	\$ 2.80	47 (Triangular (1.34, 3.73, 7.47))
		Canada	\$ 1.70	44 (Uniform(0.41, 2.98))
Test to measure anticonvulsivant blood levels	Per test	Netherlands	\$ 12.37	47
		UK	\$ 41.95	47
		Canada	\$ 26.00	47 (Uniform (12.00, 40.00))
SSPE – HCP costs	Per case	Netherlands	\$ 50,000	Assumed over 2.5 years [§]

Table 3: Itemised cost menu (2001 US\$) used in the calculations (Continued)

		UK	\$ 50,000	Assumed over 2.5 years [§]
		Canada	\$ 50,000	Assumed over 2.5 years [§]
SSPE – other costs	Per case	Netherlands	\$ 50,000	Assumed over 2.5 years [§]
		UK	\$ 50,000	Assumed over 2.5 years [§]
		Canada	\$ 50,000	Assumed over 2.5 years [§]
Average wage for women	Per day	Netherlands	\$ 68.07	40
		UK	\$ 73.06	41
		Canada	\$ 61.77	42

Assumed over 2.5 years[§] this is associated with a case of SSPE and assumed to range between US\$ 25,000 and US\$ 75,000 for both direct and indirect costs.

their distribution using Monte Carlo sampling. This provides an outcome distribution for the cost of an average measles case and allows us to report a mean and 95% credibility intervals (95% CIs) around our estimates. This "uncertainty analysis" [49] was performed using @Risk for excel [50].

By regressing the outcome variable (cost of measles case or AEFIs) against the values of the input parameters (all measured in standard deviation changes) it is possible to explore the sensitivity of the model to the different parameters.

Results

The frequency of measles complications and adverse events following measles vaccination

The model suggests that an average of 1.9% of all measles cases are hospitalised (Figure 1a). Most of the complicated cases are severe respiratory tract infections (39.5%) and otitis media (32.4%) who make up 20% of all hospitalised cases. Cases of thrombocytopenia represent the largest proportion of hospitalised cases (75.3%). This is because all thrombocytopenia cases are assumed to be hospitalised and they are relatively frequent (2.1% of cases seeking medical attention).

Figure 1b illustrates that around 8.7% of all vaccinees would develop AEFI, with 99.6% of these being fever. The next most frequent AEFI is febrile convulsions. This shows that most AEFI complications are less severe than that of measles symptoms. In effect, even with the strong assumption that all severe cases of AEFI cases would be hospitalised, only 0.1% of all vaccinations would lead to hospitalisation because of AEFI. On a relative scale, this is almost 200 times less than the proportion of children hospitalised with measles. It should be noted that this does not mean that the absolute number hospitalised AEFI cas-

es in a population where a large number of children are vaccinated and a few cases of measles still occur will be larger than the absolute number of hospitalised measles cases.

The cost per average measles case

In the following section, the results are presented in the same order for the Netherlands, UK and Canada. Our estimates of the cost to society for an average (95% CI) measles case are US\$276 (174–382), US\$307 (202–418) and US\$254 (167–347). HCP costs represent 36% to 43% of these costs. Costs of hospitalisation are somewhat higher in Canada (Table 3) explaining the larger proportion of costs attributable to HCP here. However, our estimates are similar in all three countries with their 95% CI largely crossing over (Figure 2a).

The average (95% CI) estimated costs of a typical hospitalised case from the HCP perspective are US\$967 (604–1,332), US\$1,357 (839–1,877) and US\$1,755 (1,085–2,427) (Figure 2b). The HCP costs represent 85%, 87% and 91% of the overall costs per hospitalised case to society. The average cost of non-hospitalised cases, on the other hand, is estimated at US\$206 (122–293), US\$242 (149–338) and US\$187 (115–262) with HCP costs representing 11%, 18% and 14% of the overall costs to society (Figure 2c).

The cost (95% CI) to the society per average measles encephalitis case, including sequelae, are estimated to be US\$50,500 (22,147–98,031), US\$70,059 (30,491–148,454) and US\$132,487 (36,016–132,989) and per average case resulting in febrile convulsions (including sequelae) to be US\$6,535 (2,375–16,339), US\$9,173 (3,458–23,012) and US\$9,544 (2,995–25,776).

