Cost-Effectiveness Analysis of Pertussis Vaccination of Pregnant Women in Norway

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Abstract

Norway has one of the highest rates of pertussis in Europe; while this may be due in part to higher rates of reporting, it is still a serious disease if contracted by infants. Norway's current vaccination program recommends the first pertussis vaccine at 3 months of age, leaving infants vulnerable for those first few months. One possible solution is providing expecting mothers a booster vaccine during their third trimester of pregnancy; the antibodies pass through to the infant and can protect it during the interim between birth and receipt of the first vaccine in the current program.

The objective of this analysis was to determine the cost-efficiency of maternal vaccination in the Norwegian context. A decision tree and Markov model were created to predict the QALY and cost outcomes of the current strategy and the maternal vaccination comparator. One-way, multi-way, and probabilistic sensitivity analyses were conducted to address varying risk and uncertainty within the model. The current program was estimated to cost 7,352,328 NOK with an infant cohort of 59,273; the maternal vaccination strategy cost 17,627,344 NOK and resulted in a gain of 3.67 QALYs over the current program. The ICER was calculated as 2,802,947 NOK per QALY gained. At an assumed threshold of 800,000 NOK, the maternal vaccination strategy was therefore not cost-effective.

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1 Introduction

Pertussis, also known as whooping cough, or kikhoste in Norwegian, is a bacterial infection most known for the resulting cough. It is highly contagious; for adults and older children, pertussis infections are unpleasant, but not life threatening. However, for young children, especially infants, the illness can be life threatening.[1] For instance, in 2003/2004, two infants died of pertussis in Norway.[2] Norwegian authorities recommend vaccination at 3, 5, and 12 months, as well as 2nd and 10th grade. It is unsafe to vaccinate newborns.[2] Hence, protecting infants during their first 3 months is still a challenge.

A proposed solution is to give pregnant women a booster vaccination in their third trimester to pass some of the protection on to their infant.[3] Given that vaccinating pregnant women has been shown to be safe and effective,[4] it remains to explore whether this is a cost-effective strategy before determining whether such a program should be introduced in Norway. Many such analyses have been performed using data from other countries, for example Wolf and Højgaard in Denmark[5], Westra et al in the Netherlands[6], and Atkins et al in the USA[7]. To my knowledge none have been done from a Norwegian context.

In 2016, Norway had one of the highest rates of pertussis in the EU/EØS. Norway has observed an increase in reported pertussis cases, beginning in 1997. This is believed to be due to a combination of higher rates of diagnosing and tracking pertussis, especially in older children and adults, and a real increase in infections due in part to immunity from vaccination wearing off. In 2017, of the 2,424 total pertussis cases reported in Norway, 46 were infants under 1 year old. [8] , [9], [10]

Vaccination has proven effective at preventing pertussis infection, and also making cases that are contracted milder.[11] Many countries, including the United States and United Kingdom, have begun administering the pertussis vaccine to women in their third trimester of pregnancy in order to provide passive protection to infants until it is old enough to receive its first vaccine.[12]

Pertussis can be especially dangerous to children under 1 year of age, but it is unsafe to vaccinate newborns. Pregnant women can be vaccinated in the third trimester and pass some of the protection on to their baby.[13]

The objective of this project is to determine the cost-effectiveness of vaccinating pregnant women against pertussis to provide the vaccination effects to the baby compared to the current vaccination schedule in the Norwegian context. The study aims to incorporate Norwegian data and recommendations, while retaining moderate comparability to other countries' findings. This analysis compares the current vaccination schedule to one in which infants receive protection from birth via their mother receiving a booster vaccination during the third trimester of pregnancy.

2 Background

2.1 The Disease

Pertussis, or whooping cough (Norwegian: kikhoste), is a bacterial infection of the respiratory system, generally lasting between six and twelve weeks. It is caused by the *Bordetella pertussis* bacteria.[4] The bacteria spreads via droplets, typically from coughing and sneezing. Individuals who do not appear ill can transmit the illness, though it is most contagious from the first onset of symptoms until symptoms begin to lessen (the catarrhal and paroxysmal stages of illness). The resulting cough, which is often easily identified by the "whooping" noise of gasping for breath between coughing bouts, contributes to its high level of contagiousness.[14] While intense coughing is the main symptom, not all infected individuals display this symptom. Other symptoms include those of a cold: runny nose, sneezing, and a mild fever.[15]

Pertussis' incubation period usually ranges from seven to ten days. Mild, cold-like symptoms are displayed for one to two weeks; this is considered the catarrhal stage. The paroxysmal stage lasts between two and six weeks, during which the "whooping" coughing occurs. This is the stage during which infants may experience vomiting, lack of oxygen (due to long bouts of coughing), and even death. Symptoms slowly subside over a few weeks, with individuals

slowly returning to full health. In rare cases, infants and small children can experience severe pulmonary and/or neurologic complications, including severe cases of pneumonia and intracranial bleeding.[15],[4]

2.2 Diagnosis and Reporting

Depending on how long the patient has been ill, diagnosis can require a culture or a PCR (polymerase chain reaction) assay, and an antibody sample. Since 1993, any confirmed pertussis cases must be reported/added to MSIS, the Norwegian Surveillance System of Communicable Diseases.[8]

2.3 Vaccination

Vaccines against pertussis have been available since the mid to late 1940s. While the vaccines have proven effective, they do not give lifetime immunity. This is less of an issue for adults because the symptoms are less severe in adults; the main problem with adults contracting pertussis is their potential to spread the bacteria to infants and young children. Asymptomatic adults, whom have often been vaccinated, have been identified as a reservoir of/for pertussis, and spread it to children.[4] Most of the serious cases are observed in patients who have not been vaccinated. The illness is most dangerous for infants and young children; young infants are also least likely to have been vaccinated. [16]

A whole-cell pertussis vaccine was added to Norway's childhood vaccination program in 1952. These vaccines had a high incidence of side effects, which worsened with each dose. This meant adults were discouraged from receiving booster shots. In 1998 the whole-cell vaccines were replaced by acellular vaccines, which have a lower rate of side effects.[17]
In Norway, children receive a pertussis vaccine at 3, 5, and 12 months of age, as well as in the 2nd grade. In 10th grade they receive a booster vaccine. Norway's current recommendation for adults is to receive a booster every ten years, but the uptake of booster doses among adults is low.[17]

2.4 Transplacental Immunity

Due to pertussis's contagiousness and the non-lifelong nature of the vaccine, maternal vaccination has been identified as one potential option for limiting danger to infants. A pregnant woman's antibodies to pertussis can cross to the infant via the placenta; however, as with receiving a vaccine, the protection is not permanent. The mother's antibodies from the vaccination last under four months in the infant after its birth, so it is important to continue the current vaccination schedule beginning at 3 months of age regardless of the mother's vaccination status.[4]

Many countries, including the USA, UK, Australia, and New Zealand have already begun recommending antenatal vaccination against pertussis, and follow-up observational studies have reported positive results. [18]

3 Theoretical Framework

3.1 Decision Tree

A commonly used type of model in economic evaluation is the decision tree. It charts different pathways an individuals' illness could take following an intervention. It consists of chance and decision nodes, each with their own probability, and each resulting end-state can be assigned a cost and utility.[19]

A decision tree begins with a decision node, for example, the decision to treat with an old vaccine or a new vaccine. A chance node illustrates the points of uncertainty for individuals in the tree.[19(p.329)] The chance nodes show possible outcomes of a treatment, for example, whether the individual patient responds to that treatment, or whether they experience adverse side effects. Each possible outcome has its own "branch" splitting from the chance node, with an accompanying probability dependent on the previous events.[19(p327-331)]

The pathway probability can be calculated by multiplying each probability on that pathway. The sum of all pathway probabilities must equal 1, as each pathway is mutually exclusive and

all possible outcomes are assumed to be included.[19] The costs of each pathway can also be calculated by summing the costs assigned to each branch; each outcome can be assigned a utility, for example, QALYs.[19]

One possible limitation of a decision tree is that time can be difficult to incorporate; this can be mitigated by using a combination of a decision tree and a Markov model in an analysis.[19]

3.2 Markov Model

A Markov model consists of time cycles, during which a patient is assigned a "health state" instead of the branches in a decision tree. For each cycle, a probability of a patient transitioning to a different health state can be assigned. The cost and utility for each cycle can be ascertained by multiplying the percentage of patients in each health state by the cost or utility of that health state.[19]

3.3 Cost Effectiveness Analysis

Cost effectiveness analysis is a broad term encompassing analyses in which two (or more) treatments are compared based on either the incremental cost per unit of effect or by "effects per unit of cost (life-years gained per dollar spent)."[19(p5)] The unit of effect can be any measured outcome, either general or specific to the disease. Cost effectiveness analyses can be used to evaluate whether a treatment has more effect relative to how much it costs in relation to the current standard of care or willingness to pay threshold.[19]

Cost utility analysis is a variant of cost-effectiveness. While cost effectiveness analyses focus on cost per unit of effect or effect per unit of cost, cost utility analyses use a general measure of health gain, called Quality Adjusted Life Years (QALYs). This allows comparisons of unrelated diseases to be compared and prioritized.[19(p8)]

3.4 Perspective

Results of analyses differ based on the perspective taken in the analysis. A payer's perspective can include, for example, funding and reimbursing the hospital, urgent care visits, and costs of vaccines. Generally, the payer's goal is to maximize outcome (QALY) given finite resources (remaining within the budget). If one takes the perspective of a patient who has a fixed copayment, the analysis need not factor in actual hospital costs, only the copayment and other costs the patient will pay as an individual. When evaluating the same situation from the insurer's perspective, how much the hospital charges for services is a relevant factor for the analysis. Common perspectives in cost effectiveness analyses in the health sector include payer, provider, and societal.[19]

3.5 Measuring Outcomes

QALYs are an attempt to measure both the health-related quality of life and the length of life for individuals. The measure is generalized so that different illnesses can be compared and prioritized.[20] There are six main instruments for measuring quality of life among patients, the main among them being the EQ-5D-3L, as well as four valuation methods that can be used to get a value of the measurements done with these instruments to find the QALY for a disease: Time tradeoff, standard gamble, visual analogue scale, or person trade-off.[21] Lee et al. used contingent valuation and the time tradeoff method in their research. Time tradeoff is where respondents are asked to choose between being in the sick health state for *x* amount of time, or being in perfect health, but having *y* time taken off the end of their life.[22]

