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THE SOCIETAL NET BENEFITS OF VACCINATION AGAINST MEASLES, MUMPS, AND RUBELLA

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Abstract
Although most industrialised countries have achieved high levels of immunisation against MMR, vaccination rates in countries like the Netherlands, Italy, the US and Canada has declined during the 21th century. The aim of this thesis is to examine the potential net social benefits of vaccinations against measles, mumps and rubella in Sweden by conducting a cost-benefit analysis were the costs of the current vaccination programme is compared to the costs of measles in the absence of vaccination. A decision-tree based analysis was conducted and all costs were estimated on the Swedish birth cohort of 2010. The 2-dose MMR vaccination programme was found to be cost-beneficial compared to a situation without vaccination, both when including the value of reduced mortality and when only looking at direct and indirect costs. Each vaccinated child results in savings of 4534 SEK.

Key words: public health, cost-benefit, MMR vaccination, measles
JEL codes: H510, I110, I120, I180

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Glossary of Medical Terms

Antipyretics	Medication that relieves fever such as ibuprofen and paracetamol.
Antitussives	Medication used to suppress or relieve coughing.
Convulsions	Violent, uncontrollable contractions of muscles.
Diphtheria	Upper respiratory tract illness that causes fever, bluish skin coloration, sore throat, difficulty swallowing, difficulty breathing, foul-smelling blood-stained nasal discharge and enlarged lymph nodes. Considered a medical emergency since patents may need breathing aid and can suffer heart failure.
Encephalitis	An inflammation of the brain usually caused by a virus. Symptoms includes headache and neck pain, drowsiness, nausea and fever.
Herd immunity	A form of immunity that is reached when a large enough proportion of the population is vaccinated that it provides protection for individuals who are not immunised. Based on the idea that the chains of infections are disrupted when large numbers of the population are non-susceptible to the disease. In the case of MMR herd immunity in countries like Sweden is reached when 83-94% of the population are vaccinated. In denser populated areas like Bangladesh, herd immunity requires a vaccination coverage of 98%.
Incidence	A measure of the risk of developing some new condition within a specified period of time.
Meningitis	An inflammation of the protective membranes covering the spinal cords and the brain that can be caused by bacterial or viral infections. Due to its proximity to the brain meningitis can be life-threatening and is therefore considered a medical emergency.
Morbidity	An unhealthy or diseased condition.
Mortality	The fatal outcome of morbidity, i.e. death.
Mucous membrane	The membranes lining passages of the body, such as the respiratory and digestive tracts, that open to the

	outside. The mucous membranes secrete mucus, which lubricates and protects against infection.
Otitis media	An inflammation of the middle ear.
Parotid glands	The parotid glands are salivary glands, responsible for making saliva. There are two parotid glands, one on each side of the face, in front of the ears.
Pertussis	Known as the "whooping cough", pertussis is a highly contagious bacterial disease that develops into severe coughing fits.
Pneumonia	An inflammation of the lungs with congestion caused by viruses, bacteria or irritants.
Prevalence	With regards to diseases, this implies how many are infected when observing a specific period of time.
RTI	Respiratory Tract Infection, infection of nose, sinuses, tonsils or other parts of the airways.
Small pox	An acute contagious disease caused by the variola virus that localises in small blood vessels of the skin, mouth and throat, resulting in characteristic raised fluid-filled blisters.
SSPE	Subacute sclerosing panencephalitis (SSPE), a progressive, usually fatal brain disorder occurring months or years after an attack of measles. After the appearance of symptoms, death usually occurs within 2,5 years.
Subclinical infection	Asymptomatic (without showing signs) carrying of a disease. Occur without developing explicit illness.
Tetanus	A medical condition characterised by a prolonged contraction of the skeletal muscle fibres.
Thrombocytopenia	A condition in which the blood has a lower than normal number of blood cell fragments called platelets.

1. Introduction

The use of vaccines has led to a dramatic reduction in morbidity and mortality from infectious diseases and it is considered one of the most successful medical interventions in history (Hobson-West 2003). In countries all over the world children are immunised against major diseases and vaccination serves as a cornerstone for preventive health care (Bloom et al. 2005).

The combination vaccine against measles, mumps and rubella (MMR) was licensed in 1971 in the US but it took until 1982 before it was introduced into the Swedish general childhood immunisation programme (Dannetun et al. 2004). The vaccine was first given in a single dose but later on a second one was added in order to increase the protection rate. The introduction of the MMR vaccine led to a rapid decline in incidence rates worldwide and in countries such as Sweden, the UK, and the US the required immunisation level for herd immunity was quickly reached. Herd immunity means that when a sufficient amount of the population is immunised against a vaccine preventable disease, the disease will stop spreading since it cannot find new hosts. The percentage of the population that has to be immunised depends on how infectious the disease is, the vulnerability of the population and environmental factors. Measles, for example, requires a higher level of the population to be immunised than mumps that is a less contagious disease. (Berger 1999)

Although most industrialised countries have achieved high levels of immunisation against MMR, vaccination rates in countries like the Netherlands, Germany, Italy, the US, and Canada has declined during the 21th century leading to outbreaks of foremost measles (Carabin et al 2002). Such outbreaks have been seen in Sweden as well, most recently in the city Järna where 13 measles cases where reported in February 2012 (SMI 2012:A).

If the immunisation rates were to continue to decrease this could impose a considerable burden on health care systems, individuals, and society as a whole (Carabin et al. 2003). Given the importance of vaccination and the fact that it serves as a cornerstone of preventive health care, it is important to have an updated and comprehensive economic evaluation of the MMR vaccine (Zhou et al. 2005). Economic evaluations can serve as a decision-making tool when making future choices between alternatives in the context of scarce resources (SOU 2010:39). Within health care it is often a choice between which interventions that should be prioritised. When performing an economic evaluation the costs and the consequences of at least two alternatives are compared, where one alternative can be "doing nothing". There are different evaluation techniques for doing this: cost-minimisation analysis (CMA), cost-

effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). They all estimate costs similarly but differ in their way of measuring the consequences. (WHO 2008)

The aim of this thesis is to examine the potential net social benefits of vaccinations against measles, mumps and rubella in Sweden. This will be conducted through a cost-benefit analysis of the current 2-dose MMR vaccination programme. The costs of vaccination, assuming a 95% coverage rate, will be compared to the direct, indirect, and mortality costs associated with measles cases contracted in an unimmunised population.