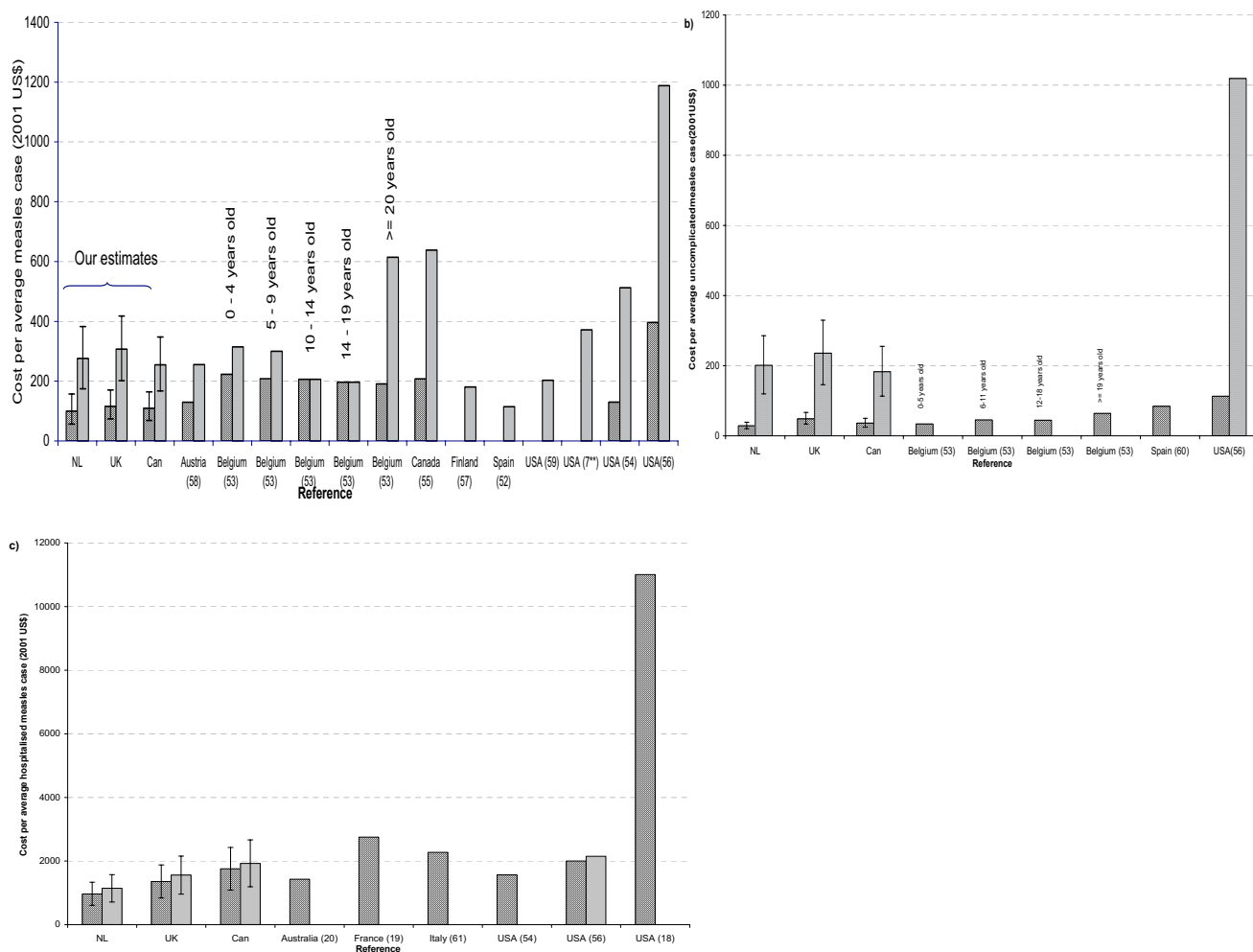


Figure 2
Societal and health care provider costs a) average case of measles, b) uncomplicated case of measles and c) hospitalized case of measles from the literature and from our estimates for the Netherlands (NL), the United Kingdom, (UK) and Canada (Can) for the proportion of cases hospitalized. Legend: (7) The societal cost excludes the cost of encephalitis. Shaded bars correspond to the health care provider costs. Full bars correspond to the societal costs.