While the goal of QALYs is to make comparisons more straightforward both within one disease group and among differing diseases, it does have weaknesses. One criticism is in the variety of ways QALYs are measured and valued; as stated above, a variety of measurement instruments are used, and studies do not always report how the QALY gains were measured or valued. This makes it difficult to know whether the two "QALYs" are truly comparable.[21]

3.5.1 Decision Criteria

3.5.1.1 ICER

The analysis will attempt to determine whether antenatal vaccination is cost effective. To do so, the Incremental Cost-Effectiveness Ratio (ICER) will be determined using the following formula:

$$ICER = \frac{(C_1 - C_0)}{(E_1 - E_0)}$$

Where C_1 and E_1 refer to the cost (in NOK) and effect (in QALYs) of the vaccination of pregnant mothers, and C_0 and E_0 refer to the cost and effect of the current vaccination program. Incremental Cost, i.e. the difference in cost compared to the relevant alternative, divided by the difference in QALYs due to the intervention.[19]

A treatment is considered dominant if it is both less expensive and more effective than the alternative.[20] A new treatment can be considered cost effective even if it is not dominant if the cost per QALY is below a given cost threshold, or compares favorably with the opportunity cost.[20]

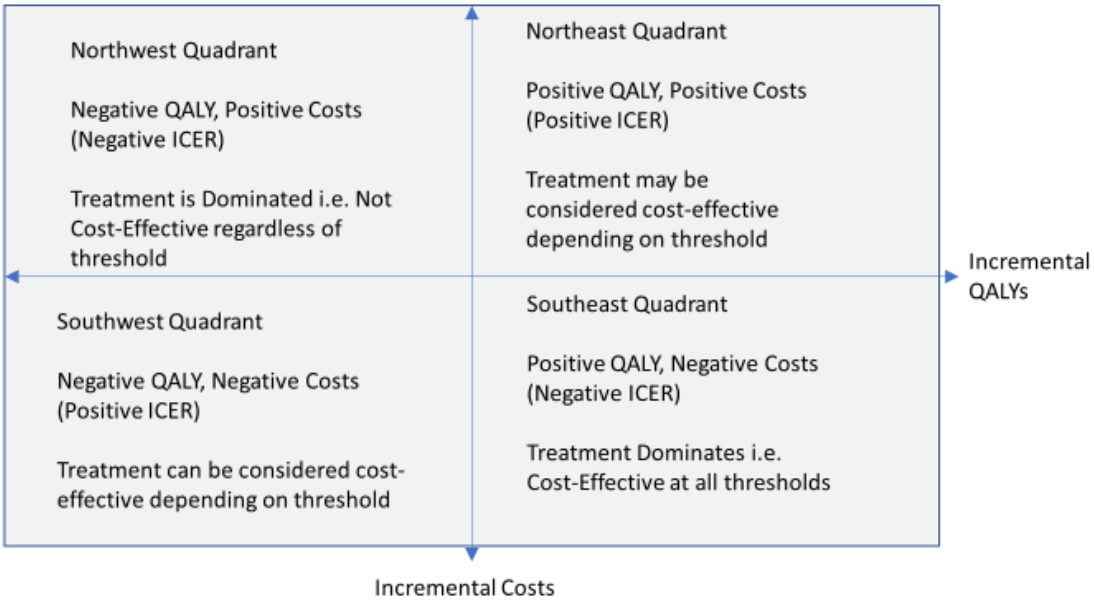
One limitation of the ICER is that a positive ICER can results from two scenarios, the first being that the treatment is effective but costs more, and the second possibility is that the treatment is less effective, but also costs less.[20]

3.5.1.2 Incremental Cost-Effectiveness Plane

The incremental cost effectiveness plane is a way of representing the likelihood of a treatment being cost effective compared to the alternative. It is separated into four quadrants: northwest, northeast, southeast, and southwest. The northwest quadrant is where the ICER will fall if the treatment is dominated, i.e. is both more expensive and less effective than the

alternative. If the ICER falls in the southeast quadrant, the treatment dominates, i.e. it is both less expensive and more effective than the alternative.[19]

Figure 1: Cost-Effectiveness Plane



3.5.1.3 Net Monetary Benefit

An alternative to using ICER for determining cost-effectiveness is to examine the Net Monetary Benefit (NMB) of a treatment. Drummond et al explain the net monetary benefit as:

A way of moving away from a ratio and placing both costs and effects on a single scale…the difference in effects between two options being evaluated is rescaled into monetary value using the cost-effectiveness threshold as a value for each unit of effect, and the difference in costs between the options is subtracted from this value.[19(p300)]

The formula for calculating the NMB is:

$$NMB = Threshold * Change\ in\ Effect - Change\ in\ Cost$$ [20(p129)]

NMB does not have the same ambiguity with multiple causes for positive outcomes.[20]

3.5.1.4 CEAC

Cost-effectiveness acceptability curves are created by calculating the proportion of times a treatment has a higher probability (than the alternative treatment) of being cost-effective at a number of different thresholds based on the results of the Monte Carlo simulation. They can be used to help visualize the uncertainty of given treatments' cost-effectiveness at different thresholds.[19,20]

3.5.1.5 Cost-effectiveness Acceptability Frontier (CEAF)

A CEAF is similar to a CEAC, but only shows the probability of being cost-effective for the treatment strategy which for each threshold is the most cost-effective. It makes it easy to visualize at which point each treatment becomes the better choice from a cost-effectiveness standpoint.[19]

3.6 Sensitivity Analysis

Uncertainty in models can come from a variety of sources. To incorporate some of this uncertainty into the analysis, researchers perform sensitivity analyses.[19]

3.6.1 One-Way Sensitivity Analyses

In a one-way sensitivity analysis, the value of one variable is changed between its "extreme but plausible maximum and minimum"[19(p394)] to see how it affects the results. These analyses may be run on any variables whose probability was uncertain, or which may be subject to change.[19] A tornado diagram provides a way to find which variables cause the most change in the ICER by combining one-way sensitivity analyses and arranging them based on their influence on the ICER.

While one-way sensitivity analyses can be informative in describing which parameters have the least or greatest effect on outcome, they cannot capture the combined uncertainty of all parameters within the model, and tend to underestimate the uncertainty in a model. To better characterize parameter uncertainty, a probabilistic sensitivity analysis may be performed.[19]

3.6.2 Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis allows all the parameters with risk or uncertainty within the model to be examined at once. This allows for a better understanding of the potential outcomes and allows for the calculation of different outcome measures, for example the Net Monetary Benefit. A probabilistic sensitivity analysis involves assigning a distribution to each parameter. These distributions are then used in a Monte Carlo simulation, which samples from these distributions randomly. The new values are used to calculate a new ICER, and then new samples are drawn. This repeats many times, typically 1,000 or 10,000 times. When there are only two treatment options, the results are often reported graphically in a scatterplot on an incremental cost effectiveness plane. [19]

3.7 Discount Rate

According to Drummond, time preference refers to the individual and societal preference for having money or resources now rather than later because we can use them for our benefit in the interim. Due to this time preference, future costs and benefits should be discounted in evaluations.[19(p53)] In Norway, the standard rate for discounting both health costs and benefits is 4 percent.[23] The formula for discounting costs, where t equals time (in years) is:

$$\frac{Cost}{(1 + discount\ rate)^t}$$

The same formula can be used for discounting QALYs; replace Cost with QALY, and use the corresponding discount rate assuming they are different.

3.8 Time Horizon

Standard practice indicates a lifetime horizon for the effects of vaccination programs affecting mortality.[23] As time can be difficult to address in a decision tree model, it often can be combined with a Markov model to include an estimate of the lifetime loss of QALYs. A Markov model can better handle probabilities which change over time via the use of multiple transitional probabilities. A Markov model consists of a number of health "states" which a patient can occupy at a given point in time, or "cycle." Two common states could be "Healthy" or "Dead." The probability of transitioning from one state to another can be varied according to how many time cycles have elapsed.[19(p331-336)]

4 Methods and Data

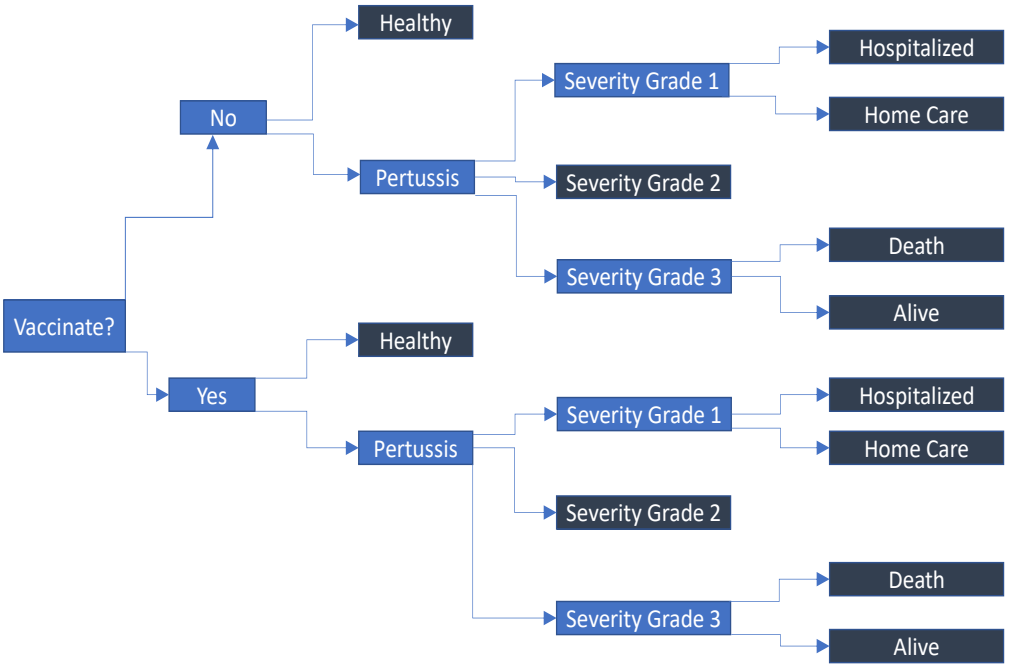
4.1 Method

This project was conducted using cost effectiveness analysis. This analysis was inspired by the model on the described decision tree from the Swedish study, with a number of deviations. The main change is the addition of a lifetime perspective, adding a Markov model to incorporate a lifetime perspective on loss of QALYs. In addition, our analysis includes adjusting probabilities and costs to Norwegian estimates, and adding the possibility of death. While a dynamic model would often be considered a better choice for estimating the spread of disease through the community, the change addressed in this study should not have a significant impact on the community due to its focus on such a short time period. This study's focus is on protecting the child, not the wider community.