Since measles is the most contagious of the three diseases (Rivière et al. 1997) and it bears the majority of the costs and vaccination related adverse events, calculations will be limited to only include the economic burden of measles. When conducting the cost-benefit analysis the value of reduced morbidity will be disregarded, since it is too complicated and time consuming to place a monetary value on the pain and suffering resulting from measles infections.

The thesis is divided into seven sections apart from the introduction. Section two consists of a medical and historical background of the diseases as well as a review of the reasons behind vaccination resistance. In the third section the theory behind health economic studies and the different ways of performing them is discussed. This is followed by a review of the current state of research within the area of MMR cost-benefit analyses in section four. The fifth section will present the model on which our analysis is based as well as the data needed for calculations. The thesis ends with the results from the analysis, a discussion about the assumptions, the validity of the results, and what conclusions can be drawn.

2. Background

2.1. Medical background

To create an understanding of the MMR diseases, their consequences, and why the vaccination programme is important, a short description of measles, mumps, and rubella will be given.

2.1.1. Measles

Measles is a very contagious acute viral infection and each case of measles is expected to generate about 16 new cases (Berger 1999). Mortality rates among infants are high and death occurs in one in 5000 cases. The virus is secreted through breathing and most susceptible people are infected through the mucous membrane in the throat or eyes. (Department of Health 2007)

The course of measles is acute with fast increasing temperature, eye irritation and cough. After a day or two red patches of hives appear on the face and then spreads to the torso and extremities. White spots usually appear on the mucous membranes of the mouth.

Complications with measles are common. Infants are usually afflicted by breathing difficulties and secondary bacterial infections like ear- or sinus infections or pneumonia. Measles can also cause (in roughly 1/1 000 cases) severe meningitis, which can lead to permanent brain damage and in some cases death. (SMI 2012:B)

2.1.2. Mumps

Mumps is worldwide a common and very contagious acute viral illness that mostly affects small children. The disease is airborne and can be transmitted via breathing but also via physical contact. (SMI 2010)

The mumps virus attacks glandular tissue, foremost the salivary glands. The disease starts out with fever and gradually increasing tenderness and swelling of the parotid glands. The glands on both sides are usually attacked and the swelling is usually so prominent that it is visible. (SMI 2010) Other glands are infected in various degrees, and if post-pubescent men are infected there is a 25% risk of testicular inflammation, which can cause sterility (Department of Health 2007). A common complication of mumps is a mild and quickly passing meningitis, which in some cases can cause a permanent hearing impairment (SMI 2010).

2.1.3. Rubella

Rubella is one of the classic children's diseases. In Sweden it has been considered almost extinct since the MMR vaccination programme was introduced. Before the MMR vaccine more than 80% of adults showed evidence of having had rubella infections (Department of Health 2007). Rubella is still very common in developing countries (SMI 2011).

Rubella is usually a mild infection and many are infected only subclinical. The disease is characterised by an upper airway infection and a patchy red skin rash that usually appears on the face and then spreads to the torso and extremities (SMI 2011).

The real danger with rubella lies in its ability to cause foetal damages. If a woman is infected early on, before 10 weeks in her pregnancy, the risk for miscarriage or deformities of the skeleton, brain, ears, and eyes is about 90%. (Department of Health 2007)

2.2. Historical background

In spite of the recognised importance and success of national vaccination programmes, anti-vaccination groups have been a part of society as long as vaccination itself, taking on a variety of positions including sanitary, religious, scientific, and political.

As recently as 1999 and 2000, there was a widespread public discussion in Sweden on adverse events linked to measles vaccine, resulting in a considerable drop in vaccine coverage compared to birth cohort of 1998 (Dannetun et al. 2004).

Regardless what the reasons for not vaccinating are, falling uptake levels and public concerns about vaccination pose a serious problem for public health policy makers. In order to keep vaccination rates high enough to provide protection for the population in general, it emphasises the importance of examining the underlying reasons for parents choosing not to vaccinate their children. (Asikainen et al. 2003)

2.2.1. The introduction of vaccines and the anti-vaccination movement

The process of vaccination started in the early 1800's after a publication by Edward Jenner, containing evidence that an inoculation with cowpox, a mild viral disease, could protect against the life threatening infection of smallpox. Jenner called this process vaccination, from the Latin word for cow, *vacca*. (Wolfe and Sharp 2002)

Widespread vaccination against smallpox began and between 1840 and 1853 several vaccination acts were passed in the United Kingdom making vaccination compulsory. Many saw this as a violation against civil liberty and in 1867 the Anti-Compulsory Vaccination League was founded. Anti-vaccination movements could also be seen elsewhere in Europe and in Stockholm the vaccination rate fell to just over 40% in 1872, as a majority of the population refused to get vaccinated. (Wolfe and Sharp 2002)

The pressure from the anti-vaccination groups in Great Britain increased and in 1885 a royal commission was assigned to investigate the evidence for vaccination as well as the standpoints given by the opponents. After seven years the commission concluded that vaccination protected against smallpox but they also suggested that vaccinations no longer should be compulsory. This resulted in a new Vaccination Act, where the Parliament allowed conscientious objection to mandatory vaccination (Wolfe and Sharp 2002). As a consequence the vaccination coverage in the United Kingdom dropped from over 95 to under 50% (Baker 2003).