Figure 2a,2b,2c shows our estimates of the societal and HCP costs and their 95%CI along with estimates reported in the literature. The reported societal costs per average measles case vary between US\$180 and US\$638, with an outlier at US\$1,188 (Figure 2a). Thus our estimates were broadly similar to most estimates available in the literature [51–58]. The proportion of the costs to HCP was also similar to that reported elsewhere, again with the exception of that outlier [55]. Only three studies in the literature have reported the cost per uncomplicated case.

Our estimates of costs from the HCP perspective are closer to the ones reported by European studies [51,52] than US studies [53,55]. Indeed, it is noteworthy that many of the higher estimates derive from US-based studies, which may partly reflect the generally higher health-care costs in the

US compared with other industrialised countries. The cost (to the HCP) per hospitalised case was very consistent between studies [19,20,53,55,60] and comparable to our estimates, with one notable (US-based) outlier [18] (Figure 2c). Unfortunately, few previous studies reported the societal cost per hospitalised case limiting comparison.

The cost of adverse events following measles vaccine

All results are again presented here for the Netherlands, UK and Canada respectively. From the societal perspective, we estimate the average (95% CI) cost of AEFI per vaccinee to be US\$ 1.55(0.28–4.35), US\$2.08 (0.48–5.52) and US\$1.58(0.41–4.15) with the cost associated with fever representing 87%, 88% and 84% of the total. The cost of AEFI per vaccinee is around 150 times less than the cost of an average measles case. This is largely, though

not entirely, because the frequency of AEFI per vaccine is low compared to the frequency of complications per measles case. Taking the average (95% CI) cost to society of each AEFI then we estimate them to be US\$18.26 (3.54–39.41), US\$ 24.49 (6.62–48.94) and US\$ 18.82 (5.35–37.24), which is still around 13 times lower than the cost of an average measles case. This is because the most frequent AEFI is fever. The difference in the country-specific estimates was mainly due to the difference in the cost per physician visit and women's salaries. The HCP costs represented 14%, 24% and 24% of the total cost. It should be remembered here that these are costs referring to one average measles case and one average case of measles-associated AEFI. These values should not be interpreted as the costs of measles and AEFIs at the population level.

Figure 3a,3b,3c compares our estimates with those derived from the literature of the cost of AEFI per vaccine and per event. Taking the average cost per event, it is clear that our estimates were similar to two studies, [53,54] though considerably less than another study [55]. Furthermore, the proportion of the costs associated with HCP was considerably larger in the latter [56], in contrast to the finding for the cost per measles case. However, when the average cost per vaccinee is compared, then our estimates were similar to that latter study [55] where it was assumed that the treatment of minor adverse events occurred in 2.5% of all vaccination doses whereas 7.5% of vaccinees had a fever in our estimate which led to a larger denominator.

Sensitivity analyses

The three most influential variables on costs for the average cost per measles case were the average number of work days lost by the mother for a non-hospitalised case, the proportion of cases not seeking medical attention and the proportion of encephalitis cases developing sequelae leading to residential care. The three most influential variables for the average cost per AEFI were the percentage of fever cases seen in a clinic, the rate of fever and the average period of absenteeism when a child had to visit a physician.

Discussion

Although measles is rare in most industrialised countries it is still important to have up-to-date estimates of the average cost per measles cases and per measles-associated AEFI to aid decisions regarding changes to measles control or elimination programmes. However, the relative scarcity of both measles and AEFI means that there is a paucity of recent data and much uncertainty in our resultant estimates. We attempted to minimise this uncertainty by basing our parameter estimates on a thorough review of the available literature. Nevertheless, considerable uncertainty remained, which we incorporated into our analysis us-

ing Monte-Carlo Simulation techniques. This meant that we could not only provide an estimate of the confidence that we have in our results, but also allowed a systematic examination of which parameters influenced the results the most. Finally, we compared our cost estimates to previously published estimates.

In general there was relatively good agreement between our estimates of the average cost of measles and AEFI and those reported in the literature (with one notable exception) [55]. Whilst this external validation lends some support to our estimates, it should be noted that some of the other estimates [53–55] have been based on a similar review of the literature [61,62] and therefore might be expected to give broadly similar results to ours (after allowing for inflation).

