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Cost-effectiveness of meningococcal vaccination of Norwegian teenagers with a quadrivalent ACWY conjugate vaccine

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ABSTRACT

In Norway, the incidence of invasive meningococcal disease (IMD) is higher among 16–19-year-olds than in the general population. Most IMD cases among teenagers are caused by serogroup Y. Since 2011, one dose of meningococcal ACWY conjugate vaccine (MCV4) has been recommended for teenagers with out-of-pocket payment. The teenagers are usually vaccinated through the school health service at age 18. This study aimed to estimate costs and health gains of introducing MCV4 to Norwegian teenagers through the national immunization program (NIP). A Markov model was used to analyze the cost-effectiveness of universal MCV4 vaccination of either 15-year-olds or 18-years-olds. Occurrences of IMD were simulated from 15 until 23 years of age. Costs were estimated from a healthcare perspective. Sensitivity analyses evaluated the impact of vaccine price, vaccination uptake, IMD incidence and discount rate. Compared to today's practice of vaccinating 18-year-olds with out-of-pocket payment, introducing MCV4 to 15-year-olds in a NIP-setting, with 90% vaccine uptake and 50% rebate on vaccine price, prevented 3.2 hospitalizations, 0.20 sequelae and 0.47 deaths among 15–23-year-olds, annually. Total costs were reduced by €30,000 and 9.7 quality-adjusted life-years (QALYs) were gained per birth cohort. The probability of cost-effectiveness was 99.0%, assuming a willingness-to-pay threshold of €86,000/QALY for severe diseases in Norway. Cost-effectiveness was highly dependent on vaccine price. Vaccination of 18-year-olds in a NIP-setting was also cost-effective, but less than NIP-vaccination of 15-year-olds. Introduction of MCV4 to the 15-year-olds in the Norwegian NIP is likely to be cost-effective given a rebate on the vaccine price.

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Introduction

Neisseria meningitidis, the meningococcus, is a common human commensal that in rare occasions cause invasive meningococcal disease (IMD). Despite antibiotic and supportive treatment, mortality from IMD remains high and many patients suffer sequelae influencing their quality of life (QoL).[1,2] Serogroups A, B, C, W, X, and Y are the most common disease-causing variants.[3] Incidence and serogroup distribution varies by region and age. IMD primarily affects infants, adolescents, and young adults.[4] Serogroup B predominates in the general population in Europe.[4,5]

Rarity of the disease and unexpected affection of previously healthy individuals make the risk of IMD at an individual level unpredictable. Influence of long-term sequelae on the patient, as well as indirect effects on family members and society, are difficult to capture fully.[6,7] In addition, the emergence of hypervirulent clones[8,9] and unforeseen outbreaks with cases spread over time[10,11] also predicts disease burden challenging at a public health level.

Both meningococcal ACWY conjugate vaccines (MCV4)[12,13] and meningococcal B protein vaccines (MenB)[14,15] have been shown to induce protective immunity. Some European countries have a general recommendation for MCV4 vaccination of adolescents, but adolescent MenB vaccination free of charge is currently not implemented in any national immunization program (NIP) in Europe.[16] In Norway, meningococcal vaccines are not implemented in the NIP, and are currently only recommended for various risk groups, including the 16–19-year-olds.

After a peak of 5.3 cases of IMD per 100,000 in 2010, the mean incidence in Norwegian 15–19-year-olds has decreased to 1.2 per 100,000 in 2017–2019.[17] Between 2017 and 2019 the mean incidence was 0.8 per 100,000 in children <5 years, and 0.3 per 100,000 in both the 5–14-year-olds and adults >19 years. Serogroup Y (75%) has predominated in the 15–19-year-olds, with no cases of serogroup B observed in this age group since 2014. In children <5 years, serogroup B (83%) has dominated, whereas serogroups W and Y are most prominent among the 5–14-year-olds (serogroups B 17%, C 17%, W 33%, Y 33%). Serogroups B, W, and Y were most common among adults >19 years (serogroups B 31%, C 4%, W 27%, Y 38%).

The majority of IMD cases in Norwegian teenagers has occurred among students taking part in the "russ" celebration, a tradition among upper secondary school graduates (mostly aged 18–19 years) including a month-long period of binge-drinking and partying with peers.[18] Due to an observed increase in IMD among teenagers involved in the "russ" celebration from 2009, a national recommendation for MCV4 vaccination was initiated from 2011 for the 17–19-year-olds and expanded to the 16–19-year-olds in 2012. Vaccination is arranged through the school health service. Despite the

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national recommendation, MCV4 is not implemented for all teenagers in the national immunization program, and vaccine cost is financed with students paying out-of-pocket. Currently, several municipalities and counties are sponsoring MCV4 for one cohort (mostly 18–19-year-old graduates) in upper secondary school. In some areas, the vaccination uptake has increased from around 40% to 80% among graduates when vaccination is given free of charge and administered on school grounds,[19] indicating that purchasing power and accessibility may influence MCV4 uptake among Norwegian teenagers. In 2019, 48% of the 18–19-year-olds were vaccinated with MCV4 nationally.[19] This practice might have contributed to the observed recent decline in incidence of IMD in teenagers.[17]

Despite the currently low incidence of IMD, there is an ongoing debate in Norway whether MCV4 should be implemented free of charge as part of the NIP for teenagers, to ensure equal access to vaccination and reduce inequality in health. This study aimed to perform an explorative evaluation of costs and health effects from a healthcare perspective to find out if introducing one dose of MCV4 to either 15-year-olds or 18-year-olds through the Norwegian NIP could be cost-effective.