2.2.2. The pertussis controversy

The resistance against vaccine continued during the 20th century. In the 1970s the safety and efficiency of the diphtheria, tetanus, and pertussis (DTP) immunisation was questioned in Europe, Japan, Australia, Soviet Union and the United States, following a publication of an article claiming that the pertussis vaccine could cause neurological injury. The media played an important role in initiating and promoting the controversy by exaggerating the potential harm of the vaccine while overlooking the danger of the pertussis itself. (Baker 2003)

Vaccination rates began to decrease and in the United Kingdom the coverage against pertussis had declined from 79% in 1973 to 31% in 1978, which caused three major epidemics of whooping cough (Robinson 1981).

The same spectrum of events could be seen in Sweden where anti-vaccine movements disrupted the immunisation against pertussis. In 1979 the DTP coverage had dropped from 90% in 1974 to only 12%. The old whole-cell pertussis vaccine was abandoned as the Swedish medical society decided to wait for a new, more effective and safer vaccine. As a result, more than 10 000 cases of pertussis were reported annually with a rate of more than 1 per 1 000, comparable to those in developing countries. (Gangarosa et al. 1998)

The long pertussis vaccine controversy finally lost its momentum in the late 1980s and immunisation rates once again reached their pre-1974 levels (Baker 2003).

2.2.3. The MMR controversy

In the late 1990s the anti-vaccination activity once again increased in the UK, this time regarding the combination vaccine against measles, mumps and rubella (MMR). The MMR vaccine was introduced in the UK in 1988 and was welcomed by the public health community since it provided the opportunity to protect a child against three very infectious viral diseases with only one injection. The vaccine was successful and in 1996 the MMR coverage was over 95%. (MacDonald 2007) The voluntary MMR vaccination programme in Sweden was initiated in 1982, leading to a rapid decline in disease incidence rates (Alfredsson et al. 2004).

The MMR controversy began in 1998, following a publication in the medical journal The Lancet by British doctor Andrew Wakefield and a number of his colleagues. In the article the authors point to the possibility of a link between the MMR vaccine and autism, although they conceded that such a link could not be proven (Wakefield et al. 1998). The Lancet paper attracted great interest among the public, politicians and news media around the world and the doubt regarding vaccine safety led to decreasing rates of MMR uptake (Holton et al. 2012). In

2005 it was down to 80% in the United Kingdom and only 58% in London (MacDonald 2007). In the United States a smaller but detectable decrease in immunisation rates could be seen (Holton et al. 2012).

The MMR controversy received much attention in the Swedish media as well and in 2000 the coverage for the first time since the late 1980s fell below the level of herd immunity amongst two-year-olds. An increasing amount of parents also chose to postpone the first vaccination of their infants (Asikainen et al. 2003).

A number of studies and investigations were made to see if a link between MMR and autism could be proven and overwhelming evidence from these studies rejected such a causal relationship (MacDonald 2007; Madsen et al. 2002; Immunisation safety review committee 2001). In 2004 the Lancet paper was retracted as ten of the original collaborators withdrew their support for the autism hypothesis (Murch et al. 2004). Despite this and the fact that no relationship between MMR and autism has been proven, vaccination rates have continued to decrease (Asikainen et al. 2003).

There may be several explanations for this continuation. One reason could be that the incidence and the prevalence of the MMR diseases are very low. When parents have to balance the risk that the vaccine might cause autism against the risk that their children might attract measles, mumps or rubella they might choose to take advantage of the existing herd immunity, hoping that enough other parents will choose to vaccinate their children. This could be seen as a version of "the tragedy of the commons" where self-interest actions undermine collective benefits. (Fitzpatrick 2004)

Other explanations for why parents choose not to vaccinate their children are due to religious or philosophical reasons. Religious groups may refuse vaccination because it does not coincide with their religiously founded beliefs about the origin of illness – illness and its outcome is the will of God with which Man shouldn't interfere. In philosophic belief systems, such as the Anthroposophy or New Age, maintaining bodily balances and gaining immunity in a natural way is the method for obtaining good health. (Streefland 2001) Exemption from vaccination is allowed in many states in the US, as long as parents can prove that their religion does not allow it (Hobson-West 2003).

Mass childhood immunisation relies on the scientific concept of herd immunity and when vaccination rates starts to fall the risk of the old diseases returning is inevitable. There has already been several minor measles outbreaks in both the US and Europe. (Fitzpatrick 2004) When this happens it increases the importance of both having a deeper understanding of the cause of the decline as

well as having up-to-date figures on the costs of the diseases and knowing how many cases will be actualised when the vaccination rate drops.

3. Conceptual framework for Health Economic Evaluations

Society is faced with an increasing demand for health care and since resources are limited it is important to evaluate the profitability and effectiveness of various health interventions. Vaccination, for example, competes with other health improving interventions such as preventive treatments, drugs and surgical treatments. In order to evaluate the economic profitability and effectiveness of different alternatives, economic evaluations can be used. These evaluations can then act as decision-making tools when deciding how to prioritise and allocate the limited resources in an efficient way, i.e. in a way that maximises welfare and health of the community. (SOU 2010:39)

All forms of economic evaluations involve identifying, measuring, valuing and comparing the costs (inputs) and consequences (outcomes) of the alternative health care programmes being considered (Drummond et al. 2005; Kobelt 2002).

Inputs include:

- *Direct costs* of providing care: direct medical costs (e.g. costs of drugs, hospitalisation, staff time, equipment) and direct non-medical costs (e.g. patients' out of pocket expenses and transportation costs).
- *Indirect costs:* production losses due to patients being off work due to illness, premature mortality as well as reduced productivity at work.

The consequences are measured as health improvements, which can be expressed in *natural units* (health effects such as cases successfully treated, life-years gained), *utilities* (preference weights such as quality adjusted life-years) or *associated economic benefits* (gains or savings).