We have not included stratified costs per age group in our analysis, as had been done in two studies [52,54], as we felt that there was insufficient data to further divide them. Nonetheless, our range of values agreed with the estimates for individuals aged less than 20 years [52]. Given that adult measles cases are usually rare, our non-age adjusted estimate is probably credible.

Accurately estimating the frequency and consequences of very rare events is difficult and expensive, requiring large-scale long-term studies, perhaps combined with sophisticated statistical methodologies (see [63] for such an example). The results of the sensitivity analyses clearly show, however, that with the exception of care for encephalitis cases, these events have very little influence on our estimates of the average cost of measles and measles-associated AEFI, precisely because they are rare. Instead, the most influential parameters are concerned with everyday events, such as the effect of child illness on parental work patterns, and the proportion of cases that visit a doctor. Substantial improvements in our estimates of the economic impact of measles (and similar infectious disease, such as chickenpox) can be obtained by concentrating on these parameters.

Conclusions

The overall cost of measles is given by the average cost of cases multiplied by the incidence. The average cost estimates provided here will be combined with incidence estimates to provide estimates of the cost of measles to industrialised countries. Such estimates could be used as a basis to estimate the potential economic gains of global measles eradication.

Competing interests

None declared.

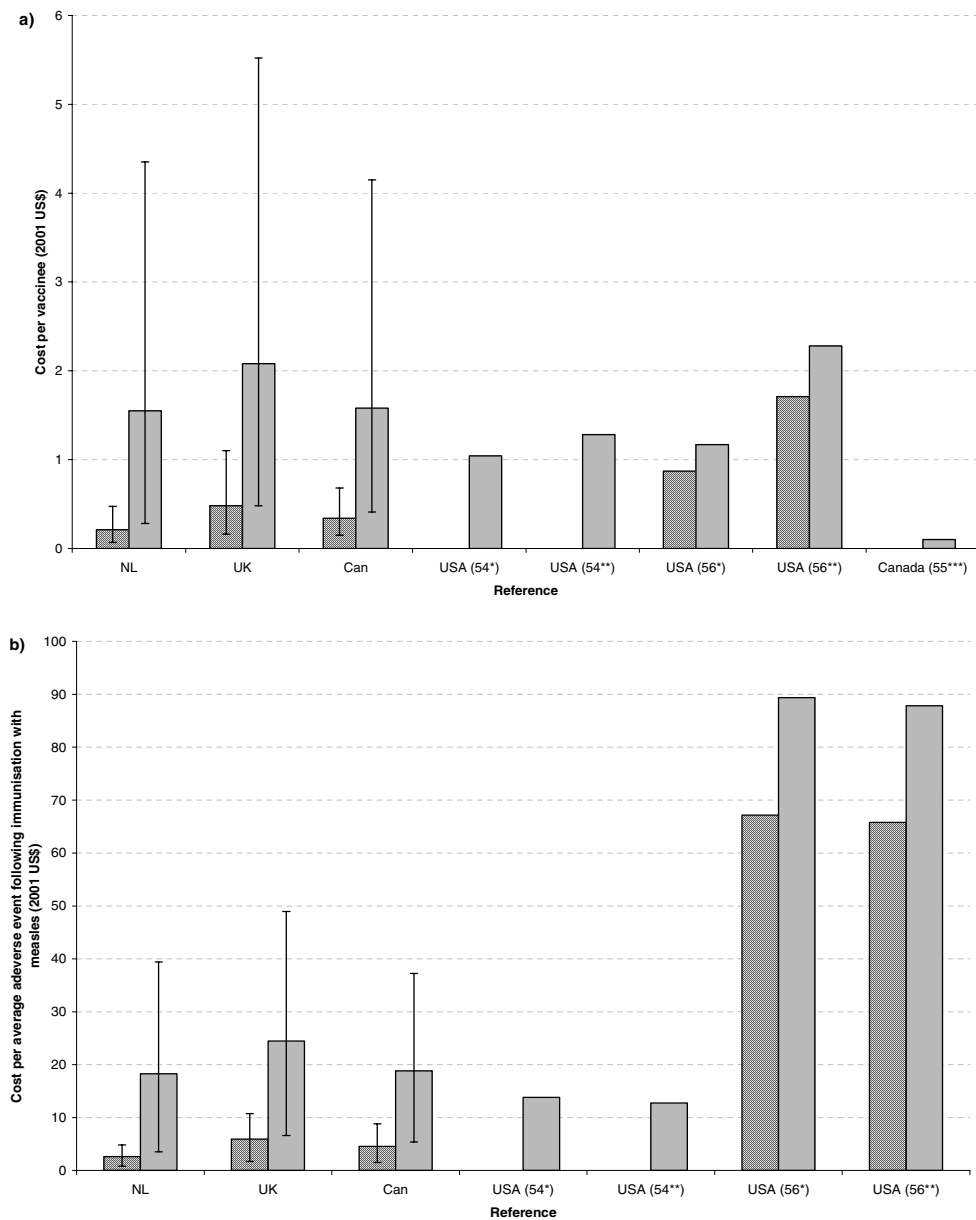


Figure 3