Materials and methods

Vaccination strategies

Three different vaccination strategies were explored (Table 1): 1) vaccinating 18-year-olds as a risk group outside the NIP with out-of-pocket payment (*Current practice*); 2) vaccinating 15-year-olds free of charge as part of the NIP (*Universal 15*) or 3) vaccinating 18-year-olds free of charge as part of the NIP (*Universal 18*). Vaccination of 18-year-olds was chosen since this is when most Norwegian teenagers currently are vaccinated and engage in the "russ" celebration. Vaccination at 15 years of age was chosen as an alternative strategy, as most teenagers in Norway start upper secondary school at 15–16 years of age.

Model

We created a probabilistic Markov cohort model in R version 3.6.2 simulating the impact of teenage MCV4 vaccination on survival, health-related QoL, and resource use from age 15 until 105 years in yearly cycles for the three vaccination strategies. Occurrences of IMD were simulated for the period from 15 to 23 years of age for all three strategies, according to vaccine effectiveness (VE) and vaccination uptake in each strategy (Figure 1). The age period 15–23 years of age was chosen to take into account the potential protection of the vaccine for all 5 years after vaccination at either 15 or 18 years of age. Modeling was based partly on ideas and templates provided by the Decision Analysis in R for Technologies in Health group.[20,21] All individuals were assumed to be at risk of getting IMD, and all IMD cases were assumed admitted to hospital in the acute phase. Hospitalized patients would either recover, suffer permanent sequelae or die (Figure 2). Individuals started in the model in the health state susceptible and were at risk of the event IMD from either of the meningococcal strains A, C, W, or Y. Individuals who acquired IMD, and thus were hospitalized in the acute phase could from there move to the health state sequelae, or they could recover. All individuals were at risk of dying, although hospitalized patients or those with sequelae were at an increased risk of death.

Input parameters (Table 2) were based on sources from Norway where available, or from high-income countries with similar epidemiology or economy. Uncertain parameters in the model were incorporated as probability distributions and simulated 1,000 times using Monte Carlo simulation. Probability distributions were created based on 95% confidence intervals (CI) or standard errors where available. For parameters where no information about the magnitude of the uncertainty was available in published sources, probability distributions were based on assumed uncertainty around the average of each parameter. One-way sensitivity analyses were based on average of runs of the probabilistic model for each extreme value.

Table 1. Overview of vaccination strategies used to model cost-effectiveness.

Strategy	Age at vaccination (years)	Vaccine uptake (%)	Funding	Vaccine rebate
Current practice	18	48	Out-of-pocket funding	0%
Universal 15	15	90	Free of charge in NIP	50%
Universal 18	18	90	Free of charge in NIP	50%

NIP – national immunization program

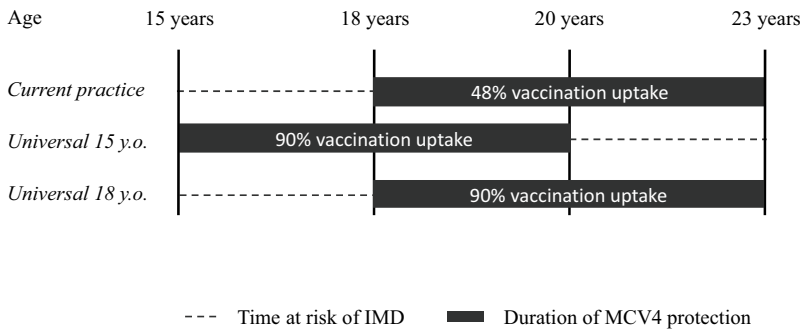

Figure 1. Illustration of time at risk of IMD, MCV4 vaccination uptake and duration of protection from MCV4 in all cohorts studied.
IMD = Invasive meningococcal disease, MCV4 = meningococcal ACWY conjugate vaccine

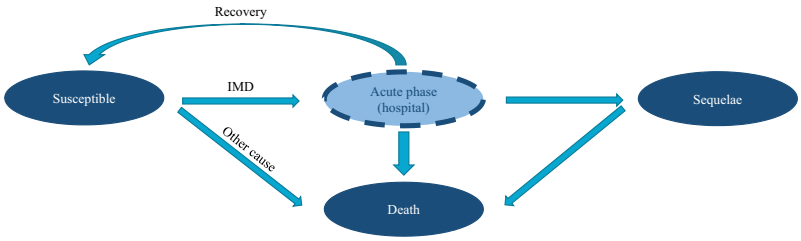

Figure 2. Markov model simulating the impact of vaccinating teenagers with MCV4.
IMD = Invasive meningococcal disease, MCV4 = meningococcal ACWY conjugate vaccine

Health effects and costs were discounted according to Norwegian guidelines for single technology assessment (STA) of pharmaceuticals,[23] hence 4% over the first 40 years, 3% from 40 to 75 years and thereafter 2%. Due to the growing use of differential discounting of health and costs,[6] we performed a separate analysis without discounting health effects, as suggested in a Norwegian official report.[24]