There are four different types of economic analyses: cost-minimisation, cost-effectiveness, cost-utility and cost-benefit. How to choose between these four depends on the research question, the nature of the treatment programme to be assessed and the clinical outcome. (Kobelt 2002)

3.1. Cost-minimisation analysis

Cost-minimisation analysis (CMA) is the preferred form of evaluation when two or more treatments produce identical outcomes. This means that the actual outcome of the treatments will not have to be analysed; only the direct costs associated with the treatments are compared to find the alternative that has the lowest costs. Cost-minimisation analyses are often used when supporting and justifying the introduction of new and cheaper drugs. (Kobelt 2002)

3.2. Cost-effectiveness analysis

The basis for the cost-effectiveness analysis (CEA) is to extract as much health as possible given the limited amount of resources (SOU 2010:39). The CEA is used when two or more treatments or processes have the same intended outcome, but different degrees of effectiveness. It examines both the costs and the outcomes of the treatments, where outcomes are measured in natural units such as "cases successfully treated" and "life-years gained". The results are expressed using the ratio of the change in costs to benefits of an intervention or treatment. (Kobelt 2002)

An example of a situation where CEA can be used is when examining the best way of prolonging life after kidney failure. Hospital dialysis and kidney transplantation are two mutually exclusive programmes that both are used for this purpose and have the same outcome of interest – life-years gained – but they may differ in costs as well as in their success of achieving the intended outcome. (Drummond et al. 2005)

3.3. Cost-utility analysis

Most of modern medicine is not only concerned with improving the quantity of life but also the quality. In the cost-utility analysis (CUA), which can be thought of as an extension of the cost-effectiveness analysis, both life expectance and quality of life is included in a single index, Quality-Adjusted-Life-Years, QALYs. (Kobelt 2002)

The quality adjustment is based on a set of values, or weights, called utilities and one value is assigned to each possible health state. These weights range from 0 to 1 where 0 equals death, or the worst possible case, and 1 equals full health. The gain from an intervention is the number of QALYs obtained. (Drummond et al. 2005)

Cost-utility analyses can be seen as a compliment to a cost-effectiveness analysis that compares treatments in different disease areas and clinical outcome measures (Kobelt 2002).

3.4. Cost-benefit analysis

In the cost-benefit analysis (CBA) the costs, improved health implications and other benefits of the medical programme is measured in monetary terms, making it possible to compare projects across sectors as well as establishing if a project is desirable from a societal point of view (Kobelt 2002).

As shown in the formula below, the CBA compares the discounted future streams of incremental benefits with incremental costs in order to find a project's *net present value* (NPV). A health care effort that generates a positive

NPV implies that the programme will increase social welfare. (Drummond et al. 2005)

$$NPV = \sum_{t=0}^{T} \frac{B_t}{(1+r)^t} - \sum_{t=0}^{T} \frac{C_t}{(1+r)^t}$$

B_t	= benefits in monetary terms derived in year t
C_t	= costs in monetary terms derived in year t
$1/(1+r)$	= discount factor at annual interest rate r
T	= life expectancy

Drummond et al. (2005) describes three different methods for adjusting health outcomes to monetary terms: human capital, revealed preferences and stated preferences of willingness-to-pay. To estimate the monetary value of premature death the statistical value of life measurement can be used (Hultkrantz and Svensson 2008).

3.4.1. Human capital approach

The human capital approach values health status by measuring the present value of a person's future earnings. The consequences of a treatment not only include direct medical costs but also the reduced economic productivity that results from disability or premature death, and therefore a monetary value is placed on the reduced productivity using market wage rates.

The human capital approach has a few measurement difficulties. Firstly, even though in theory the wage rate reflects the marginal productivity this is not always the case since there might be imperfections in the labour market; the wage rate may reflect inequalities such as race or gender discrimination. Secondly, if the study is made from a societal point of view the healthy time gained that cannot be sold for a wage also has to be considered. Take for example a stay at home parent that after a treatment can continue looking after the children. Since this could not be measured using market wage rates economists have to place shadow-prices on these non-market resources; either by using an opportunity cost of time argument or a replacement cost approach.

In addition to these measurement difficulties the method has also been criticised for its way of valuing benefits. Instead of basing it on a person's individual valuation of benefits a third party view is taken about people's worth to society in terms of their productivity potential, something that is not in line with the principles of welfare economics. (Drummond et al 2005; Robinson 1993)

3.4.2. The revealed preference approach

The revealed preference (RP) approach involves observing behaviour and using these observations as a basis for valuing benefits, i.e. extracting measurements from actual choices made by individuals in markets. Obtaining preferences can be done by observing people's attitude towards risk and thereby derive their personal valuations from this behaviour. Some people may for example accept a higher pay for undertaking a more dangerous job while others will spend money on cars with enhanced safety features to reduce the risk of injury or death. (Drummond et al. 2005) Due to the more collective salary formation in Europe than in the US, the size of the risk compensation is harder to distinguish and the use of RP to determine risk preferences is very limited (Hultkrantz and Svensson 2008).

The strength of this approach is that it is based on actual consumer choices involving health or other benefits versus money. The weakness is that it is only applicable in a limited number of situations. (Drummond et al. 2005; Robinson 1993)

3.4.3. Stated preferences of willingness to pay

In the stated preferences (SP) of willingness to pay approach people are asked to state their preferences about different choices in hypothetical situations in monetary terms. This method can be used when wanting to estimate, for example, how much an individual is willing to pay in order to obtain certain benefits or avoid the costs of illness. This way the value that people attach to health outcomes can be established. (Robinson 1993)

One problem with this approach is that peoples' willingness to pay is often linked to their level of income. Answers may reflect the value people attach to money itself as well as their valuation of the benefits of health care. (Robinson 1993)