Societal and health care provider Adverse Event Following Immunisation costs. a) per vaccinee and b) per adverse event from the literature and from our estimates for the Netherlands (NL), the United Kingdom (UK) and Canada (Can). Legend: * estimates are for all adverse events associated with measles-only vaccine ** estimates are for all adverse events associated with MMR vaccine *** Cost per vaccinee associated with the second dose of MMR only, the frequency of adverse event with the 2nd dose being assumed to be 10% those of the 1st dose. Shaded bars correspond to the health care provider costs. Full bars correspond to the societal costs.

Authors' contributions

HC and WJE designed the study, reviewed the literature, collected and analysed the data, directed the project and were responsible for writing the paper. UK reviewed the analysis plan, results and paper and provided economical expertise throughout the project. SH extracted the epidemiological and economical data for the Netherlands, reviewed the analysis plan and results. VHN extracted the epidemiological and economical data for Canada, reviewed the analysis plan and results. All authors read and approved the final manuscript.

Additional material

Appendix

The file "appendix.doc" contains two very large Tables describing the literature reviewed to obtain ranges of values for our parameter estimates. This is a word file.

Click here for file
[<http://www.biomedcentral.com/content/supplementary/1471-2458-2-22-S1.doc>]

Acknowledgments

The World Health Organisation provided partial funding for this study and the WHO European Office provided support for data collection. We thank Dr. Ana Maria Henao Restrepo, Dr. Bernardus Ganter and all the participants at the measles workshop in Copenhagen, October 2000, for useful suggestions and help in designing the questionnaire. Dr. Hélène Carabin is funded by the Wellcome Trust and Dr. John Edmunds by the UK Medical Research Council. Finally, we would like to thank Karen Grimsrud to have taken the time to fill in the questionnaire.