Epidemiology

The average Norwegian cohort of 15-year-olds has been fairly consistent at around 65,000 individuals in the last years.[25] The model only included IMD among age groups directly affected by the different vaccination strategies described above, and only included cases caused by MCV4-targeted serogroups. Data on IMD incidence were extracted from The Norwegian Surveillance System for Communicable Diseases (MSIS) between January 2008 and December 2017.[17] Cases of IMD are mandatorily reported to MSIS and administration of vaccines to the Norwegian Immunisation Registry SYSVAK.[19] The incidence of IMD in the study period might have been influenced by the increase in MCV4 uptake from zero to nearly 50% in some age groups between 2008 and 2017. We wanted to compare the cost-effectiveness of the different vaccination strategies if each strategy had been implemented *before* the recommendation of MCV4 to 16–19-year-olds in 2011/2012 induced a more widespread use of MCV4 among Norwegian teenagers. We therefore adjusted the observed cases of IMD registered in MSIS according to vaccination uptake in the cohorts registered in SYSVAK and the estimated vaccine effectiveness, in order to calculate a "baseline" incidence of IMD if MCV4 had not been used among teenagers in 2008–2017. In this way, we were able to analyze differences in cost-effectiveness between just a recommendation for the use of MCV4 among selected 16–19-year-olds with out-of-pocket payment (*Current practice*) to that of implementing MCV4 in the national immunization program to a full cohort of teenagers with the vaccine fully financed by the government (*Universal 15* or *Universal 18*). With the adjusted incidences, we then calculated mean incidences for the full ten-year period (medium incidence), the first five-year period (high incidence) and the last five-year period (low incidence) to incorporate the effect of incidence variations in the model. The number of IMD cases per birth cohort in each year was relatively low. The number of cases was therefore combined for the age groups 15–17, 18–19, and 20–23-year-olds, respectively, in order to even out random fluctuations in IMD (Table 2). Probabilities of sequelae (amputation, hearing loss, seizures, and skin scarring) were based on a review by Olbrich et al.[2] The distributions of sequelae were based on medians, minimum and maximum values reported in the review.

Vaccine effectiveness and vaccination uptake

Assumed VE of MCV4 was extrapolated from a phase III immunogenicity study among 11–18-year-olds comparing two well-known types of MCV4.[12] We pooled the percentage of seroconversion for different serogroups into one estimate based on a weighted average of effects for the diffe
rent serogroups, giving a VE of 73% (95%CI 71–76%) (Table 2). Duration of protection was assumed to be 5 years.[26,27] Possible waning of vaccine protection was not included in the model. Herd effect of MCV4 has only been shown in one study.[28,29] Since our study was explorative, we chose a static model not accounting for possible herd effect of MCV4.

The vaccine uptake in the universal strategies was assumed to be 90%, based on 88% uptake for the human papilloma virus vaccine and 93% for the diphtheria-tetanus-pertussis-polio booster among Norwegian 16-year-olds in 2018.[30] In sensitivity analysis, the uptake in a NIP setting was varied between 80 and 95%. With the current recommendation of out-of-pocket payment of MCV4 vaccination of 16–19-year-olds, vaccine uptake among 18–19-year-olds has gradually risen from 16% in 2012 to 48% in 2018, adapted from ref. 19.[19] Therefore, in the strategy, *Current practice*, the level of vaccine uptake was set to 48%.

Quality-adjusted life-year (QALY) weights

In order to comply with Norwegian guidelines for STA of pharmaceuticals,[23] data on health-related QoL were based on the EQ-5D standardized generic instrument,[31] and quality-adjusted life-year (QALY) weight among the healthy, general population was based on two Swedish studies[32,33] (Table 2). QALY weights for hospital stay and for having sequelae were based on a previous economic evaluation.[34] Patients with sequelae (amputation, skin scarring, hearing loss and seizures) were assumed to have sequelae for the rest of their lives. The event "hospital stay" was assumed to last for 10 days based on a publication by Stoof et al.[35]

Costs

Costs were calculated in European euro (€) with an exchange rate of 9.60 Norwegian kroner (NOK) per € estimated from an

Table 2. Model input parameters.

Variable	Base case	Range 95% CI	Reference
Epidemiology of IMD and sequelae			
Yearly cases per 100,000 (15–17 years old)	0.98	0.65–1.37[a]	17,19
Yearly cases per 100,000 (18–19 years old)[b]	2.79	1.81–3.43[a]	17,19
Yearly cases per 100,000 (20–23 years old)[b]	0.46	0.28–0.59[a]	17,19
Mortality (%)	8.3	7.5–9.1	1
Amputation (%)	3.0	1.5–6.1 [c]	2
Skin scarring (%)	4.7	1.3–16.9 [c]	2
Hearing loss (%)	6.5	3.2–13.4 [c]	2
Seizures (%)	2.0	0.3–15.3 [c]	2
Vaccine protection and coverage			
Vaccine effectiveness (%)	73	71–76	12
Duration of vaccine protection (years)	5		25,26
Coverage "*Current practice*" (%)	48		Adapted from 19
Coverage "*Universal*" strategies (%)	90	80–95[d]	29
QALY weights and durations			
General population (QALY)			31,32
Hospital stay (QALY)	0.95	0.94–0.96	33
Sequelae (QALY)	0.84	0.73–0.90	33
Length of hospital stay (days)	10	2.7–17.3[e]	34
Costs and cost items			
Hospital cost meningitis (€)	11,228	8,982–13,473 [f]	37
Hospital cost sepsis >18 y.o. (€)	10,404	8,323–12,485 [f]	37
Hospital cost sepsis <18 y.o. (€)	15,052	12,042–18,062 [f]	37
Hospital cost ventilator and other ventilatory support (€)	34,150	27,320–40,980 [f]	37
Lifetime costs related to having amputation (€)	105,110	84,088–126,132 [f]	38
Lifetime costs related to having skin scarring (€)	4,886	3,909–5,863 [f]	38
Lifetime costs related to having hearing loss (€)	60,348	48,279–72,418 [f]	38
Lifetime costs related to having seizures (€)	1,118,599	838,949–1,398,249 [f]	38
Vaccine price (€)	40.82		36
Vaccine rebate in NIP setting (%)	50	25–75 [g]	Assumption based on previous tenders in Norway
Time used per vaccination (hours)	0.16	0.08–0.24 [h]	Estimates from three different communities in Norway
Other administrative costs with vaccination (€)	0.9	0.4–1.7[i]	Estimate from two different communities in Norway
Hourly wage doctors (€)	40.2		24
Hourly wage nurses (€)	26.9		24
No. of close contacts	17.04	3.20–42.23	Estimate based on 146 reported cases in Norway
Time spent on contact tracing (hours)	116.2	67.5–200 [j]	Based on assumption from municipal doctors.
Cost of one dose antibiotic to close contacts (€)	0.6		36
Other assumptions			
Discount rate (%)	4, 3 and 2 depending on time (0 for health effects in scenario analysis)		22
Hospital admissions due to meningitis (%)[k]	65	63–67	34
Hospital admissions due to septicemia (%)	35	33–37	34
Proportion of hospital stays with meningitis that require ventilator (%)	1.0	0.5–2.0	Assumption from infectious disease specialist
Proportion of hospital stays with septicemia that require ventilator (%)	25	20–30	Assumption from infectious disease specialist
Exchange rate NOK per €	9.60		35
Maximum threshold for cost-effectiveness (€ per QALY)	85,972		23,41