4.1.1 Decision Tree

A decision tree with multiple health states was created, differentiating healthy infants from those with pertussis. Infants with pertussis were further divided by severity. As in the Swedish analysis, three grades of illness were defined. Grade 1 was infected, but healthy enough to receive home care. Grade 2 was recommended to have hospitalization for observation and some complications. Grade 3 encompassed severe complications, including the possibility of death. Figure 2 below shows the various decision pathways in the model.

Figure 2: Decision Pathways for Pertussis Decision Tree (Maternal Vaccination)



4.1.2 Markov Model

A basic Markov model with two health states: Alive and Dead was added to the analysis model. The Markov model consisted of 100 cycles, each of which represented 1 year. The probability of moving from Alive to Dead was based on Norwegian statistics by age group from 1998-2018.[24] Table A shows the rates below. The Markov model was implemented to incorporate a patient's lifetime perspective, as recommended in the Guidelines for the

submission of documentation for single technology assessment (STA) of pharmaceuticals.[24] No additional costs were included in the Markov model, as all costs were assumed to have been incurred during the illness and contained within the decision tree.

Table A: Average Death Rate By Age, For Markov Model							
Age	**Death Rate**	**Age**	**Death Rate**	**Age**	**Death Rate**	**Age**	**Death Rate**
1	0.0002988	26	0.0005890	51	0.0028172	76	0.0320302
2	0.0001715	27	0.0005996	52	0.0030488	77	0.0362499
3	0.0001300	28	0.0005929	53	0.0034172	78	0.0409190
4	0.0001145	29	0.0006256	54	0.0037644	79	0.0457123
5	0.0001106	30	0.0005778	55	0.0041240	80	0.0512766
6	0.0000962	31	0.0006365	56	0.0043743	81	0.0583950
7	0.0000908	32	0.0006572	57	0.0048600	82	0.0650540
8	0.0000744	33	0.0006668	58	0.0052121	83	0.0731989
9	0.0000857	34	0.0007194	59	0.0059371	84	0.0820662
10	0.0000845	35	0.0007480	60	0.0065361	85	0.0922601
11	0.0000931	36	0.0007970	61	0.0070916	86	0.1033124
12	0.0001067	37	0.0008302	62	0.0079574	87	0.1152953
13	0.0001076	38	0.0008680	63	0.0086113	88	0.1287978
14	0.0001321	39	0.0009641	64	0.0096451	89	0.1442881
15	0.0001835	40	0.0010112	65	0.0103649	90	0.1611436
16	0.0002786	41	0.0010750	66	0.0117180	91	0.1782976
17	0.0003480	42	0.0011584	67	0.0128500	92	0.1991555
18	0.0004885	43	0.0012768	68	0.0142730	93	0.2135379
19	0.0005087	44	0.0013646	69	0.0154548	94	0.2360806
20	0.0005876	45	0.0015177	70	0.0167808	95	0.2601346
21	0.0005143	46	0.0016959	71	0.0190315	96	0.2809120
22	0.0005779	47	0.0018404	72	0.0210131	97	0.3048656
23	0.0005448	48	0.0020329	73	0.0232118	98	0.3226963
24	0.0005822	49	0.0022470	74	0.0256798	99	0.3316140
25	0.0005661	50	0.0024898	75	0.0290259	100	0.3685319

4.1.3 Patient group

The patient group consists of all infants born in Norway. The analysis estimates a population of 59,273 infants based on the average number of live births per year 2008-2018.[25]

4.1.4 Intervention

As previously noted, the current vaccination scheme consists of vaccination of infants at 3, 5, and 12 months of age and in the 2nd and 10th grades. The intervention is vaccination of pregnant women in their third trimester in addition to the current vaccination schedule. For simplification and comparability purposes, the costs of the current vaccination schedule were not included as there would be no difference in these costs.

4.2 Data

4.2.1 Probabilities

For our analysis, we have broken this stage down into 3 severity grades, which match Folkhälsomyndigheten's study. Grade 1 is least severe, Grade 2 is moderately severe; Norwegian health authorities recommend hospitalization for observation at this stage.[26] Grade 3 is most severe. For comparability and simplicity, the probability of contracting each grade of pertussis was based on the Swedish severity breakdown data. The probability of contracting Grade 1 pertussis was set to 0.5161; Grade 2 to 0.2151; and Grade 3 to 0.2688.[27]

Norway recommends hospitalization for observation in grade 2 pertussis cases, so for grades 2 and 3, the probability of hospitalization was set to 1.[26] For grade 1, the Swedish rate of hospitalization, 35.42 percent, was used based on an assumption of similar parental leave policies and healthcare systems. Different countries have different hospitalization guidelines; for example, Sweden does not have the same recommendation that all 2nd degree cases be hospitalized. For the model, it was assumed that all patients with severity Grade 2 or 3 were hospitalized; these rates were examined in the sensitivity analyses.

The probability of contracting pertussis was 0.001132. To get this number, data from the European Centre for Disease Prevention and Control was used. The number of reported cases (1208 total) in children under 1 year old from the years 2000-2017 was averaged (67.1111)[9] and then divided by the average number of live births (59,273). It was assumed most of these

cases were in children under 3 months of age given Norway's impressive vaccination rate of 96 percent coverage in 2 year olds[8]; lower rates were explored in the uncertainty analysis.

Probability of death was based on the two deaths in 2003/2004. Those were the only two deaths in the 2000-2017 time period, so the probability of death given pertussis is 2 out of the 1208 total reported cases from 2000-2017 equals 0.001655629. This probability was explored in the sensitivity analysis. Because decision trees follow probability paths, and it was assumed all deaths come from Grade 3 cases, the probability of death was divided by the probability of Grade 3 pertussis; i.e. the probability of death given Grade 3 pertussis was used in the model.

Maternal vaccination as a strategy for inoculating infants in Norway is currently only applied to influenza vaccines. This makes it difficult to predict the adoption rate for other, serious illnesses. For the treatment, the probability of pregnant women receiving the vaccination was assumed to be at 60 percent as in Folkhälsomyndigheten's study.[27] This variable was further examined in the sensitivity analyses.

The reduction in incidence of pertussis was set at 90 percent. This was based Amirthalingam et al. 2014, an observational study following up on the efficacy of the UK's maternal vaccination program. They found a vaccine effectiveness rate of 90 percent (95% CI 84 to 95) when examining cases in children younger than two months old whose mothers received a vaccine. The authors concluded that the maternal vaccination program had been successful, and credited both the passive immunity in the infants and the reduced exposure rate in the mothers.[28]

4.2.2 Costs

This analysis used the perspective of the payer/health care sector. This means the indirect costs to society, for example time taken off work to care for sick children, costs of travel to the hospital, etc are not included. As the analysis focuses on the first few months postpartum, at least one parent can be assumed to be at home on leave to care for the child regardless of health status.

The cost estimates of a hospital stay for each severity grade were established in consultation with healthcare experts. As Norway calculates costs based on a per-stay rate as opposed to a per-day rate, length of stay was not included as a relevant variable in the model. Hospital costs were based on the DRGs sampled in consultation with healthcare professionals. The value of one DRG point was listed as 44,654 NOK. Each case of Grade 1 pertussis was estimated to cost 31,883 NOK; Grade 2 cost 332,538 NOK; and Grade 3 was assigned a cost of 119,182 NOK per case. Grade 1 home stay was estimated to be 146 NOK, which is the lowest cost for a legevakt (emergency/urgent care) visit (73 NOK) multiplied by 2, as in the Guidelines for the submission of documentation for single technology assessment (STA) of pharmaceuticals.[23] As Norway recommends pertussis grade 2 and above be admitted to hospital, no home stay costs were necessary. All hospitalization outcomes assume a legevakt visit (146 NOK) in addition to the hospitalization costs. Table B, below, shows the calculation inputs for the hospitalization costs of the three pertussis grades.

Table B: Estimated Costs of Hospital Stay per Grade of Severity

Pertussis Grade	DRG Code	DRG Cost	Multiplier	Estimated Cost (NOK)
1 (Mild)	98B	44654	0.714	31,882.96
2 (Moderate)	475A	44654	7.447	332,538.34
3 (Severe)	475B	44654	2.669	119,181.53

The cost to vaccinate pregnant women was based on the price of one Boostrix Polio vaccine. This cost was set at 316.20 NOK[29], following White Paper guideline of making calculations using a drug's maximum pharmacy retail price. As there will be an unknown rebate for government purchase of vaccines, this cost was closely examined via the sensitivity analyses. As pregnant women already attend regularly scheduled prenatal appointments, it was assumed there would be no other increase in direct costs.

The cost of educating healthcare professionals on the new vaccination recommendations was estimated at 3 million NOK based loosely on previous information campaigns (personal communication: Margrethe Greve-Isdahl), and was explored in the sensitivity analysis.

As we were analyzing from the perspective of the payer, Cost of Death was assumed to be 0 NOK, in addition to all expenses incurred by treating Grade 3 pertussis.

4.2.3 Utilities

For utility estimates, QALYs were used. QALY during illness was based on the findings of two studies by Lee et al.[30], [31] In 2005, two articles were published with Lee as head author. "Health-state valuations for pertussis: methods for valuing short-term health states," presented the results of research establishing QALY values for individuals in three age groups: infants, adolescents, and adults. Most analyses of the cost effectiveness of pertussis used QALY values based off these; not all of them gave their QALY calculations, which are assumed to have varied based on estimated length of illness. As length of illness was not used in our cost calculations, the Swedish calculations of QALY per severity grade, which took into account the average length of illness, were used. For Grade 1 illnesses, it was assumed quality of life was the same whether treatment was received at home or in the hospital. Once adjusted for length of illness in the Swedish study, Grade 1 illness had a QALY of 0.96; Grade 2 was 0.94, and Grade 3 was 0.92; these are the numbers used in this analysis. QALY for Healthy infants and adults was set at 1.00; QALY in the health state of Dead was 0.[27]

4.3 Discounting

Value of money and QALYs should be discounted over time, as immediate benefits are valued more highly. The discount rate was set at 4 percent for both utility and costs based on The Guidelines for the submission of documentation for single technology assessment (STA) of pharmaceuticals from the Norwegian Medicines Agency (NoMA aka Statens Legemiddelverk).[23]

4.4 Assumptions

The vaccine only transfers protection to the infant when the mother receives it during the third trimester of that pregnancy, so the model does not take in to account whether this is the first or any later pregnancy.[32]

The model assumes that all infants who died experienced the most severe grade of illness (Grade 3).

