Vaccine 33 (2015) 268–275

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Evaluation of serogroup C and ACWY meningococcal vaccine programs: Projected impact on disease burden according to a stochastic two-strain dynamic model☆

David M. Vickers[a,b], Andrea M. Anonychuk[c,d], Philippe De Wals[e], Nadia Demarteau[c], Chris T. Bauch[b,f,g,*]

[a] Computational Epidemiology and Public Health Laboratory, University of Saskatchewan, Saskatoon S7N 5C9, Canada
[b] Pythagoras Consulting, Guelph N1H 2L3, Canada
[c] GlaxoSmithKline Vaccines, 1300 Wavre, Belgium
[d] Abbott Laboratories, Diagnostics Division, Abbott Park, IL 60064, USA
[e] Department of Social and Preventive Medicine, Laval University, Quebec City G1V 0A6, Canada
[f] Department of Mathematics and Statistics, University of Guelph, Guelph N1G 2W1, Canada
[g] Department of Applied Mathematics, University of Waterloo, Waterloo N2L 3G1, Canada

ARTICLE INFO

Article history:
Received 22 January 2013
Received in revised form 9 September 2013
Accepted 18 September 2013
Available online 6 October 2013

Keywords:
Dynamic model
Neisseria meningitidis
Meningococcal vaccines
Invasive meningococcal disease
Immunization programs
Stochastic model
Strain replacement

ABSTRACT

Objective: Advisory committees in Canada and the United States have updated recommendations for quadrivalent meningococcal conjugate vaccines against serogroups A, C, W135, and Y. Our objective was to evaluate optimally effective meningococcal vaccination policies using a stochastic dynamic model. Canada was used as an example.
Methods: Our stochastic dynamic model of *Neisseria meningitidis* (*Nm*) transmission in an age-structured population assumed partial cross-immunity among two aggregated serogroup categories: 'AWY' containing A, W135, and Y; and 'Other' containing B, C, and ungroupable types. We compared the impact of monovalent C versus quadrivalent ACWY vaccination on *Nm* carriage and invasive meningococcal disease (IMD). Our model was parameterized with Canadian epidemiological and demographic data and employed probabilistic sensitivity analysis.
Results: Routine infant immunization at 12 months and boosting at 15 years with a quadrivalent vaccine is projected to have the largest impact on total IMD incidence: a 74% reduction over 40 years. Routine infant immunization with a monovalent vaccine at 12 months only has much less impact and also generates strain replacement appearing after approximately ten years of continuous use.
Conclusions: Immunizing infants at 12 months and boosting adolescents at 15 years with an ACWY vaccine is predicted to be most effective at reducing IMD incidence.

1. Introduction

Neisseria meningitidis (*Nm*) is an important cause of meningitis and septicemia worldwide [1]. Although the epidemiology of invasive meningococcal disease (IMD) varies globally, nearly all disease is caused by serogroups A, B, C, W135, X, and Y [2]. While devastating epidemics of IMD continually occur in the 'meningitis belt' of sub-Saharan Africa, elsewhere (e.g., Europe, the United States, and Canada), IMD incidence is less than 10 per 100,000 population per year [2,3].

Despite the public health importance of *Nm* as a pathogen, it is widely regarded as a commensal of the respiratory tract [3]. IMD is a rare consequence of infection that occurs when *Nm* bacteria colonizing the mucosal surfaces of the nasopharynx penetrate the mucosal tissue and invade the bloodstream, causing meningitis and fulminant septicemia [3] or other complications [4]. In Europe and North America, the peak of carriage is observed in teenagers and young adults, and the peak of disease in young infants, with a second peak of lower magnitude in teenagers [1]. Asymptomatic nasopharyngeal infections engender development of immunity both at the individual level (direct protection) and the population level (herd protection). However, the exact nature and mechanisms of naturally acquired immunity are not completely understood [5].

* Corresponding author at: Department of Applied Mathematics, University of Waterloo, 200 University Avenue West, Waterloo, Ontario N2L 3G1, Canada. Tel.: +1 519 888 4567x32250; fax: +1 519 837 0221.
E-mail address: cbauch@uwaterloo.ca (C.T. Bauch).