QALY – quality-adjusted life-year
[a]Low estimate is average of the years 2013–2017, High estimate is the average of the years 2008–2012.
[b]Yearly incidence adjusted according to MCV4 vaccination coverage
[c]Low and high estimates are lowest and highest reported incidence in review by Olbrich,
[d]Assumption based on previous experience with childhood vaccination
[e]95% confidence interval is based on calculations from interquartile range reported in the article (ref 34)
[f]Assumed ± 20% for costs reported only as means
[g]Assumption based on previous tenders in Norway
[h]Estimates from three different communities in Norway, minimum reported assumed serves as low end of range, median as mean and maximum as high end of range
[i]Estimate from two different communities in Norway, range: ±50%
[j]Upper and lower estimate based on assumption from two municipal doctors. Midpoint calculated based on endpoints, assuming log-normal distribution.
[k]Incorporated into the model as 100% subtracted the percentage with septicemia to avoid sum of two probabilities above 100%

average of exchange rates from 2018[36] (Table 2). In the strategy of *Current practice*, the price of MCV4 was based on the official retail price in Norway as given by the Norwegian Medicines Agency (NoMA).[37] Vaccines included in the Norwegian NIP are procured through national tenders. In the two universal strategies, a 50% price rebate was assumed as a base case estimate. This rebate was extensively varied in a one-way sensitivity analysis from 25 to 75%, based on experience with tenders on long-term contracts for vaccines already implemented in the Norwegian NIP.

Costs of hospital stay were based on annually published official estimates for 2018 of average costs provided by the Norwegian Directorate of Health.[38] These estimates are based on the diagnosis-related group (DRG) system, which has separate groups for patients presenting with meningitis and septicemia, the latter group divided into age groups above and below 18 years of age.

Time and resources used for school-based vaccination of adolescents were estimated using information provided by municipalities that are currently offering school-based meningococcal vaccination. Probability distributions were assumed to vary between minimum and maximum of values provided by the different municipalities.

Norwegian guidelines for the management of IMD cases recommend prophylaxis with one dose of ciprofloxacin and one dose of MCV4 to close contacts of IMD cases. Costs and time spent on contact tracing and prophylactic treatment were based on information provided by municipal doctors and nurses. Estimates of number of hours spent on contact tracing was assumed as a lower and upper end of a confidence interval. Salaries for nurses and doctors were based on average hourly wages as reported by Statistics Norway.[25] The estimate for the number of close contacts per IMD case was based on records from Norwegian IMD cases in the last decade. Estimates of lifetime costs for patients living with sequelae were based on a Canadian study from 2017.[39] This study was chosen due to strong and rigorous reporting of all relevant costs related to sequelae. Canadian dollars were converted into NOK and adjusted based on consumer price index before being converted into €.

According to Norwegian guidelines for STA of pharmaceuticals,[23] costs were gathered based on an extended healthcare perspective, implying that factors as productivity loss arising from the inability to work were not included. The Norwegian guidelines explicitly state that health-related costs borne by patients and relatives should be included in the analyses. Thus, costs related to vaccines paid out-of-pocket by 48% of the graduating students in the scenario *Current practice* were included in the analysis, similar to costs related to a potential vaccination program free of charge to all teenagers. Costs of adverse events monitoring after MCV4 vaccination were not included in the model, because such events were assumed either minor and/or of short duration.[40,41]

When the ratio between incremental costs divided by incremental effects (i.e., the incremental cost-effectiveness ratio (ICER)) is below a certain level (willingness-to-pay threshold), the intervention in question is regarded as cost-effective compared to the comparator. We assumed a maximum willingness-to-pay threshold for cost-effectiveness of €86,000 (NOK825,000) per QALY gained. The exact national threshold is uncertain, and our assumption was based on indications from two Norwegian official reports, proposing this maximum level for high priority diseases with high severity.[24,42] There are yet no estimated threshold for Norway based on which health interventions are displaced when new health interventions are introduced. The best estimate so far is probably the estimate by Woods et al.,[43] which translates to approximately €35,000 per QALY gained for 2018.

Results

Comparison of the strategies Current practice vs Universal 15

Vaccinating a cohort of 15-year-olds with MCV4 as part of the Norwegian NIP with an estimated uptake of 90% (i.e., *Universal 15*) would result in 4.26 IMD-related hospitalizations during the 8-year-period from 15 to 23 years age, compared to 7.41 hospitalizations if vaccinating 48% of 18-year-olds (i.e. *Current practice*) (Table 3). In the same period, a change from *Current practice* to *Universal 15*, would lead to a reduction of 0.47 deaths and 0.20 sequelae in each birth cohort. This means that about every 2 years we would avoid a death, and every 5 years a sequelae due to IMD caused by serogroups A, C, W, or Y if MCV4 was included in the NIP for 15-year-olds.