In various instances, it has been assumed that the disease is very similar in Norway as it is in Sweden. This is based on that they are two small, neighboring countries. This applies to the probability of each severity grade, the grade 1 hospitalization rate, and, with regard to the calculation of QALYs, the model assumes standard lengths of illness are the same as in neighboring Sweden.

The ICER analysis set a cost-effectiveness threshold of 800,000 NOK per QALY based on previous cost-efficiency analyses performed. This is also in accordance with current recommendations to use a cost-effectiveness threshold of up to 3 multiplied by the estimated opportunity cost in Norway, which the government has suggested to be at 275,000 NOK per QALY if the disease is very severe.[33]

Given that QALY weights used in the model are all above 0.9, it would be reasonable to assume in the probabilistic sensitivity analysis that a QALY has a maximum likely range between 1 and 0; hence it was assumed no illness would be "worse than death." Therefore, a beta distribution was used for QALY weights.[20]

4.5 Sensitivity Analysis

The analysis addressed parameter uncertainty in the model via one-way and probabilistic sensitivity analyses.

4.5.1 One-Way Sensitivity Analyses

Examination of various potential aspects which could play a major role in the cost effectiveness were analyzed via sensitivity analysis. The sensitivity analysis consisted of one-way analysis of each independent variable that had uncertainty, shown in Table C below:

Table C: One-way sensitivity analysis variables				
Variable	Value in Model	Minimum	Maximum	Increment
Probability of Pertussis (Incidence)	0.0011	0.0005	0.01	0.0005
Probability of Death from Pertussis	0.0062	0	0.01	Varies
Probability Mother Receives Vaccine	0.60	0.50	1.00	0.05
Vaccine Effectiveness	0.90	0.70	1.00	0.05
Probability of Hospitalization with Grade 1 Pertussis	0.3522	0.00	1.00	0.1
QALY Grade 1	0.96	0.50	1.00	Varies
QALY Grade 2	0.94	0.50	1.00	Varies
QALY Grade 3	0.92	0.50	1.00	Varies
Cost of Outreach	3,000,000 NOK	0 NOK	10,000,000 NOK	250,000 NOK
Cost of Vaccine	316.20 NOK	50 NOK	400 NOK	50 NOK
Cost of Treatment – Grade 1 Home Care	146 NOK	0 NOK	1,200 NOK	Varies
Cost of Treatment – Grade 1 Hospitalized	31,883 NOK	0 NOK	120,000 NOK	5,000 NOK
Cost of Treatment –Grade 2	332,538 NOK	150,000 NOK	750,000 NOK	25,000 NOK
Cost of Treatment –Grade 3	119,182 NOK	70,000 NOK	190,000 NOK	5,000 NOK

4.5.2 Uncertainty in the Model

There is uncertainty in the model because we cannot predict all inputs perfectly. Some variables have less uncertainty than others based on factors such as sources and variations.

4.5.2.1 Probabilities

The incidence of pertussis (probability of contracting pertussis) in the Norwegian population was estimated based on previous years' data. As this is just an average based on reported cases, the number could have huge variations depending on what percentage of cases go unreported, as well as actual variations by year.

The probability of dying from pertussis was based on Norwegian historical data; deaths are a rare occurrence, and thus are difficult to predict.

The probability of hospitalization for grade 1 pertussis was based on Swedish data; therefore, there is much uncertainty regarding differing hospitalization criteria in addition to general variability. As home care was estimated as costing the payer 146 NOK, and hospitalization at this severity cost 31,883 in the model, it was thought this probability may have the potential to increase costs significantly.

The probability of pregnant women receiving the vaccine can potentially vary greatly, so it is relevant to explore how many need to participate in the program for it to be cost effective.

As the effectiveness of the vaccine increases, the QALYs gained should increase. As the effectiveness in the model is based on an observational study from the UK, this variable was especially uncertain. As this was the main treatment variable, it was expected to have a significant influence on ICER.

4.5.2.2 QALY Values

As has been discussed, the QALY values were based on interviews with adults after themselves or their older children recovered from pertussis; therefore, the QALY values may be significantly higher than calculated.

4.5.2.3 Costs

All costs were assumed to be uncertain. The cost of the vaccine was predicted to have a significant impact on the results, while the costs of outreach and hospitalizations were predicted to have a real but lesser impact on the difference in costs between the two vaccination programs.

4.5.3 Multi-way Sensitivity Analysis

The probability of each severity grade was an interesting variable in that some studies suggest that those who have been vaccinated but still contract pertussis often have less severe symptoms than those who were unvaccinated. As the probability of each severity grade was linked to the probability of the other severity grades (they cannot have a combined total probability over 1), a separate analysis was done exploring the ICER if 10 percent of Grade 2 cases became Grade 1 and 10 percent of Grade 3 cases became Grade 2 in those receiving maternal vaccination; this was repeated with 90 percent of cases in Grades 2 and 3 as well.

A multi way sensitivity analysis was also run on the QALYs for severity Grades 1 through 3; while these were independent variables in the model, it was determined their analysis would be more informative for all of the QALYs to have been adjusted proportionally. In other words, in the real world it would not make sense for the QALY of Grade 1 to move to a value of 0.5 while the QALY values of Grades 2 and 3 remained 0.94 and 0.92 respectively. Therefore, the changes in QALY values were adjusted at once for the three severity grades.

4.5.4 Probabilistic Sensitivity Analysis

Additionally, a probabilistic analysis was run using a Monte Carlo simulation with 1,000 iterations. The transition probabilities and QALYs were fitted to the Beta distribution by the method of moments as described by Briggs.[20(p88-89)] Cost distributions were found using a Gamma distribution, fitted as described in Briggs.[20(p91)] Table D below shows the distributions for the Decision Tree.

Table D: Probabilistic Sensitivity Analysis Decision Tree Variables and Values		
Variable	Deterministic Value	Distribution
Probability of Contracting Pertussis	0.0011	Beta
Probability of Death	0.0062	Beta
Prob. of Contracting Pertussis Once Vaccinated	0.0001	Log Normal
Prob. of Mother Receiving Vaccine	0.6	Beta
Prob of Grade 1 Pertussis	0.5161	Dirichlet
Prob of Grade 2 Pertussis	0.2151	Dirichlet
Prob of Grade 3 Pertussis	0.2688	Dirichlet
Prob of Hospitalization Grade 1	0.3522	Beta
QALY Grade 1 Pertussis	0.96	Beta
QALY Grade 2 Pertussis	0.94	Beta
QALY Grade 3 Pertussis	0.92	Beta
Cost of Vaccine	316.20 kr	Gamma
Cost of Outreach	3,000,000 kr	Gamma
Cost of Emergency/Urgent Care Doctor Visit	146 kr	Gamma
Cost of Hospital Stay Grade 1 Pertussis	31,882.96 kr	Gamma
Cost of Home Stay Grade 1 Pertussis	146 kr	Gamma
Cost of Hospital Stay Grade 2 Pertussis	332,538.34 kr	Gamma
Cost of Hospital Stay Grade 3 Pertussis	119,181.53 kr	Gamma

For variables without standard error or confidence intervals from the literature, standard error rates were estimated to reflect uncertainty. Because we felt more uncertain regarding the cost estimates than QALY estimates, we assumed costs to have a higher uncertainty. For calculation of the beta distribution, the QALY values were assigned a standard error of 0.1. For the gamma distributions, cost values were assigned a standard error of 0.2.

The QALYs for healthy and dead infants and adults was assumed to not have uncertainty, so were left at 1 and 0, respectively; in other words, they were not considered variables in the probabilistic analysis. Additionally, as the death rates in the Markov model were based on

historical population data, they were also assumed to have little uncertainty and were not included as variables in the probabilistic analysis.

5 Results

For the cohort of 59,273 infants, the current vaccination schedule had estimated costs resulting from pertussis of approximately 7,352,328 NOK, and the maternal vaccination treatment cost approximately 17,627,344 NOK. This means the maternal vaccination treatment cost approximately 10,275,016 NOK more than the current schedule and gained approximately 3.67 QALYs.

5.1 ICER

The maternal vaccination treatment had an ICER of 2,802,947 NOK. That means adopting maternal vaccination resulted in additional expenses of approximately 2,802,947 NOK per QALY gained.