3.4.4. Statistical value of life

The statistical value of life (SVL) is a method for calculating the monetary value of reduced mortality. The SVL estimation does not reflect an individual's willingness to pay for saving his or her own life, which is deemed to be infinite. It is derived implicitly from the formula:

$$SVL = \frac{Mean\ Willingness\ To\ Pay}{Risk\ reduction}$$

The mean willingness to pay for a certain percentage of risk reduction is used to then approximate the monetary value of a saved life. (Hultkrantz and Svensson 2008)

SVL can be used in socio-economic calculations given that two criteria are met. Firstly, the measurements that are to be evaluated cannot be directed to specific identified individuals, i.e. decisions regarding prioritisation have to be made without knowing who are favoured and disfavoured. Secondly, the measurements have to infer small changes in risk of ill health and premature death. This means that SVL can be used when evaluating measurements that increase safety in traffic and health care programmes such as vaccinations. (SIKA 2009:3)

In modern economic literature there are two methods to estimate SVL: the Stated Preference (SP) approach and the Revealed Preference (RP) approach, which are discussed in section 3.4.2 and 3.4.3 respectively. In Sweden, and Europe at large, the most common method to place a monetary value on SVL is the SP approach. The SP method measures preference in terms of stated willingness to pay in hypothetical situations, using goods not usually traded in markets. (Hultkrantz and Svensson 2008)

The SP method for calculating the statistical value of life, used by institutions such as the Swedish Trafikverket, is not completely uncontroversial. The estimated SVL in their study is based on the first generation of SP techniques performed in the 1980's, which today are considered to be quite primitive.

A few follow-up studies made in the late 1990's underlined the discrepancy between actual behaviour and stated choices in SP-studies but in spite of this many researchers speak in favour of the SVL calculated by Trafikverket. The reason is mainly because it is in line with results from other studies with conservative estimations. (Hultkrantz and Svensson 2008)

4. Previous Research

During the late 1960's through the 1980's extensive studies regarding the costs and the effectiveness of MMR vaccinations were carried out due to the anticipated launch of national MMR vaccination programmes. The aim of these studies was to compare costs that would have occurred without an immunisation programme to the costs attributed to measles, mumps and rubella cases (White et al. 1985; Axnick et al. 1969). Some studies have concentrated on the effects of only measles since it is the most infectious of the three and it has the highest morbidity frequency (Axnick et al. 1969). Regardless of observational starting points and approaches, all studies conclusively show evidence of a substantial positive net benefit of vaccinations compared to having a non-immunised population (White et al. 1985; Axnick et al. 1969).

Since the societal value of MMR vaccinations were determined and widely accepted as positive, there were no large published studies on MMR or its effectiveness during the 90's. Vaccinations against these childhood diseases were regarded as one of the most cost-effective health interventions to date, as well as a great success of preventive medicine (Zwanziger et al. 2001). The MMR controversy of '98 caused the vaccination coverage to decrease in both the United States and in Europe. Most of the economic studies that showed positive net savings for the MMR vaccinations were more than 20 years old, so there was a need for new studies since medical costs and government expenditure policies had changed. By estimating hypothetical birth cohorts the MMR vaccination programme was evaluated to be cost saving from both a direct cost and a societal cost view compared to the absence of immunisation (Zhou et al 2004; Zhou et al 2005). The US department of health and human services estimated that for each dollar spent on MMR vaccinations 16.34 dollars were saved in direct medical costs, not even taking indirect costs such as loss of production into account (U.S Department of Health and Human Services 1999). In line with these results there have been a few studies focusing solely on the cost-savings from immunisation against measles, showing great economic gains from vaccination (Carabin et al. 2002; Carabin et al. 2003).

The need for a new type of municipal and governmental decision-making regarding vaccinations and immunisation programmes was recognised in Sweden as a result of an extensive study by Socialstyrelsen (SOU 2010:39), placing a greater emphasis on the importance of health economic evaluations. Since the introduction of vaccines in routine vaccination programmes is costly, the net benefits of the vaccinations have to be determined as positive (Bergman and Persson 2008). No new studies on the cost-savings from MMR vaccinations using Swedish numbers have been performed lately, only post-implementation surveillance of the effectiveness of the programme (Dannetun et al. 2004).

5. Method and data

We applied a decision analysis model using average probabilities based on a study by Carabin et al. (2002). The first decision tree (Figure 1) shows measles cases divided into two categories: complicated cases and non-complicated cases. Unlike Carabin et al. (2002) we assume all cases of measles are reported. Complicated measles cases are further divided according to type of complication and a proportion of each complication will be hospitalised, based on a statistical average. Of those attracting febrile seizures or encephalitis and that are hospitalised a proportion is also going to be in need of long-term care.

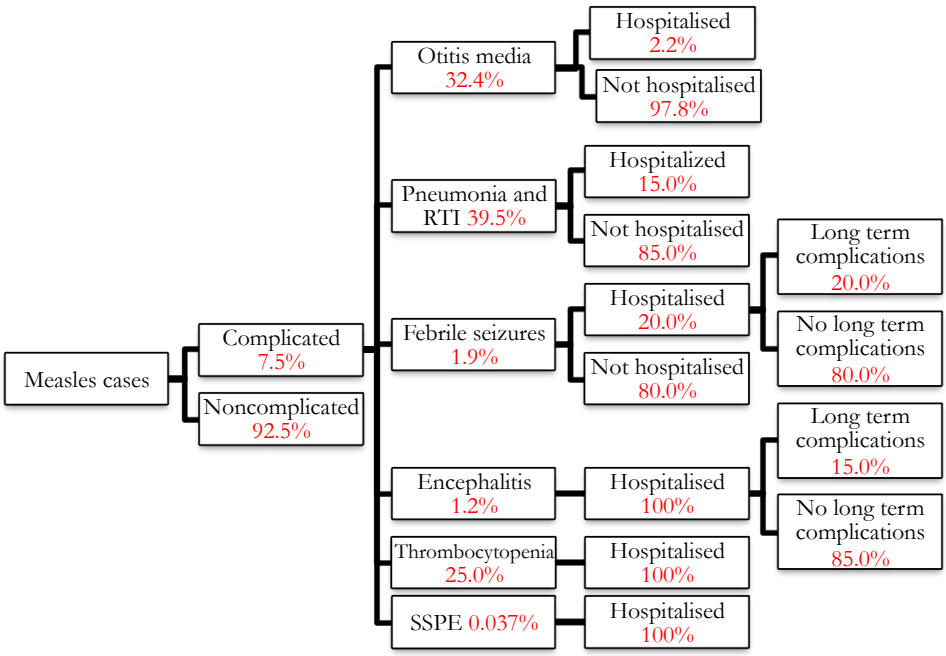

FIGURE 1

The second decision tree (Figure 2) shows the proportion of people vaccinated that are likely to develop adverse reactions due to the vaccine. The adverse events included are those that are associated with the measles component of the MMR vaccine.