References

- De Serres G, Gay NJ, Farrington CP: **Epidemiology of transmissible disease after elimination.** *Am J Epidemiol* 2000, **151**:1039-48
- Cronin M, Fitzsimmons GJ: **Measles outbreak in the Republic of Ireland: update.** *Eurosurveillance Weekly* 2000, **4**
- Outbreak of measles in an army base in Germany.** *Eurosurveillance Weekly* 2001, **5**
- Measles outbreak, Netherlands.** *Wkly Epidemiol Rec* 2000, **75**:119-21
- Measles outbreak – Netherlands, April 1999 – January 2000.** *MMWR Morb Mortal Wkly Rep* 2000, **49**:299-303
- Clarkson JA, Fine PE: **The efficiency of measles and pertussis notification in England and Wales.** *Int J Epidemiol* 1985, **14**:153-68
- Axnick NW, Shavell SM, Witte JJ: **Benefits due to immunization against measles.** *Public Health Rep* 1969, **84**:673-80
- Davis SF, Strebel PM, Atkinson WL, et al: **Reporting efficiency during a measles outbreak in New York City, 1991.** *Am J Public Health* 1993, **83**:1011-5
- McDonnell IF, Jorm LR: **Measles epidemic in western Sydney.** *New South Wales Public Health Bulletin* 1994, **5**:59-60
- Miller DL: **Frequency of complications of measles, 1963. Report on a National inquiry by the Public Health Laboratory Service in Collaboration with the society of medical officers of health.** *Br Med J* 1964, **2**:75-8
- Miller CL: **Severity of notified measles.** *Br Med J* 1978, **1**:1253-5
- Godoy P, Dominguez A, Alvarez J, et al: **Measles epidemiology in Catalonia (Spain): implications for a regional vaccination programme.** *Int J Epidemiol* 1999, **28**:558-62
- van den Hof S, van den Kerkhof JH, ten Ham PB, van Binnendijk RS, Conyn-van Spaendonck MA, van Steenbergen JE: **[Measles epidemic in the Netherlands, 1999–2000].** *Ned Tijdschr Geneesk* 2001, **145**:2529-33
- Grimsrud K: **Cases of measles in the Alberta's (Canada) outbreak.** *Personal Communication* 2001
- Godoy P, Dominguez A, Camps N, et al: **[Validity of the notifications of red measles based on clinical diagnosis in Catalonia, Spain].** *Enfermedades Infecciosas y Microbiologia Clinica* 1999, **17**:180-3
- Dales LG, Kizer KW, Rutherford GW, Pertowski CA, Waterman SH, Woodford G: **Measles epidemic from failure to immunize.** *West J Med* 1993, **159**:455-64
- Hanratty B, Holt T, Duffell E, et al: **UK measles outbreak in non-immune anthroposophic communities: the implications for the elimination of measles from Europe.** *Epidemiol Infect* 2000, **125**:377-83
- Mason WH, Ross LA, Lanson J, Wright HT Jr: **Epidemic measles in the postvaccine era: evaluation of epidemiology, clinical presentation and complications during an urban outbreak.** *Pediatr Infect Dis J* 1993, **12**:42-8
- Loras-Duclaux I, David L, Peyramond D, Floret D, Lachaux A, Hermier M: **[Epidemiological study and cost evaluation of measles in Lyons hospitals over a 5-year period].** *Pédiatrie* 1988, **43**:451-4
- Shiell A, Jorm LR, Carruthers R, Fitzsimmons GJ: **Cost-effectiveness of measles outbreak intervention strategies.** *Aust N Z J Public Health* 1998, **22**:126-32
- Farrington CP: **Subacute sclerosing panencephalitis in England and Wales: transient effects and risk estimates.** *Stat Med* 1991, **10**:1733-44
- Madge N, Diamond J, Miller D, et al: **The National Childhood Encephalopathy study: a 10-year follow-up. A report on the medical, social, behavioural and educational outcomes after serious, acute, neurological illness in early childhood.** *Dev Med Child Neurol* 1993, **35**:1-118
- Hart YM, Shorvon SD: **The nature of epilepsy in the general population. I. Characteristics of patients receiving medication from epilepsy.** *Epilepsy Res* 1995, **21**:43-9
- Carabin H, Gyorkos TW, Soto JC, Penrod J, Joseph L, Collet J-P: **Estimation of direct and indirect costs due to common infections in toddlers attending daycare centres.** *Pediatrics* 1999, **103**:556-64
- Hastings A, Hostler A, Solen A: **Measles: who pays the cost?** *Br Med J (Clin Res Ed)* 1987, **294**:1527-8
- Brisson M, Edmunds WJ: **The cost-effectiveness of varicella vaccination in Canada.** *Vaccine* 2002, **20**:1113-25
- Duclos P, Ward BJ: **Measles vaccines: a review of adverse events.** *Drug Saf* 1998, **19**:435-54
- National Advisory Committee on Immunization: **Canadian Immunization guide.** Ottawa, Canadian Medical Association 1998
- National Health and Medical Research Council: **The Australian Immunisation Handbook.** Canberra, AGPS 2000
- Taylor B, Miller E, Farrington CP, et al: **Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association.** *Lancet* 1999, **353**:2026-9
- Kaye JA, del Mar Melero-Montes M, Jick H: **Mumps, measles and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis.** *BMJ* 2001, **322**:460-3
- Strauss B, Bigham M: **Does measles-mumps-rubella (MMR) vaccination cause inflammatory bowel disease and autism?** *Can Commun Dis Rep* 2001, **27**:65-72
- Miller D, Wadsworth J, Diamond J, Ross D: **Measles vaccination and neurological events.** *Lancet* 1997, **349**:730-1
- Barlow WE, Davis RL, Glasser JW, et al: **The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine.** *N Engl J Med* 2001, **345**:656-61
- Virtanen M, Peltola H, Paunio M, Heimonen OP: **Day-to-day reactivity and the healthy vaccinee effect of Measles-Mumps-Rubella Vaccination.** *Pediatrics* 2000, **106**:e62-e68
- Davis RL, Marcuse E, Black S, et al: **MMR2 immunization at 4 to 5 years and 10 to 12 years of age: a comparison of adverse clinical events after immunization in the Vaccine Safety Datalink project. The Vaccine Safety Datalink Team.** *Pediatrics* 1997, **100**:767-71
- Lieu T, Black SB, Ray GT, Martin KE, Shinefield HR, Weniger BG: **The hidden costs of infant vaccination.** *Vaccine* 2000, **19**:33-41
- Netten A, Curtis L: **Unit costs for health and social care 2000.** Canterbury, Personal Social Services Research Unit 2000