5.2 Sensitivity Analyses

5.2.1 One-Way Sensitivity Analyses

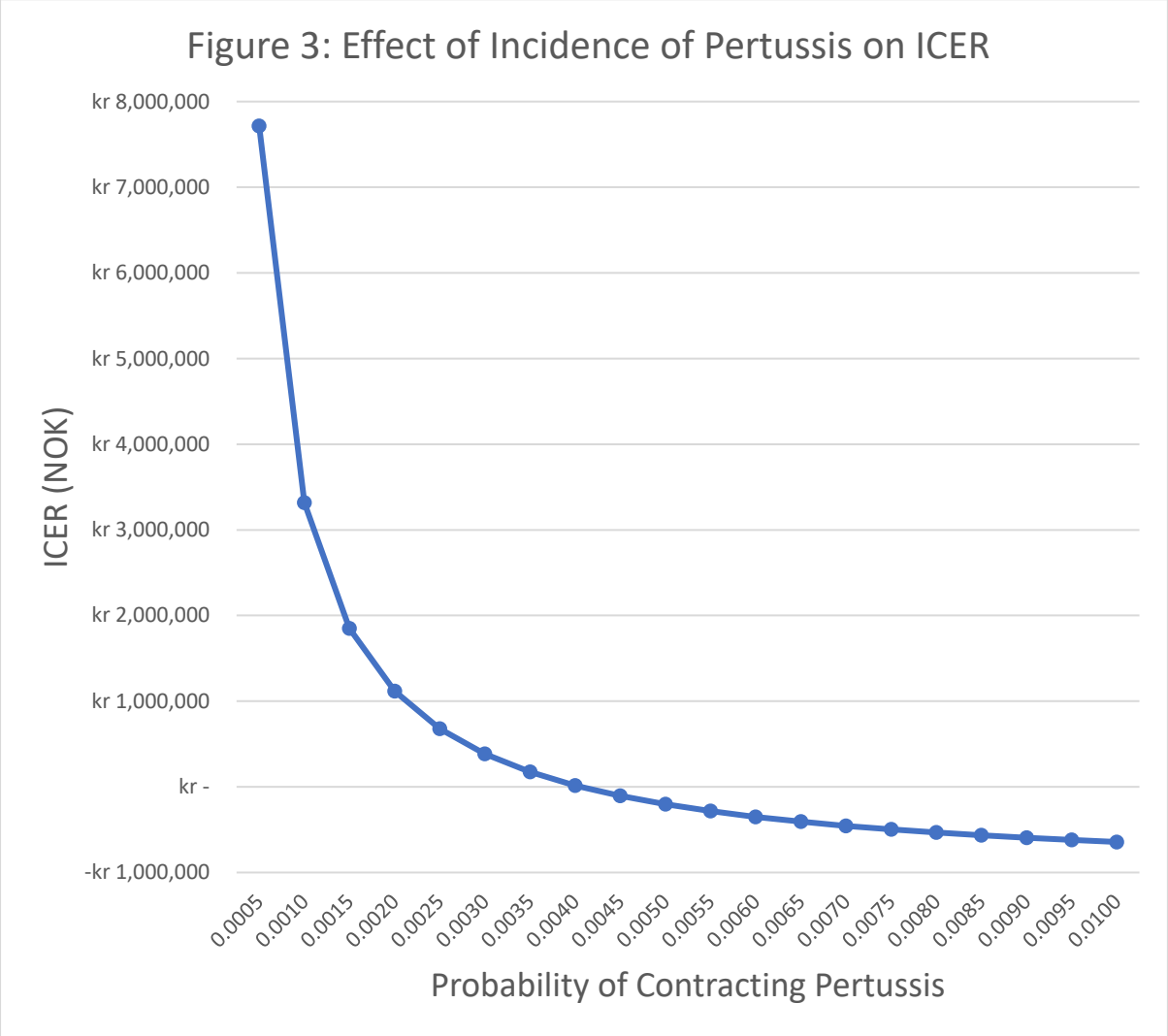
One-way sensitivity analyses were performed on each variable deemed to have uncertainty. Results are as follows.

5.2.1.1 Probabilities

As probability of death from pertussis increased, ICER decreased. As the death rate was based on only two deaths, and even one additional death would greatly increase the death rate; therefore, it was an important variable to examine. The ICER was quite sensitive to the death rate. Increasing the death rate to 0.0085, which is reasonable with one additional death, decreased the ICER from 2,802,947 to 2,389,170 NOK.

As probability of mother receiving vaccine increased, ICER decreased. Perfect adoption, where 100% of pregnant women received the vaccine, led to an ICER of approximately 2,475,266 NOK; this reduced the ICER by approximately 327,351 NOK when compared with the P used in the model, 0.60.

Incidence of pertussis, or probability of getting pertussis, had some effect on the cost, but the incidence would have to nearly double the initial estimate of 0.0011 to get under the cost-effectiveness threshold.



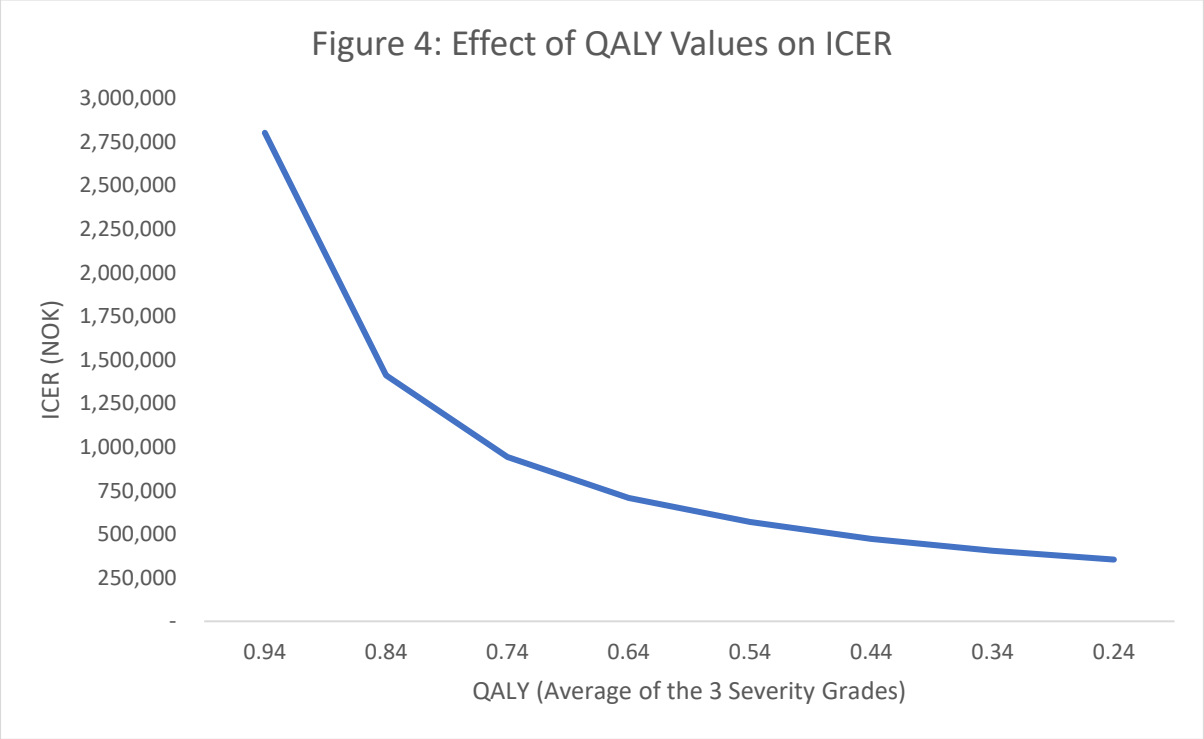
The effectiveness of the vaccine had a significant role in the ICER; lowering the effectiveness from 90 to 50 percent resulted in the ICER increasing from 2,802,947 NOK to 5,911,419 NOK.

Probability of contracting each severity of disease was a more complex task due to there being three variables dependent on each other. As the literature had indicated the potential for previously vaccinated individuals to have a milder form of pertussis if they did contract it, a manual table was created. What would happen if 10 percent of those vaccinated, but contracted severity grades 2 and 3 had the severity of their illness lowered by one severity grade? What if that number were 90%? The ICERs became 2,784,596 NOK and 2,645,463 NOK, respectively; by reducing severity Grades 2 and 3 by 90 percent, there was a savings of nearly 6 percent.

The probability of hospitalization given Grade 1 pertussis did not have a large effect on ICER. When all Grade 1 cases were assumed treated at home (probability of hospitalization set equal to zero), the ICER was 2,859,971. When all Grade 1 cases were assumed treated in the hospital (probability set to 1), the ICER was 2,698,044.

When 10 percent of Grade 2 cases became Grade 1 and 10 percent of Grade 3 cases became Grade 2 in those receiving the maternal vaccine, the ICER became 2,784,596 NOK; when the percentages was increased to 90 percent, the ICER became 2,645,463 NOK.

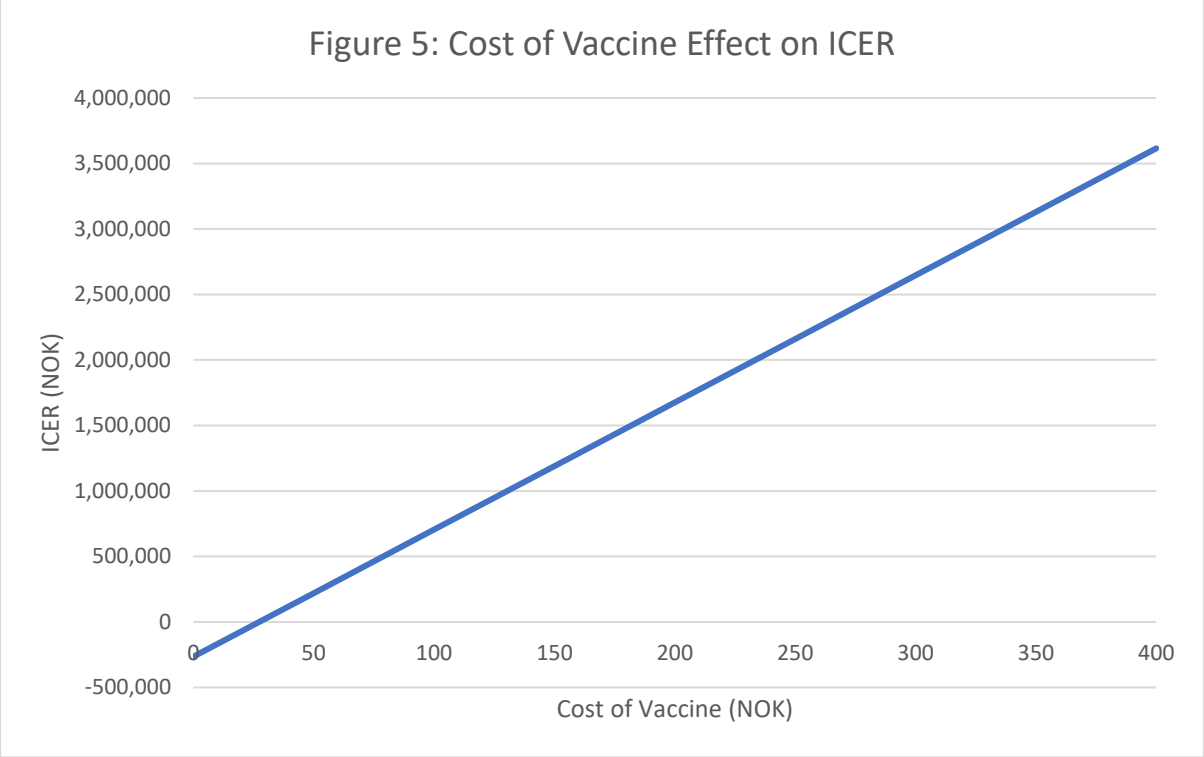
5.2.1.2 Quality Adjusted Life Years



When adjusted together, the QALYs had a large impact on ICER. In Figure 4, above, the effect of QALY values on ICER is displayed. When the QALY values reached an average of 0.64, meaning Grade 1 had a value of 0.66, Grade 2 a value of 0.64, and Grade 3 a value of 0.62, the ICER was brought down to 707,656 NOK.