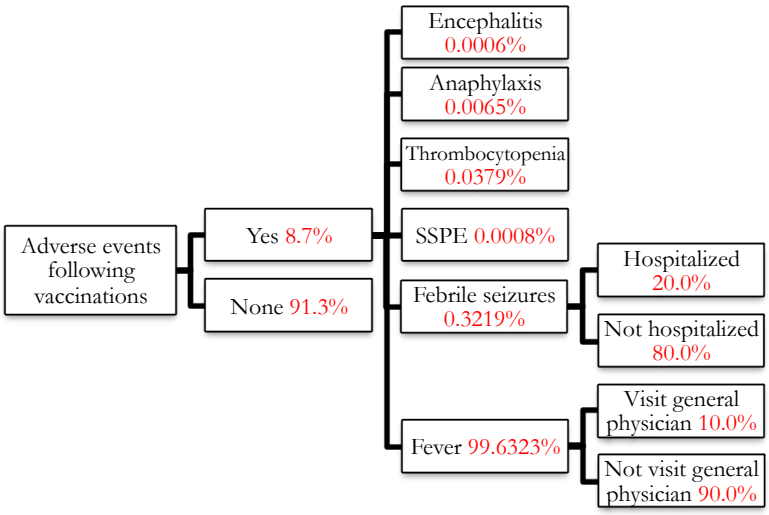

FIGURE 2

Our analysis is based on two scenarios: the absence of MMR vaccination and the present level of immunisation with the MMR vaccination programme. The

effects are evaluated on the Swedish birth cohort of 2010, a population of 120 000. Without the presence of a vaccination programme, 95% of the population is assumed to be infected with measles by the age of 30 (White et al. 1985). This rate of infection of the 2010 birth cohort is based on the assumption that the rest of the population is completely unimmunised, since the effects of a single unimmunised cohort is difficult to estimate. When calculating the costs of the vaccination programme, the current nation-wide immunisation average of 95% will be used, which is high enough to achieve herd immunity.

In order to calculate the societal net benefits of the vaccination programme a cost-benefit analysis will be performed. If the NPV of the project is positive, there is no need to perform a more complicated and costly analysis that includes the decrease in morbidity, such as assigning monetary values to pain and suffering. Should our cost-benefit analysis result in a negative societal gain we cannot draw any specific conclusions about the profitability of the programme.

All costs included in the analysis are in SEK and were updated to the price level of 2010 using the Consumer Price Index. Through a extensive analysis of previous studies we have based our calculations on the best available numbers. Future costs and benefits were discounted at a 3% annual rate, a discount rate that is often used when calculating and analysing the societal time-preferences in Sweden in terms of both costs and positive effects (Bernfort 2009).

According to Zhou et al. (2003) about 92% of all measles cases occur during the first four years of life. For simplicity we assume that all are infected in their second year.

5.1. Costs associated with measles

5.1.1. Direct costs

Direct health care costs include costs that are associated with the medical treatment of measles as well as the resulting complications. Complications included in the analysis are otitis media, pneumonia and RTI, febrile seizures, encephalitis, thrombocytopenia, and SSPE.

TABLE 1 UNITS UNCOMPLICATED CASES

Item	Units bought
Number of antipyretics bought [a]	0.6
Number of cough syrup bought [a]	0.85
Number of antibiotics bought [a]	0.5
Number of visits to general physician [b]	0.75
Number of working hours missed [c]	14

[a] Cases seeking general physician and not

[b] Average for all uncomplicated cases

[c] Average for cases seeking general physician and not

Both the costs for complicated as well as uncomplicated cases are taken into account. Direct costs for uncomplicated cases and complicated non-hospitalised cases include over the counter (OTC) bought drugs, visits to a general physician, and prescribed antibiotics. These are calculated using costs from Table 2 multiplied with the average number of OTC drugs bought, visits to a general physician, and antibiotics prescribed as shown in table 1, all based on a study by Carabin et al. (2002).

For complicated cases that are hospitalised, the direct costs included are the costs for stay at hospital in normal ward and intensive care unit. These numbers are based on a study by Carabin et al. (2003) that compares the cost measles in industrialised countries, and we have used the country specific numbers for Sweden, indexed to 2010 SEK.

The average length of stay for all hospitalised cases is four days of which 3.8 days are spent in normal ward and 0.2 days in an intensive care unit (Carabin et al. 2002). We assume that the annual cost of chronic epilepsia is 11 500 SEK, based on the study by Zhou et al. (2005), and that the child contracts epilepsia at the age of eight (Carabin et al. 2002). The average life expectancy in Sweden is 80 years. The total direct costs for SSPE is assumed to be 500 000 SEK per case (Carabin et al. 2002).