Expected discounted QALYs per individual would be 22.4 with *Current practice*. Changing to the *Universal 15* strategy would give a 0.00015 increase in expected QALYs per person, translating to 9.67 QALYs gained per birth cohort (Table 3). Total costs would decrease with €30,000, assuming 50% rebate on the vaccine price in the NIP-setting. This would give both a slight decrease in costs and an increase in effects, resulting in *Universal 15* being what is referred to as a "dominant" strategy.

Our simulations indicated that there was a 100% chance of *Universal 15* being more effective (i.e., giving more QALYs) than *Current practice* and a 54% chance of being less costly (Figure 3). Overall, there was a 99% chance of *Universal 15* being cost-effective compared to *Current practice* when assuming a willingness-to-pay threshold of €86,000/QALY for severe diseases (Figure 4), although the uncertainty related to the input parameters indicates large variability around the estimated cost-effectiveness ratio (Figure 3). Given the estimate of assumed displacement of other services, there was an 85% probability that introducing the MCV4 vaccine would give more health than the health displaced if the resources were taken from other health services (Figure 4).

Sensitivity and scenario analyses for the strategies Current practice vs Universal 15

Potential effects of variations in vaccine rebate, vaccination uptake, IMD incidence and discount rates on the ICER were explored comparing the *Universal 15* strategy with *Current practice* in a tornado diagram (Figure 5).

Not surprisingly, a 75% rebate on the current MCV4 vaccine price in Norway was even more cost-effective than the

Table 3. Costs and health gains of vaccination with one dose of MCV4. Estimates are displayed per birth cohort. *Current practice* refers to today's practice of vaccinating 18-year-olds outside a NIP setting (48% uptake, retail vaccine price) and is therefore the base case strategy in the model. *Universal 15* and *Universal 18* refers to vaccination in a NIP setting (90% uptake, 50% rebate on vaccine price) of 15-year-olds and 18-year-olds, respectively. Estimates for the *Universal 15* or *Universal 18* strategies are the results of comparing these strategies individually with the base case strategy *Current practice*.

	Current practice 48% vaccination	*Universal 15* 90% vaccination	*Universal 18* 90% vaccination	Costs and gains – *Universal 15* vs *Current practice*	Costs and gains – *Universal 18* vs *Current practice*
Hospitalizations (IMD-related)	7.41	4.26	4.26	3.15	3.15
Sequelae (IMD-related*)	0.47	0.27	0.33	0.20	0.14
Deaths (any cause)	124.1	123.6	123.7	0.47	0.38
QALYs (discounted)	1,456,575	1,456,585	1,456,583	9.67	8.32
Costs** (€) (discounted)	1,600,000	1,570,000	1,580,000	− 30,000	− 20,000

NIP – national immunization program; IMD – invasive meningococcal disease; QALYs – quality-adjusted life-years; MCV4 – meningococcal ACWY conjugate vaccine
* In the model, IMD-related deaths are added to deaths from other causes, while for hospitalizations we only count IMD-related.
** Rounded to nearest 10,000

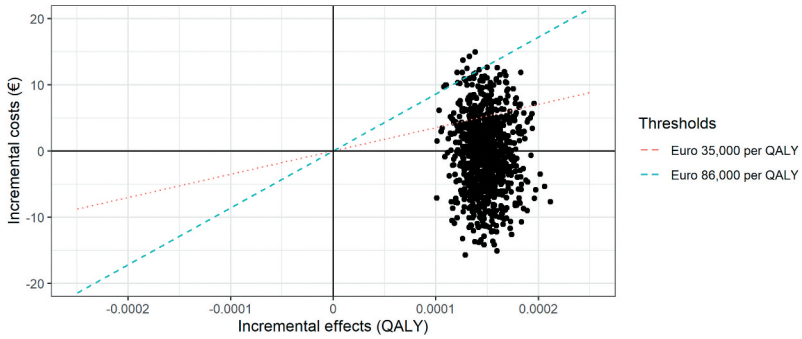

Figure 3. Scatterplot of simulations comparing the strategy *Universal 15* with *Current practice*. Dotted red line represents the threshold for displaced health interventions of €35,000 per QALY and dashed blue line the willingness-to-pay threshold of €86,000 per QALY.
QALYs = quality-adjusted life-years

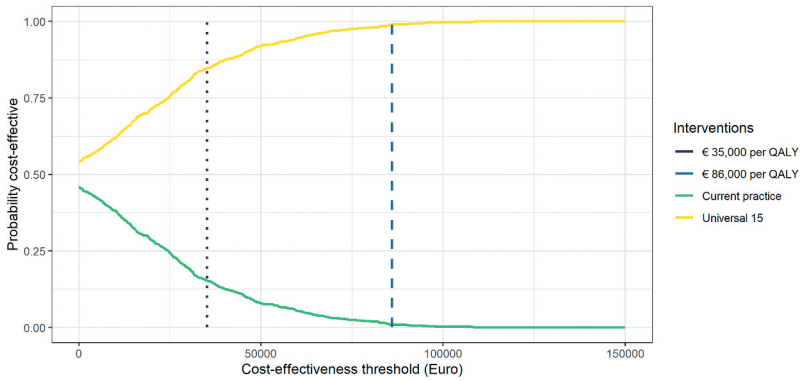

Figure 4. Cost-effectiveness acceptability curve comparing the strategy *Universal 15* (yellow line) with *Current practice* (green line). Dotted purple line represents threshold for displaced health interventions of €35,000 per QALY and dashed blue line the willingness-to-pay threshold of €86,000 per QALY.
QALY = quality-adjusted life-year

base case of 50% rebate. With only 25% rebate, the ICER would be €58,000 per QALY gained, which is still below the willingness-to-pay threshold.