5.2.1.3 Costs

Cost of vaccine was an interesting variable to analyze because, while the guidelines state that the costs should be calculated based on the maximum price, it can be assumed the government negotiates an unknown discount. As shown in Figure 5, below, the one-way sensitivity analysis showed that if the cost per vaccine were 100 NOK instead of the 316.20 NOK used in the model, the ICER would be approximately 705,144 NOK, which is below the 800,000 NOK threshold.



Cost of outreach was also an interesting variable based on it being a predominantly one-time expenditure with minimal upkeep costs. When the cost of outreach was removed, i.e. set to zero, the ICER became approximately 1,984,569 NOK. An outreach cost of 5,000,000 NOK brought the ICER up to 3,348,531 NOK.

As predicted, the cost of an urgent care visit did not have a large impact on ICER. Removing the fee entirely resulted in an ICER of 2,804,390 NOK, while increasing it to 1,000 NOK resulted in an ICER of 2,794,504 NOK.

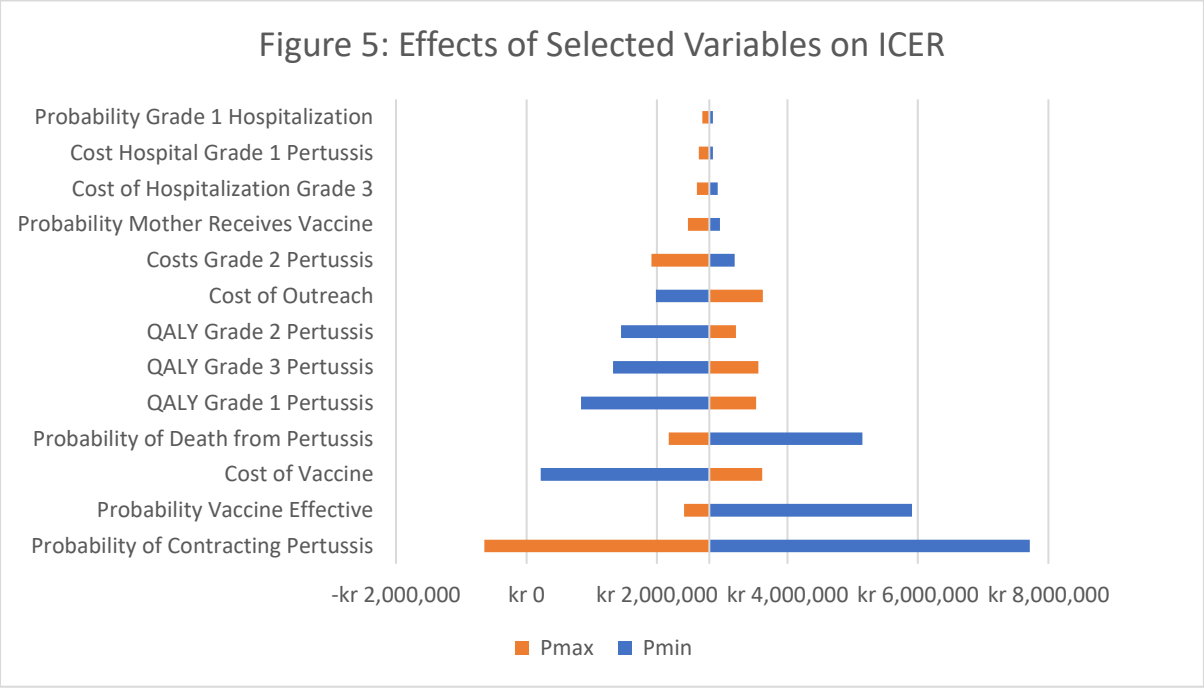
The cost of treating Grade 1 pertussis at home also had a minimal impact on ICER; setting the cost to zero resulted in an ICER of 2,803,429 NOK, while increasing it to 1,000 NOK led to an ICER of 2,800,289 NOK.

As cost of hospitalization went up, regardless of severity grade, the ICER decreased. This can be explained as: as the cost of hospitalization increases, the value of prevention also increases; the cost-effectiveness of the vaccine increases because it leads to fewer hospitalization events. When the cost of hospitalization of Grade 1 Pertussis was set to zero, the ICER became 2,860,234 NOK; when the cost was set at 120,000 NOK, the ICER became

2,644,619. For Grade 2 pertussis, when the cost of hospitalization was set to 150,000 NOK, the ICER became 3,191,111 NOK; at 750,000 NOK for hospitalization, the ICER became 1,915,224. With Grade 3 pertussis, the ICER ranged from 2,933,639 NOK when hospitalization costs were set to 70,000 NOK to 2,614,756 NOK with a hospitalization cost of 190,000 NOK.

5.2.1.4 Summary of One-Way Sensitivity Analyses

As can be seen in the tornado diagram, Figure 5, the costs of treating each grade of pertussis had little impact on the ICER. Note that the QALYs for the respective grades of pertussis were varied independently (one at a time) for this figure.



Pmax = Assumed maximum value of input parameter

Pmin = Assumed minimum value of input parameter

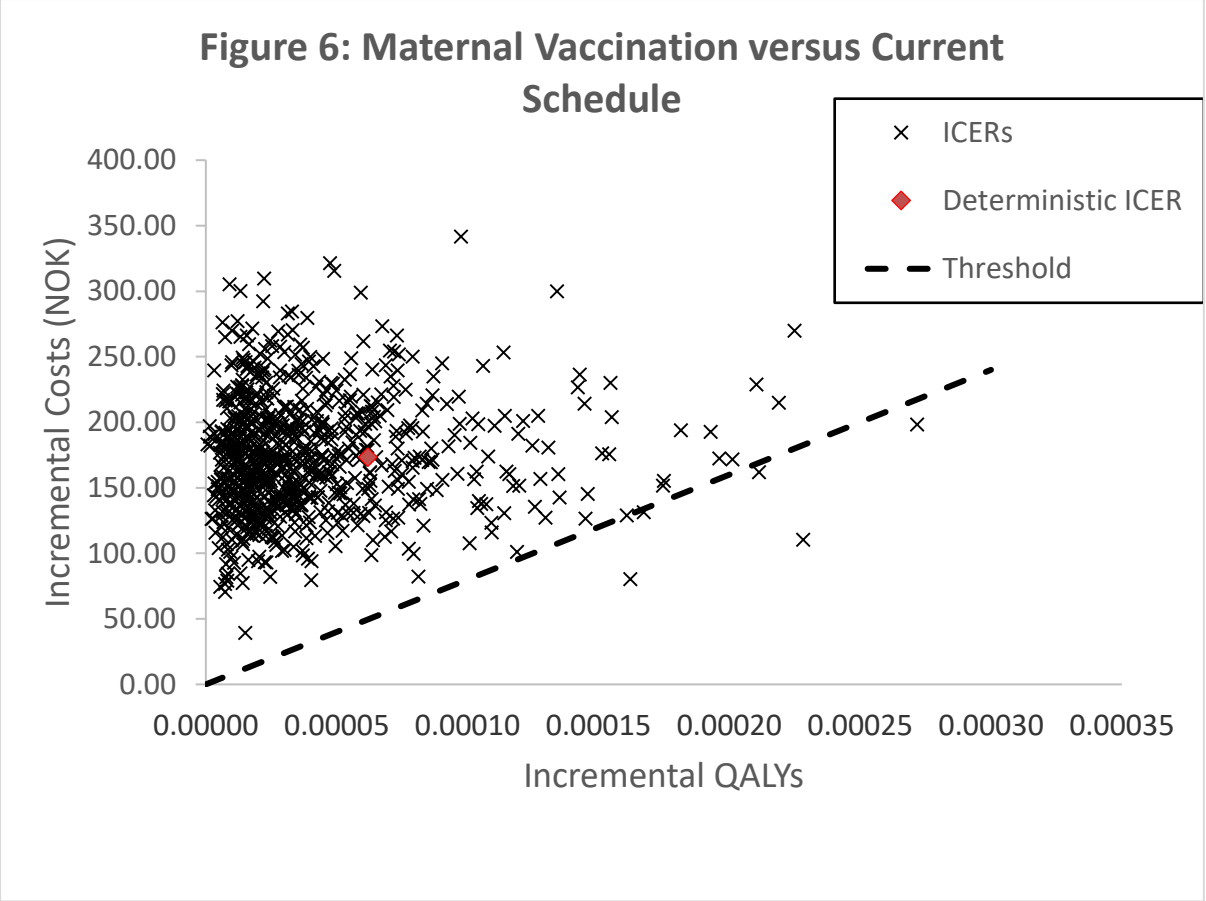
Overall, the ICER was most sensitive to changes in the probability of contracting pertussis, vaccine effectiveness, the cost of the vaccine, and the probability of death from pertussis. The cost of hospitalization variables did not have a major impact on the cost-effectiveness, nor

did the cost of outreach or probability of hospitalization with grade 1 pertussis. A summary of the one-way sensitivity analysis results is below, in Table E.