39. Institute of Health Economics: **A national list of provincial costs for health costs: 1997/8**. Edmonton, Institute of Health Economics 2000
40. Statistics Netherlands: **Income, wage, labour costs and working hours of employees**. Amsterdam, Statistics Netherlands 2001 [http://www.cbs.nl/en/figures/keyfigures/sip_400z.htm]
41. National Statistics: **New Earning Survey 2000. Average weekly Earnings**. London: National Statistics. The official UK statistics site 2001 [http://www.statistics.gov.uk/statbase/xsdataset.asp]
42. Statistics Canada: **Ottawa: Statistics Canada 2001** [http://www.statcan.ca/english/Pgdb/People/Labour/labor01a.htm]
43. Organisation for Economic Co-Operation and Development (OECD): **Health Data 1998**. Paris: Organisation for Economic Co-Operation and Development (OECD) 1998
44. IMS Canada: **Retail pharmacy dispensed prescription costs: Canada and provinces**. Montreal: IMS Canada 1999
45. British National Formulary: **London: British National Formulary 2001** [http://bnf.vhn.net/home]
46. Boots the Chemist: **Price of OTC drugs in the UK**. Boots 2001 [http://bnf.vhn.net/home]
47. Heany DC, Sander JWAS, Shorvon SD: **Comparing the cost of epilepsy across eight European countries**. *Epilepsy Res* 2001, **43**:89-95
48. **Historical Currency Exchange Rates**. OANDA 2001 [http://www.oanda.com/convert/fxhistory]
49. Sanchez MA, Blower SM: **Uncertainty and sensitivity analysis of the basic reproductive rate**. *Am J Epidemiol* 1997, **145**:1127-37
50. **@Risk: Risk Analysis and simulation add-in for Excel (version 4)**. New York (NY), Palisade Corporation 2000
51. Taracena DP, Monton JL, Cristobal P, Gonzalez F, Casas J: **[The cost of measles in Spain]**. *An Esp Pediatr* 1983, **19**:383-8
52. Beutels P, van Damme P, van Casteren V, Gay NJ, De Schrijver K, Meheus A: **The difficult quest for data on "vanishing" vaccine-preventable infections in Europe: the case of measles in Flanders (Belgium)**. *Vaccine* 2002
53. White CC, Koplan JP, Orenstein WA: **Benefits, risks and costs of immunization for measles, mumps and rubella**. *Am J Public Health* 1985, **75**:739-44
54. Pelletier L, Chung P, Duclos P, Manga P, Scott J: **A benefit-cost analysis of two-dose measles immunization in Canada**. *Vaccine* 1998, **16**:989-96
55. Miller MA, Redd S, Hadler S, Hinman A: **A model to estimate the potential economic benefits of measles eradication for the United States**. *Vaccine* 1998, **16**:1917-22
56. Ekblom M, Elo O, Laurinkari J, Niemela P: **Costs and benefits of measles vaccination in Finland**. *Scand J Soc Med* 1978, **6**:111-5
57. Wiedermann G, Ambrosch F: **Cost-benefit calculations of vaccinations against measles and mumps in Austria**. *Dev Biol Stand* 1979, **43**:273-7
58. Bloch AB, Orenstein WA, Stetler HC, et al: **Health impact of measles vaccination in the United States**. *Pediatrics* 1985, **76**:524-32
59. Carrasco JL, Lardinois R: **Formula for calculating vaccine profitability**. *Vaccine* 1987, **5**:123-7
60. Moiraghi Ruggeni A, Zotti Z, Pedronetto A, Milano R, Garella D, Sacchetti C: **I ricoveri ispedalieri in Torino per morbillo e relative complicanze nel periodo 1973-1983: valutazioni sanitarie ed economiche, in rapporto alla opportunita dell'intervento vaccinale**. *Bol Ist Sieroterio Milano* 1986, **65**:502-11
61. Hatzianreou E, Halpern NT, Brown RE, Watson GA: **Cost-benefit analysis of the measles-mumps-rubella (MMR) vaccine**. Arlington, VA: Center for Disease Control and Prevention 1994