Changing vaccination uptake to 80% or 95% resulted in incremental increases in QALYs of 8.54 and 10.2, respectively, and differences in costs of -€186,000 and €49,000. Assuming a willingness-to-pay threshold of €86,000/QALY for severe diseases, this resulted in both 80% and 95% uptake being cost-effective, and 80% uptake was also cost-saving.

Varying the IMD incidence from medium (i.e., the whole 10-year period) in the base case to low (i.e., the last 5-year period) indicated a gain of 6.32 QALYs, while a change from medium to high incidence (i.e., the first 5-year period) gave a gain of 12.5 QALYs. Furthermore, a high incidence was cost-saving compared to the base case incidence, while the low incidence gave a small increase of €400 per cohort, giving an ICER of €63 per QALY gained.

When performing the analysis without discounting health effects, differences in QALYs increased to 26.6 per birth cohort when comparing *Universal 15* to *Current practice*. Although incremental effect is considerably higher without discounting QALYs, the costs are the same, indicating that *Universal 15* still produces more QALYs and reduces costs compared to *Current practice*.

We did also perform an analysis of the expected value of perfect information for all parameters (data not shown) based

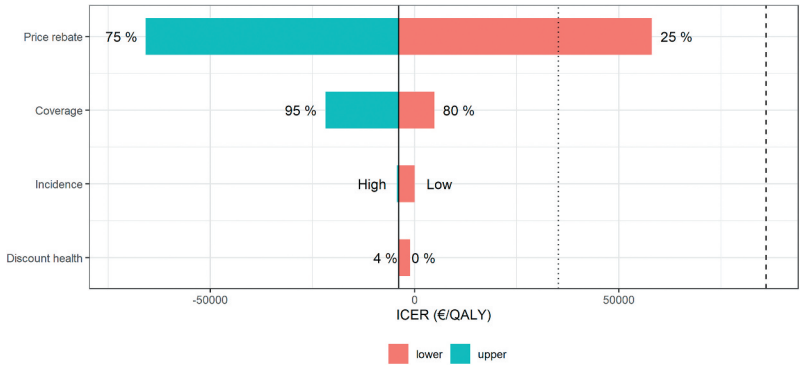

Figure 5. Tornado diagram of one-way sensitivity analysis on selected inputs with strategies *Universal 15* compared to *Current practice*. Red indicates the lower boundaries and blue the upper boundaries for sensitivity analyses of input parameters in the model. Dotted line represents the threshold for displaced health interventions of €35,000 per QALY and dashed line the willingness-to-pay threshold of €86,000 per QALY. Black solid line represents input parameters used for base case cost-effectiveness calculations in the strategy *Universal 15* (50% vaccine rebate, 90% vaccine uptake, medium IMD incidence and 2–4% discount rate). ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life-year, IMD = Invasive meningococcal disease

on methods developed by Strong and colleagues.[44] Due to the high probability of cost-effectiveness and since only the vaccine rebate was informing this probability, the graph was not informative.

Comparison of the strategies Current practice vs Universal 18

We also looked into potentially vaccinating the 18-year-olds instead of the 15-year-olds with MCV4 in a NIP-setting (*Universal 18)*, with 90% uptake and 50% rebate on the vaccine price. Compared to *Current practice*, the *Universal 18* strategy lead to an annual reduction of 3.2 hospitalizations, 0.14 sequelae, and 0.38 deaths per cohort. Lifetime QALYs gained was 8.32 and costs were reduced by €20,000, giving an ICER below zero. The intervention had a 98% probability of being cost-effective compared to C*urrent practice*, when assuming a willingness-to-pay threshold of €86,000/QALY for severe diseases (Figure 6).

The *Universal 18* strategy averted fewer IMD cases and the probability of cost-effectiveness was lower compared to the *Universal 15* strategy (Table 3). Since the *Universal 18* strategy was both more costly and less effective, the *Universal 18* strategy was "dominated" by the *Universal 15 strategy*.

Discussion

Main findings

Vaccinating the 15-year-olds with one dose of MCV4 in a NIP-setting (*Universal 15*) is 99% likely to be cost-effective compared to *Current practice* of vaccinating 18-year-olds with out-of-pocket payment, when assuming a willingness-to-pay threshold of €86,000/QALY for severe diseases in Norway. Changing from the strategy *Current practice* to *Universal 15* will prevent three hospitalizations annually, one sequelae every 5 years and one death every 2 years among the 15–23-year-olds. In addition, the intervention will be cost-saving, with a reduction in incremental costs of €30,000. Vaccine price and incidence of IMD have the greatest impact on the probability of cost-effectiveness of implementing MCV4 for the 15-year-olds in the NIP.