TABLE 2 UNIT COSTS (2010 SEK)

Item	Unit	Price
Hospitalisation (normal ward) [a]	per day	4 238
Hospitalisation (intensive care unit) [a]	per day	8 487
Visit to general physician [a]	per visit	761
Antipyretics [b]	per pack	39
Cough syrup [b]	per pack	58
Antibiotics [b]	per course	193
SSPE costs [c]	per case	500 000
Cost of epilepsia [d]	per year	11 500
Average wage [e]	per day	947
Delivery of MMR [a]	per dose	10
MMR [f]	per dose	337

[a] Average value based on Carabin et al.(2003), converted from USD using an exchange rate of 0.1 (1 USD = 10 SEK)

[b] Average value based on Apoteket's price list

[c] Average value based on Carabin et al. (2002) estimated over 2.5 years, converted from USD using an exchange rate of 0.1 (1 USD= 10 SEK)

[d] Average value based on Zhou et al.(2005), converted from USD using an exchange rate of 0.47 (1 USD= 6.8 SEK)

[e] Average wage per day in Sweden 2010 (SCB)

[f] Cost of MMR vaccination in Sweden 2010

5.1.2. Indirect costs

Indirect costs include productivity losses caused by parents who miss work to care for their sick children at home and taking them to the hospital or general physician. The average period of absenteeism from work caused by complicated measles cases is assumed to be 2 days for non-hospitalised cases and for hospitalised cases equal to the hospitalisation period (Carabin et al. 2002). For uncomplicated cases, the average number of working hours missed is 14 hours (Carabin et al. 2002). When a child is infected by SSPE, a parent is assumed to be absent from work 40 days (Zhou et al. 2004). Costs for production loss were calculated by multiplying the number of days of missed work with the daily wage rate.

5.1.3. Valuation of mortality reduction

SSPE, encephalitis and thrombocytopenia all result in cases of premature death. The following case-fatality ratios were used: 100% for SSPE, 0.05% for encephalitis and 0.46% for thrombocytopenia (Zhou et al. 2005). In order to calculate the monetary value of the reduced mortality following vaccination the statistical value of life (SVL) measurement was used. Hultkrantz and Svensson (2008) recommend a SVL of 21 MSEK in the price level of 2006. Converting this to the value of 2010, using consumer price index, we get a value of 22.4 MSEK.

5.2. Costs and adverse events associated with vaccination

The cost of each MMR dose is assumed to be 350 SEK, an average based on the costs from different municipalities in Sweden, and the delivery costs of the MMR vaccine is estimated to 10.23 SEK (Carabin et al. 2003). The costs of administration are disregarded since we assume that the first MMR-dose is given at a routine visit to paediatrician and that the second one is given at school.

When calculating the costs of adverse events the probabilities in Figure 2 are used. Costs for adverse events are then calculated in the same way as the costs for measles complications. For fever, the most common adverse event, we assume that parents miss two hours from work when taking the child to a general physician and then stay home for one day to care for the sick child.

6. Results

6.1. Costs of vaccination programme

The costs of the 2-dose MMR vaccination programme in the birth cohort of 2010, leading to a 95% immunisation coverage, equals 74.7 MSEK.

The total costs of the adverse events following vaccination (Table 3) are 1 MSEK, resulting in a total cost of the vaccination programme of 75.8 MSEK, 664 SEK per vaccinated child.

TABLE 3 COSTS OF ADVERSE EVENTS ASSOCIATED WITH VACCINATION (2010 SEK)[A]

Parameter	Direct costs	Indirect costs	Total costs
Encephalitis			
Hospitalised	998	212	1 211
Anaphylaxis			
Hospitalised	3 863	863	4 726
Thrombocytopenia			
Hospitalised	63 071	13 417	76 488
SSPE			
Hospitalised	37 395	2 832	40 227
Febrile seizures			
Hospitalised	107 138	22 791	129 928
Non-hospitalised	34 869	45 581	80 450
Fever			
Non-hospitalised	709 010	1 115	710 125
Total			**1 043 154**

[a] Based on the Swedish birth cohort of 2010

6.2. Costs of disease without vaccination

The frequency of measles in the absence of a vaccination programme would be 114 000 in a cohort of 120 000. Of these 8550 would be complicated, 22 will have long term complications and 13 will suffer a premature death. When summarising the costs of the measles cases occurring in an unimmunised population the total societal cost would be 592.6 MSEK. This results in a total cost of 5198 SEK per case.

TABLE 4 COSTS OF DISEASE WITHOUT VACCINATION (2010 SEK) [A]

Parameter	Direct costs	Indirect costs	Total costs
Non-complicated	73 513 899	164 667 264	238 181 163
Complicated			
Otitis media			
Hospitalised	1 022 588	217 529	1 240 116
Non-hospitalised	3 698 710	4 835 068	8 533 778
Pneumonia and RTI			
Hospitalised	8 500 044	1 808 161	10 308 204
Non-hospitalised	3 919 065	5 123 123	9 042 188

Febrile seizures			
Hospitalised	545 150	115 966	661 117
Non-hospitalised	177 423	231 933	409 356
Long term complications			272 102
Encephalitis			
Hospitalised	1 721 528	366 210	2 087 738
Long term complications			1 021 232
Monetary value of premature death			1 084 199
Thrombocytopenia			
Hospitalised	35 865 162	7 629 371	43 494 534
Monetary value of premature death			207 804 821
SSPE			
Hospitalised	1 490 951	112 915	1 603 866
Monetary value of premature death			66 858 942
Total			**592 603 356**

[A] Based on the Swedish birth cohort of 2010 (120 000)

6.3. Net social benefits

When calculating the net social benefits of the MMR vaccination programme, benefits are seen as the savings from avoided measles cases, i.e. direct and indirect cost-savings, and the reduced mortality resulting from the use of vaccine. The costs of the vaccination programme include the MMR-dose, delivery and the adverse events associated with vaccination.

The 2-dose MMR vaccination programme was found to be cost-beneficial. When only including direct healthcare costs and productions losses the net savings are 241 MSEK, adding the value of reduced mortality results in total net savings of 516.9 MSEK. Each vaccinated child yields savings of 4534 SEK.