Table E: One-way sensitivity analysis results				
Variable	Parameter min	Parameter max	ICER min (NOK)	ICER max (NOK)
Probability of Pertussis (Incidence)	0.0005	0.01	7,716,700	-643,068
Probability of Death from Pertussis	0	0.01	5,149,979	2,182,683
Probability Mother Receives Vaccine	0.50	1.00	2,966,622	2,475,596
Vaccine Effectiveness	0.70	1.00	3,913,233	2,414,347
Probabililty of Hospitalization with Grade 1 Pertussis	0.00	1.00	2,859,971	2,698,044
Cost of Outreach	0 NOK	6,000,000 NOK	1,984,569	3,621,324
Cost of Vaccine	50 NOK	400 NOK	220,398	3,615,936
Cost of Treatment – Grade 1 Home Care	0 NOK	1,200 NOK	2,803,429	2,799,463
Cost of Treatment – Grade 1 Hospitalized	0 NOK	120,000 NOK	2,860,234	2,644,619
Cost of Treatment –Grade 2	150,000 NOK	750,000 NOK	3,191,111	1,915,224
Cost of Treatment –Grade 3	70,000 NOK	190,000 NOK	2,933,640	2,614,757

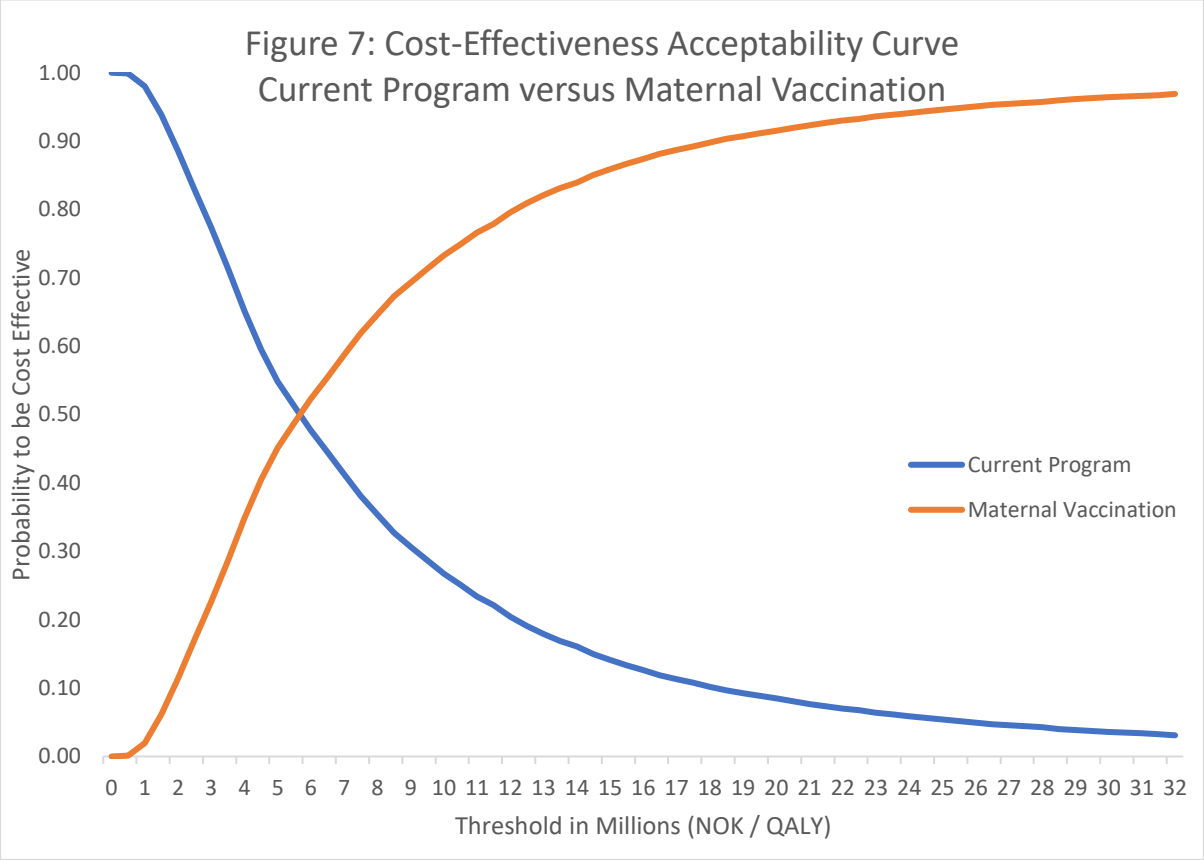
5.2.2 Probabilistic Analysis (Introducing a Stochastic Element)

The analysis was run based on the parameters set out in the methods section. (See Table D). As can be seen in the scatterplot below (Figure 6), all outcomes from the probabilistic analysis are in the northeast quadrant of the incremental cost-effectiveness plane. This means the maternal vaccination program neither dominates nor is dominated by the current vaccination strategy. Maternal vaccination is both more effective, but also more expensive than the current strategy; therefore, cost-effectiveness depends on the threshold.[19]



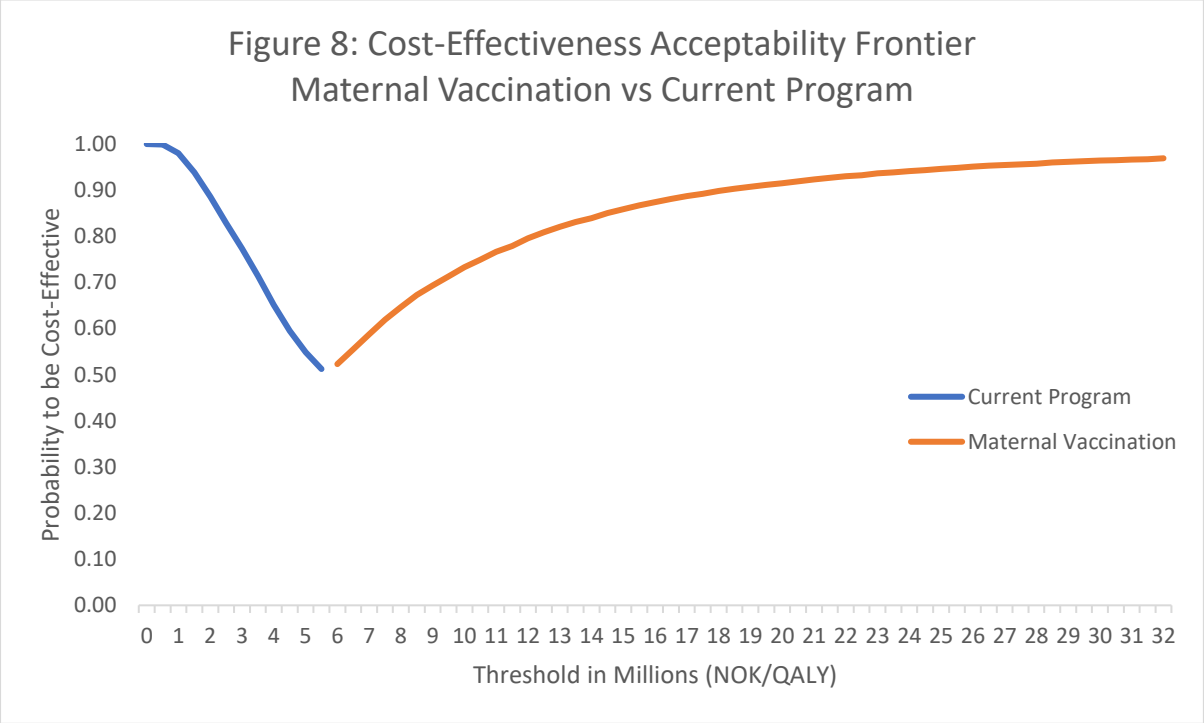
The mean incremental QALY was 0.000041, and the mean incremental cost of the probabilistic simulation was 173.86. Based on the means and the scatterplot, the deterministic model's output (0.000062, 173.35) seems to be a reasonably likely outcome.

5.2.2.1 CEAC (based on Net Monetary Benefits from PSA)



As can be seen from the CEAC (Figure 7) above, the maternal vaccination program is unlikely to be cost-effective until the threshold reaches nearly 10 million NOK. At a threshold of 12 million NOK, the maternal vaccination program has an 80 percent chance of being cost-effective.

5.2.2.2 CEAF



As can be seen in Figure 8 above, the CEAF shows the two vaccine programs becoming approximately equally likely to be cost-effective at a threshold of 5.5 million NOK. Below that, the current program is more likely to be cost-effective; with thresholds above 5.5 million NOK, the maternal vaccination program is more likely to be cost-effective.

6 Discussion

6.1 Main results

Based on the one-way sensitivity analyses, the negotiated price per vaccine seems more important to cost-effectiveness than the costs of outreach or hospital costs. The ICER was most sensitive to the probability of contracting pertussis; this means that a maternal vaccination program would be most cost effective in years where there is an outbreak. The price of the vaccine was also a significant variable; negotiating a low price would greatly decrease the cost of the maternal vaccination program, and therefore increase the cost effectiveness.

As previously noted, as probability of death from pertussis increased, ICER decreased. This makes sense in that as the negative outcome increases, the value of prevention increases (fewer deaths saves money).

6.2 Comparison with Other Countries

Many similar cost-effectiveness analyses have been performed using data from other countries. This study aimed to incorporate Norwegian data and recommendations, while retaining moderate comparability to other countries' findings. These results are limited in that many countries do not have the same high income as Norway, and therefore their cost-effectiveness thresholds are considerably lower.[34]

6.2.1 Folkhälsomyndigheten (2015)

The Public Health Agency of Sweden (Folkhälsomyndigheten) conducted a similar analysis in 2015. They found that a maternal vaccination scheme would cost approximately SEK 660,000 (~771,551 NOK adjusted for inflation) per gained QALY compared with the current strategy of vaccination at 3, 5, and 12 months. No sensitivity analyses were reported. The Swedish study did not refer to any threshold for cost-effectiveness indicating whether the reported cost per QALY would be cost-effective in a Swedish setting. Given that other cost-effectiveness analyses published the same year report a threshold of SEK 500,000, it is likely that maternal vaccination was not cost-effective in a Swedish setting. Although, the Swedish study did not find maternal vaccination cost-effective, they pointed out that Sweden's main method of pertussis follow-up for children is via interviews with caretakers (parents) after the illness ends; out of respect for the families, parents of children who died were not contacted.[27] This may cause underreporting of duration of cough, complications, and average length of hospital stay. Given this likely underreporting, it seems likely that the vaccine would have been more cost-effective if these data were more complete, and therefore perhaps even below the assumed cost-effectiveness threshold. [27]

The results of this study should be reasonably comparable to the portion of Folkhälsomyndigheten's study comparing the maternal vaccination strategy to their current strategy. The main differences of significance are likely in Norway's smaller population and the inclusion of a lifetime perspective. Additionally, the probability of contracting pertussis in the Swedish study was 0.0016, while in this analysis, the rate, estimated based on historical Norwegian figures, was 0.0011. Despite not including a lifetime perspective, Folkhälsomyndigheten found 8.04 QALYs among an infant cohort of 109,089, while this analysis found 3.67 QALYs among an infant cohort of 59,273 with a lifetime perspective. This is mostly explained by the differences in pertussis incidence. When Folkhälsomyndigheten's pertussis probability of 0.0016 is inserted into the model, the QALYs increase to 5.18. This means the per capita increase in QALYs was higher than that of Folkhälsomyndigheten, which is probably due to the difference in time perspective.[27]

When 0.0016 was input into this model, the resulting ICER was 1,666,868 NOK compared to Sweden's 771,551 NOK. Part of this difference can be explained by Norway having different healthcare costs and this model's inclusion of estimated initial outreach costs, while the Swedish-based study did not.[27]

6.2.2 Wolf and Højgaard 2017

In Denmark a similar study was performed for VIVE (Viden til Velfærd), under Denmark's National Research and Analysis Center for Welfare, by Wolf and Højgaard in 2017. As in Folkhälsomyndigheten's study, the Wolf and Højgaard examined a variety of strategies for vaccination, including cocooning, shifting the standard vaccination scheme forward one month, and maternal vaccination. This analysis differed from Folkhälsomyndigheten's in that the "utility" used for analysis was each case of pertussis, not QALYs. The study concluded that maternal vaccination would prevent 61.3 cases of pertussis in infants annually, and cost DKK 158,226 (219,880 NOK when adjusted for inflation) per avoided case of pertussis. One-way sensitivity analyses were performed, including the variables vaccine effect, cost of outreach campaign, and DRG costs.[5]

As outcome was cases of pertussis prevented instead of QALYs, comparison opportunities are limited outside of the specific disease.