Vaccination of the 18-year-olds as part of the NIP (*Universal 18*) was also found to be cost-effective compared to *Current practice*. However, as the incidence rate in 15–17-year-olds was more than double that of the 20–23-year-olds, the *Universal 18* strategy was more costly and gave lower health gains than the *Universal 15* strategy. We have previously shown that the meningococcal carriage rate in Norwegian teenagers was higher in upper secondary school students (15–19-year-olds) than in lower secondary school students (12–15-year-

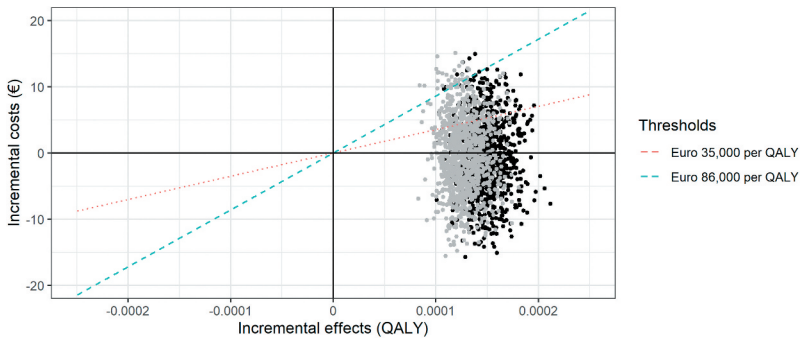

Figure 6. Scatterplot of simulations for comparing the strategies *Universal 15* and *Current practice* (black dots) versus comparing *Universal 18* and C*urrent practice* (gray dots). Dotted red line represents the threshold for displaced health interventions of €35,000 per QALY and dashed blue line the willingness-to-pay threshold of €86,000 per QALY. QALYs = quality-adjusted life-year

olds).[45] Since duration of protection from MCV4 is estimated to be at least 5 years,[26,27] and since the incidence of IMD among the 15–17-year-olds is higher than among the 20–23-year-olds, it would be advantageous to vaccinate the 15-year-olds.

There is no official explicit threshold for cost-effectiveness in Norway. We have therefore compared our results in the likely lowest and highest thresholds that would be relevant for implementing a meningococcal vaccine in the Norwegian NIP. Assuming the levels of meningococcal disease observed during the past years, universal vaccination of the 15-year-olds would be cost-effective, regardless of whether the lowest or highest threshold for cost-effectiveness are used.

Comparison with other countries

Cost-effectiveness of MCV4 vaccination of adolescents in a NIP-setting has been evaluated in a few published studies.[39,46–51] To our knowledge, our study is the first using a healthcare perspective and where the study population has not been primed with meningococcal vaccine in infancy. An Australian study using a healthcare perspective showed that introducing a booster dose of MCV4 to the 15–19-year-olds in addition to MCV4 at 12 months age would lead to an ICER above the current willingness-to-pay threshold and only a 35% probability of being cost-effective.[47] In a US study, MCV4-vaccination of 11-year-olds without a catch-up would probably exceed the willingness-to-pay thresholds adapted for other vaccines implemented in the NIP.[49] When assessing the same scenario, but with addition of a catch-up program, the intervention would be cost-effective from a societal perspective if accounting for herd immunity.[48] Similarly, a Dutch study evaluating primary vaccination with MCV4 at 14 months and a booster dose at 12 years of age showed cost-effectiveness when accounting for herd immunity.[46] In Canada, where MCVC is provided at 12 months and MCVC or MCV4 in adolescence, switching from MCVC to MCV4 among the 12-year-olds would be cost-effective when assuming herd immunity and a high IMD incidence or declining vaccine prices.[50]

Some of the aforementioned studies were highly dependent on high IMD incidence and low vaccine price for a positive result, and the majority of the studies would not reach cost-effectiveness without accounting for herd effects.[39,46–51] Teenagers and young adults have higher rates of meningococcal carriage and play an important role in transmission of the bacterium.[52] Even though herd effects have been established for meningococcal conjugate vaccines against serogroup A (MCVA)[53] and C (MCVC),[54] there is only one study to our knowledge that has indicated possible herd effects for MCV4.[28] Adding herd effects would have made our results even more cost-effective, but without changing the conclusion. The willingness-to-pay threshold for diseases with high severity such as IMD is much higher in Norway compared to many other European countries, as well as in Canada and Australia.[39,46,47,50] In the UK for example, the threshold was for many years assumed to be between £20,000/QALY and £30,000/QALY, and later reduced to £12,936/QALY.[55] In some cases with severe diseases, however, a threshold of £50,000 has been assumed. Similarly, the threshold in Norway has been estimated to about €35,000 per QALY,[43] although the government has decided to use thresholds in the range between €29,000/QALY and €86,000/QALY, depending on severity.[24,42] Applying a lower threshold in our calculations would imply a lower probability of cost-effectiveness for MCV4 vaccination of Norwegian teenagers, but would not change the conclusion that the vaccination is both increasing health and reducing costs. As the epidemiology, vaccination programs, healthcare systems, insurance policies, and willingness-to-pay thresholds are country-specific, comparison of cost-effectiveness of vaccine interventions between different countries are challenging.

Decisions regarding implementation of a meningococcal vaccine in the NIP

Cost-effectiveness analyses tend to disfavor interventions on rare and severe diseases such as IMD. Generating adequate data on the magnitude of long-term or late-onset sequelae and their impact on for example future productivity loss or the need for special education and social welfare, requires systematic and long-term follow-up of a significant number of patients.[6] More subtle sequelae such as psychiatric, psychosocial, or cognitive conditions may be difficult to capture fully and are probably underreported.[56] Indirect effects on the QoL of relatives or caregivers of IMD patients can be significant,[57] but have not commonly been included in cost-effectiveness analyses.