TABLE 5 SUMMARY OF RESULTS (2010 SEK)

Parameter	Costs
Cost of MMR-dose and delivery	-74 707 052
Costs of adverse events following vaccination	-1 043 154
Total costs of vaccination programme	*-75 750 206*
Direct and indirect costs of measles cases in absence of vaccination	316 855 394
Cost-savings of vaccination without value of reduced mortality	*241 105 188*
Value of reduced mortality	275 747 962
Total net social benefits	**516 853 150**
Total net social benefits per case	**4 534**

6.4. Sensitivity analysis

Sensitivity analysis is a useful tool when assessing the robustness of economic estimates and the impact of potential changes. Our assumed infection rate of measles, 95% in an unimmunised population, generates a very high economic

burden for the disease. To investigate how dependent our positive net social benefit for the MMR vaccination programme is on the number of measles cases we experimented with different rates of infection.

Keeping the vaccination rate constant at 95% but decreasing the number of measles cases to only 12% in the birth cohort of 2010, the cost for vaccination remains 75.8 MSEK and the cost of measles, including direct, indirect, and mortality costs, is 74.9 MSEK. This means that the MMR vaccination programme will remain cost-beneficial as long as the number of infected individuals surpasses 12% of the population. When disregarding the value of reduced mortality, more than 22% of the population has to be vaccinated in order for the vaccination programme to remain cost-beneficial.

To confirm the accuracy of our initial estimates the discount rate was varied from zero to seven per cent. In doing so we discovered that it only had a marginal effect on the societal net benefits. The importance of changing the discount rate is less in our study than in other studies (Rivière et al. 1997, Zhou et al. 2005) since we have not separated our calculations into different age groups, but assumed all cases occur in the second year of life.

7. Discussion

The results of our study clearly indicate that the MMR immunisation programme results in substantial societal net benefits as well as considerable reductions in the morbidity and mortality associated with measles. However, there are a few assumptions and limitations that have been made that compromise the accuracy of our estimations.

A compromising factor is that, since the incidence of measles as well as the adverse events following vaccination is relatively low, there is a scarceness of recent data and therefore much uncertainty in our resultant estimates. Through a thorough review of available literature to base our parameters on we have attempted to minimise this uncertainty as much as possible. Furthermore, the probabilities of the potential consequences of measles are from an American study using American demographic situations and population tendencies (Carabin et. al 2002). There is the possibility of cultural differences between Sweden and the US, resulting in different proportions of measles cases leading to the specific outcomes.

The statistical value of life estimation is a large contributor to the benefits associated with the MMR vaccinations since the monetary value of each premature death is very high. To account for this we also calculated the societal net gains in the absence of SVL to evaluate whether the programme was still

cost-beneficial. Even though the net gains per vaccination were notably reduced, the NPV was still positive.

The strength of our analysis lies in the fact that we generally have tried to use as low figures for the costs associated with measles as possible, and high costs for the vaccination programme and the adverse events that follow, in order to establish a base line of the societal net benefits of MMR vaccinations. The most obvious example of this is that we did not assign a specific proportion of the costs of the MMR vaccination programme to measles, even though we have not included the economic burden for mumps or rubella, diseases that still generate high costs to society. Should they also be included in the analysis, the benefits of immunisation would be underlined further.

Another understatement of costs is the rather conservative assumption that a parent will only miss 40 days of work when caring for a child with SSPE, which will die within two and a half years. In addition to this, but not quantified in our analysis, is the value of the decrease in morbidity, i.e. the decrease in pain and suffering to measles-patients as well as their family and friends. If these were taken into account the actual societal net benefits would be higher.

The results of this analysis are consistent with, and supported by, results from other studies such as Carabin et al. (2002), Carabin et al. (2003) and Zhou et al. (2004) although these are not directly comparable due to different assumptions and methodology. However, it still indicates certain validity in our estimations. In conclusion, under even the most conservative assumptions, the national MMR programme is highly cost-beneficial and results in substantial cost savings.

7.1. Future studies

To more accurately evaluate the optimal level of vaccination we would have to have access to more specific data on how many measles cases occur at different vaccination levels. A definition of the optimal level of vaccination is the immunisation coverage where it is no longer cost-beneficial to vaccinate a larger proportion of the population. For instance, the costs of increasing vaccination coverage from 90 to 99% may not exceed the benefits of avoided measles cases, meaning that at percentages above 90, the MMR vaccination programme would yield a negative net social benefit.

8. Summary

The use of vaccines has led to a dramatic reduction in morbidity and mortality from infectious diseases and it is considered one of the most successful medical interventions in history. The combination vaccine against measles, mumps and rubella (MMR) was licensed in the US in 1971 and was introduced into the

Swedish general childhood immunisation programme in 1982. Through the use of the MMR vaccine high levels of immunisation was quickly reached in most industrialised countries but in recent years vaccination rates in countries like the Netherlands, Italy, the US, and Canada has declined. If the immunisation rates were to continue to decrease it could impose a considerable burden on health care systems, individuals, and society as a whole.

This thesis set out to examine the potential net social benefits of vaccinations against measles, mumps and rubella in Sweden by conducting a cost-benefit analysis. Calculations only include the economic burden of measles, since it is the most contagious of the three and also bears the majority of the costs associated with the MMR diseases and the vaccination related adverse events. The costs of the current vaccination programme were compared to the costs of measles in the absence of vaccination. The analysis was based on a decision-tree model and all costs were estimated on the Swedish birth cohort of 2010.

The 2-dose MMR vaccination programme was found to be cost-beneficial. When only including direct healthcare costs and productions losses the net savings are 241 MSEK, adding the value of reduced mortality results in total net savings of 516.9 MSEK. Each vaccinated child results in savings of 4534 SEK.

Even under the most conservative assumptions the MMR immunisation programme results in substantial societal net benefits as well as improves the health of the population, decreases pain and suffering, and saves many children from premature deaths.

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