6.2.3 Westra et al 2010

In Westra et al's 2010 analysis focusing on the Netherlands, maternal immunization was concluded to be cost effective from a payer's perspective, and even cost-saving from a societal perspective.[6] The authors' model predicted 174 cases of pertussis in infants would be prevented. The analysis of maternal vaccination resulted in a predicted cost per QALY of 3,500 Euros (33,028 NOK adjusted for inflation); however, this study differed from Folkhälsomyndigheten's study in that the authors included the mothers' potential to contract pertussis in their model. This may have contributed to the higher effect gain for the cost. The authors estimated the vaccine's effectiveness when given to the mother at 89 percent. This study included mortality in their model based on the number of deaths (5) reported over a seven-year period.[6]

This Dutch analysis found an ICER of 114,200 USD per QALY when assuming no underreporting and a payer's perspective; with inflation that equates to approximately 804,106 NOK.

6.2.4 Atkins et al 2015

A 2015 study by Atkins et al regarding the cost effectiveness of pertussis vaccination in pregnant women in the USA found the cost per QALY of $114,000 USD (1,124,023 NOK adjusted for inflation), and predicted the annual infant death rate for pertussis would be reduced from 16 to 7. They based their conclusion on a 91 percent risk reduction of pertussis in infants. QALY estimates were, as in the Swedish and Dutch studies, based on Lee's studies. The analysis was conducted from a societal perspective and had a 20-year time horizon.[7]

While Atkins' QALY estimates were somewhat lower, that may be explained by their consideration of adult pertussis cases and QALY losses in addition to that of infants. Also, this study was from a societal perspective, which generally includes more costs (and therefore more prevented costs, as well). [7]

6.2.5 Summary of Comparison to Other Countries' Studies

As each country has different healthcare systems, population densities (transmission rates), and treatment guidelines, as well as different relevant cost-effectiveness thresholds, the results of this analysis are only applicable to Norway, and not to other countries.

As this analysis was based on the payer's perspective, it may be difficult to generalize this to countries where the costs vary greatly by region, hospital group, or insurance provider.

While compliance, or the probability of pregnant women receiving the vaccine, did not have a large effect, it is still an aspect to consider, especially combined with potential outreach costs. In regions or countries with low vaccination rates, the cost effectiveness would be lower.

6.3 Strengths and Weaknesses of the Analysis

6.3.1 Strengths

This model incorporated a number of significant factors affecting the cost-effectiveness of a maternal vaccination program. It added both a lifetime perspective aspect as well as the QALY loss due to death. It also managed to incorporate a large amount of uncertainty through the sensitivity analyses.

Through the Monte Carlo simulation and resulting CEAC and CEAF, this analysis was also able to include information on cost-effectiveness at various thresholds. In a way, thresholds represent opportunity costs; money allocated to this program cannot be used on another program.

6.3.2 Limitation Part 1: Efficiency Data

While NoMA's Guidelines prefer randomized controlled trials for data on relative efficacy of treatments,[23] such a trial is probably not performed on such a specific population (pregnant women) because it is considered standard practice not to test medicines on pregnant women.[18] Therefore, relative efficacy of the vaccine was based on the results of Amirthalingam et al's 2014 observational study from the UK.[28]

6.3.3 Limitation Part 2: Data

Costs not included. A societal or other broader perspective could include funeral costs, decreases in productivity for grieving family, lifetime loss of productivity for infant, etc.

The analysis estimated the cohort based on the birthrate from the last ten years. However, the birthrate has been dropping recently, so the cohort analysis may be overestimating the affected population, especially if the trend continues.[35]

As the death rate was based on only the two deaths in 2003 and 2004, it is very sensitive. Any additional deaths have a large impact on the model; had data collection been extended a few more years, another death would have been included, thus raising the death rate significantly. The one-way sensitivity analysis did capture this element of uncertainty.

6.3.4 Underreporting

Unlike the Dutch and USA-based analyses, this analysis did not factor in underreporting. This was partly due to Norway having a relatively high rate of reporting and diagnosis, but could be included as a variable in future studies.[8]

6.3.5 Alternative Treatments

Other country-specific studies included more vaccination options, for example cocooning or vaccination at birth. Cocooning is where both parents, and sometimes any other major

caregivers or those in close contact with the infant, are vaccinated against pertussis, in an attempt to "cocoon" the infant from the most common sources of transmission. As those studies found that maternal vaccination was more effective than cocooning, they were left out. The vaccination at birth strategy was also not examined because the goal is to protect infants as early as possible, and immunity from vaccination does not take effect immediately.[36]

6.3.6 Norwegian Hospitalization and Severity Data

Another limitation of this model was the lack of hospitalization rates for Norwegian cases; this would have made the model more accurate, but based on the one-way sensitivity analyses, it does not seem the hospitalization rate had a large impact on the overall costs; a more complex model could have also addressed the assumption that all deaths came from grade 3 severity cases.

The model does not account for rare but serious cases in which permanent damage occurs; this applies to both the decision tree and Markov model, and also the QALYs used in the analysis. While these conditions could have been added to the model to make it more realistic, all models will always be simplifications of reality. Furthermore, adding these would have made the vaccine even more cost effective in that the current strategy's QALYs would be reduced, while the effects would be lessened on the maternal vaccination branches.

6.3.7 QALYs

QALYs have a number of limitations. As mentioned earlier, there are a variety of ways of measuring and valuing them, and it is not always easy to determine the methods used by a particular study. As the QALYs for this study are for infants, who cannot complete QALY measurement surveys themselves, creates another limitation. While the limitation of comparability was minimized for comparisons among the other maternal vaccination studies because they all used Lee's QALY estimates as their source, the comparability with other diseases or even other age groups with pertussis may be limited.

While QALYs in general can be difficult to judge impartially, measuring them appropriately for infants provides further challenges. The QALY estimates used in this analysis came from Lee's 2005 study, in which adults who had recently had pertussis or had an older child (11-17 years old) with pertussis were interviewed about their preferences. The infant QALY estimate came from asking these adults to imagine they had a one-month old baby suffering from pertussis.[30] This may be the best way to get data in a non-insensitive manner, but the data may not be as accurate as if parents of infants with or without pertussis were interviewed. The respondents may be biased because their recent experience was with the much milder cases seen in older children and adults.

One limitation inherent in cost utility analyses is that QALYs are not perfect; rather, they are the best measure we have come up with so far. Various authors find fault with QALYs; criticisms include equity issues (may undervalue treatments for the elderly and very sick individuals), difficulty in defining perfect health, and the incorporation of health states with values below zero (worse than death).[37], [38]

Additionally, NoMA's Guidelines generally require QALYs based on patient-reported EQ-5D measures; [23] however, as the patients in this case are too young to report their quality of life, Lee's study results were used. While QALYs leave challenges for general comparisons with other studies, it does allow for some comparison when, as in the case of this analysis and the other country studies (except Denmark, which did not use QALYs at all), it's reasonable to compare them because they all used the same source (Lee) for their QALYs.

6.3.8 Other Limitations and Considerations

An EVPI (Expected Value of Perfect Information) was not included in the analysis, so no clear conclusions could be drawn regarding which parameters it would be most cost-effective to perform more research on.

6.4 Recommendations for future studies

6.4.1 Building on the Current Model

The decision tree and Markov model have the potential to be expanded to incorporate more possibilities and outcomes. Some articles mentioned that the vaccine leads to decreased severity of pertussis in previously vaccinated individuals. Future analyses could follow up on this information by incorporating these lower rates of Grades 2 and 3 pertussis in passively immunized infants into the decision tree. The more severe potential negative complications of severe pertussis cases, such as permanent neurological damage, could also be incorporated into the Markov model, adding both costs and decreased QALYs to that portion of the analysis. Additionally, the hospitalization rates and probabilities of each severity grade could be based on Norwegian data if that becomes available.

Future analyses could also incorporate different perspectives, for example the societal perspective and its inclusion of decreased economic productivity, could also be calculated in future analyses.

6.4.2 Future Models and Studies

Another possibility for future analyses would be the creation of a dynamic model, where source of infection was included; but it would be likely this would only increase cost effectiveness because the mother would also be "not infected" and therefore QALYs gained would increase without increasing any costs. Future research could also factor in underreporting; this may be complex as reporting levels may differ regionally. Another interesting addition in a dynamic model could be adding the recommended prophylactic treatment with erythromycin for unvaccinated children who come in contact with someone diagnosed with pertussis.[26]

A new study could somewhat address the limited QALY data; if ethics allow, one could at least interview the parents of infants who recently recovered from pertussis. This could be incorporated as part of the follow-up interviews conducted by Sweden's Public Health

Agency, for example. However, it may be more effective to continue varying the QALYs in the models.

Alternatively, another study could replace QALYs with prevented cases of pertussis, as in Wolf's analysis for Denmark. While QALYs are currently the recommended utility measure for Norway,[23] the ease of comparability within the disease among differing countries may be useful.

7 Conclusion

This analysis did not find vaccination of pregnant women cost-effective at the current list price, assuming an initial outreach costing 3 million NOK and a vaccine cost of 316.20 NOK. When the cost of the vaccine was lowered from 316.20 NOK to 100 NOK, the ICER became 705,144, making the program cost effective at the 800,000 NOK threshold.

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