62. Center for Disease Control and Prevention: **Public attitudes towards immunization**. Atlanta: Center for Disease Control and Prevention 1977
63. Miller C, Farrington CP, Harbert K: **The epidemiology of subacute sclerosing panencephalitis in England and Wales 1970-1989**. *Int J Epidemiol* 1992, **21**:998-1006
64. van den Hof S: **Costs of measles in the Netherlands**. *Personal communications* 2001
65. Cope ANK, Frank PF, Montgomery J, et al: **Measles-Duval County, Florida, 1991-1992**. *Morb Mortal Wkly Rep* 1993, **42**:81-3
66. Mansoor O: **Vaccine adverse events reported in New Zealand 1990-5**. *N Z Med J* 1997, **10**:270-2
67. Chavez G, Ellis A: **Pediatric hospital admissions for measles. Lessons from the 1990 epidemic**. *West J Med* 1996, **165**:20-25
68. Bentsi-Enchill A, Hardy M, Koch J, Duclos P: **Adverse events temporally associated with vaccines - 1992 report**. *Can Commun Dis Rep* 1995, **21**:117-128
69. D'Souza RM, Campbell-Lloyd S, Isaacs D, et al: **Adverse events following immunisation associated with the 1998 Australian measles control campaign**. *Commun Dis Intell* 2000, **24**:27-33
70. Department of Health: **Measles Rubella (MR) Immunisation Campaign in England 1994. One Year On**. London: Department of Health 1995
71. Patja A, Davidkin I, Kurki T, Kallio MJ, Valle M, Peltola H: **Serious adverse events after measles-mumps-rubella vaccination during a fourteen-year prospective follow-up**. *Pediatr Infect Dis J* 2000, **19**:1127-34
72. Chen RT, Moses JM, Markowitz LE, Orenstein WA: **Adverse events following measles-mumps-rubella and measles vaccinations in college students**. *Vaccine* 1991, **9**:297-9
73. Roberts RJ, Sandifer QD, Evans MR, Nolan-Farrell MZ, Davis PM: **Reasons for non-uptake of measles, mumps, and rubella catch up immunisation in a measles epidemic and side effects of the vaccine**. *BMJ* 1995, **310**:1629-32
74. Rosenthal S, Chen R: **The reporting sensitivities of two passive surveillance systems for vaccine adverse events**. *Am J Public Health* 1995, **85**:1706-9
75. Griffin MR, Ray WA, Mortimer EA, Fenichel GM, Schaffner W: **Risk of seizures after measles-mumps-rubella immunization**. *Pediatrics* 1991, **88**:881-5
76. Okuno Y, Nakao T, Ishida N, et al: **Incidence of subacute sclerosing panencephalitis following measles and measles vaccination in Japan**. *Int J Epidemiol* 1989, **18**:684-9
77. Jonville-Bera AP, Autret E, Galy-Eyraud C, Hessel L: **Thrombocytopenic purpura after measles, mumps and rubella vaccination: a retrospective survey by the French regional pharmacovigilance centres and pasteur-merieux serums and vaccines**. *Pediatr Infect Dis J* 1996, **15**:44-8
78. Miller E, Waight P, Farrington CP: **Idiopathic thrombocytopenic purpura and MMR vaccine**. *Arch Dis Child* 2001, **84**:227-9

Pre-publication history

The pre-publication history for this paper can be accessed here:

<http://www.biomedcentral.com/1471-2458/2/22/prepub>

Publish with **BioMed Central** and every scientist can read your work free of charge

"BioMedCentral will be the most significant development for disseminating the results of biomedical research in our lifetime."

Paul Nurse, Director-General, Imperial Cancer Research Fund

Publish with **BMC** and your research papers will be:

- available free of charge to the entire biomedical community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours - you keep the copyright



Submit your manuscript here:

<http://www.biomedcentral.com/manuscript/>

editorial@biomedcentral.com