With high developmental costs of new and technologically advanced vaccine platforms, some new vaccines have become expensive. If the decisions on whether to implement vaccines in a NIP were solely based on the intervention being cost-effective, few of the more costly vaccines would have a chance of achieving cost-effectiveness, maybe affecting the incentive for further vaccine development against rare diseases like IMD. The challenge could partly be overcome by accepting higher willingness-to-pay thresholds for more severe conditions such as recommended in Norwegian guidelines for STA of pharmaceuticals.[23] Another measure could be to adjust for the challenges of capturing the impact of long-term sequelae by adding a QALY adjustment factor, such as done by the Joint Committee on Vaccination and Immunisation in the UK.[6] Incorporating both a healthcare and a more broad societal perspective in the models might also contribute to a more balanced calculation.[6]

Fortunately, health technology assessments for publicly financed meningococcal vaccination lean on more than economic evaluations. Other factors include societal preference and acceptability, equity in health[6,7], and feasibility of the intervention. Unexpected affliction of previously young and healthy individuals induces anxiety in the population and high media uptake. Prevention of severe diseases and especially those affecting young people have a high priority both to the public and other stakeholders.[7] Observations of a high vaccine uptake among the 18-year-olds with out-of-pocket payment in Norway[19] indicate that the acceptability of MCV4 vaccination is high. Introducing MCV4 in the NIP would promote equity in access to health and probably increase the vaccine uptake among Norwegian teenagers, as already observed in regions

sponsoring MCV4. Including MCV4 in the NIP for the 15-year-olds would easily be feasible since the framework for vaccination is already established. From a political and public health perspective, a universal vaccination program against IMD might also mitigate the unforeseen costs related to outbreak responses[10,11] and the need for rapid changes in immunization practice.[8,9]

Strengths and limitations

Cost-effectiveness studies usually apply a societal perspective, sometimes combined with a health-care perspective. Experiences from some countries indicate that including a wide range of societal costs in the analysis may be pivotal for the outcome.[6,7] By using a healthcare perspective, our model did not capture the costs and burdens of IMD fully, which might have underestimated the benefits of vaccination. However, adhering to the Norwegian government's recommendation of using a healthcare perspective makes our calculations more applicable for the Norwegian settings.

When exploring uncertainty of single parameters, the recommended choice of modeling strategy is still to use a probabilistic model, as for instance pointed out by Claxton and colleagues.[58] In essence, there are two ways to do this; the simple way shown in our tornado diagram (Figure 5) or an analysis of expected value of perfect information for parameters. We did also perform such an analysis based on methods developed by Strong and colleagues,[44] but due to high probability of the intervention being cost-effective (99%) and only one parameter informing this probability (the vaccine rebate), the graph was not informative. Instead, we included vaccine price, incidence of IMD and vaccination uptake in a tornado diagram as we believe these would be the most important parameters for Norwegian policy makers in the discussion regarding implementation of MCV4 into the NIP for teenagers. In addition, a discount rate was included since there is an ongoing discussion in Norway whether to discount health effects.[24]

For all input data, we aimed at the best possible level of detail that would also be feasible in the model. In the case of sequelae after meningococcal disease, we found good sources for occurrence of different specific sequelae. For costs, however, our best available estimate was the estimate of lifetime loss due to different sequelae combined.[39] Although these approaches to data for sequelae were clearly different, we concluded that neither introducing more detail without data on one side nor reducing detail on the other side would make the model closer to a real life setting.

Country-specific data on mortality rate, frequency, quality-of-life impact and costs of acute and long-term sequelae from IMD were unfortunately not available from Norway. Using data from other countries with different epidemiology and healthcare systems might have over- or underestimated our results.

Vaccination uptake of MCV4 among Norwegian 18–19-year-olds is currently high (48%) and might have contributed to the observed drop in IMD incidence among Norwegian teenagers since 2010. We therefore attempted to wash out the effect of this MCV4 protection financed by out-of-pocket payments, to estimate a baseline incidence to assess a naïve population in all strategies. If the lower incidence of IMD was caused by natural fluctuation or other unknown factors instead of a vaccine effect, our incidence estimates might have been too high and might imply an overestimation of cost-effectiveness.

We did not account for waning of vaccine effectiveness during the eight-year study period, which might have overestimated vaccine protection. Cost-effectiveness studies from other countries evaluating implementation of adolescent MCV4 vaccination have assumed a VE similar to that for MCVC.[39,46–51] The VE used in our model was based on assumed protection from serum bactericidal antibodies as a correlate of protection which, compared to other similar studies, might have underestimated the cost-effectiveness. However, more recent evaluations have indicated a lower VE for MCV4[59,60] compared to MCVC.

As mentioned, the present analysis was intended as an exploratory analysis to find out whether meningococcal vaccination in Norway *could be* cost-effective. We therefore constructed a simpler Markov model instead of a more complex dynamic model. Since the intervention proved to be cost-effective in a Markov model, adding indirect effects would probably not change the conclusion of this study as such effects typically would avert even more IMD cases.

Conclusions

IMD is a rare, but highly severe disease striking young and previously healthy individuals unexpectedly. The benefits of meningococcal vaccination are high and risks of adverse events low. In a NIP-setting in Norway, vaccinating the 15-year-olds with one dose of MCV4 would be more cost-effective than vaccinating the 18-year-olds, but vaccination at either age has a high probability of being cost-effective, assuming a high vaccination uptake and a rebate on the vaccine price in a national tender. Implementing MCV4 in the NIP free of charge would contribute to better equity in health and comply with both public and political desire. Future health economic evaluations should strive to obtain Norwegian data on the frequency, impact, and costs of short- and long-term sequelae in survivors of IMD. Furthermore, exploring the costs from a societal perspective and using a more complex and dynamic model to assess the impact of herd effects should be considered, especially if assessing cost-effectiveness of the more expensive meningococcal B vaccines.

Authors contributions

SVW, LMN, DAC, GT, and TW initiated and designed the study. SVW drafted the manuscript. TW performed economic calculations. All authors contributed to the interpretation of the data, to writing and revising the manuscript, and to approval of the final manuscript. All authors attest they meet the ICMJE criteria for authorship.

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Disclosure statement

The authors declare that there are no conflicts of interest.

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