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http://dx.doi.org/10.1016/j.vaccine.2013.09.034

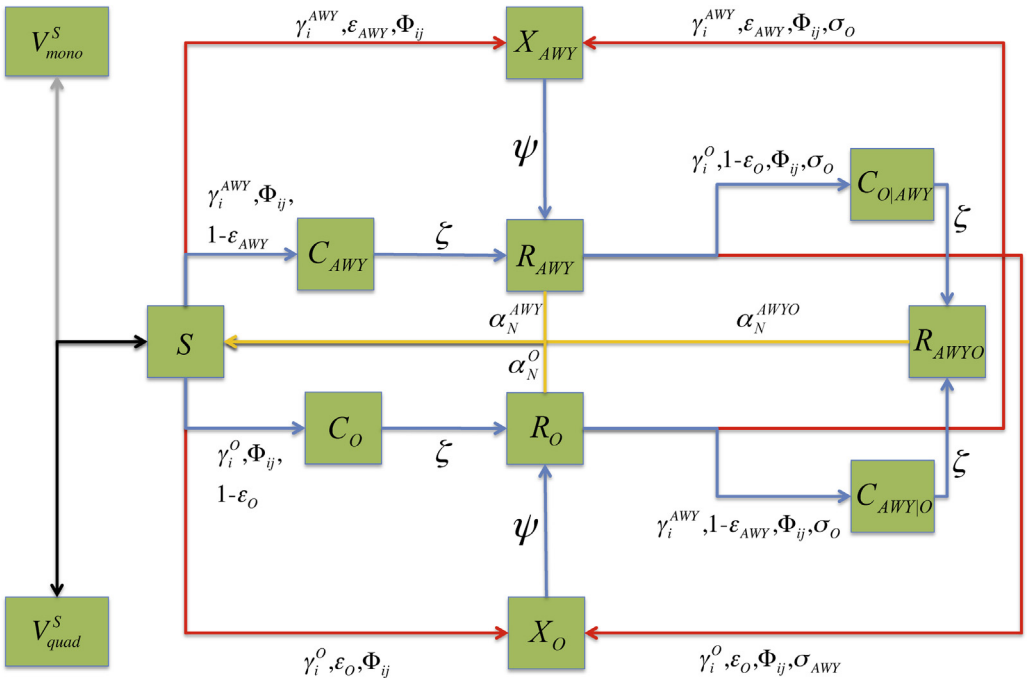

Fig. 1. Model diagram. S: susceptible; C_{AWY} (C_O): carrying 'AWY' ('Other'); $C_{AWY;O}$ ($C_{O;AWY}$): carrying 'AWY' while immune to 'Other' ('Other' while immune to 'AWY'); R_{AWY} (R_O, R_{AWYO}): immune to 'AWY' ('Other', both); X_{AWY} (X_O): IMD due to 'AWY' ('Other'); V^S_{mono} (V^S_{quad}): vaccine immunity due to C vaccine (ACWY vaccine); blue transitions represent infection and recovery to natural immunity; yellow represents loss of natural immunity; red transitions represent development of IMD; black represents development of vaccine immunity or loss of vaccine immunity for the ACWY vaccine; gray represents development of vaccine immunity or loss of vaccine immunity for the C vaccine; green represents recovery from IMD to a state of natural immunity. Corresponding parameters occur next to each arrow; see Supplementary File, Tables S1 and S2 for details.

Current control strategies are aimed at reducing transmission, preventing IMD, and enhancing host resistance [4]. Recent progress in preventing and controlling IMD has benefitted from the introduction of monovalent conjugate vaccines against serogroup C. Since being adopted, many countries have experienced a substantial decline in serogroup C disease [2]. Since 2001, Canada's National Advisory Committee on Immunization (NAC) has recommended meningococcal C conjugate vaccine ('C vaccine') for infants through to young adults. This has significantly reduced serogroup C IMD incidence, especially in populations where vaccine uptake was early and widespread [6].

However, concerns have arisen over vaccine-induced 'strain replacement', where control of one serogroup creates an empty ecological niche than can be filled by other serogroups [7]. Multivalent vaccines may potentially be more likely to prevent strain replacement. In 2007, NACI recommended use of quadrivalent conjugate meningococcal vaccines for serogroups A, C, Y and W135 ('ACWY vaccine') for the control of outbreaks caused by A, Y, or W135; close contacts of IMD cases caused by these serogroups; immunization of those aged 2–55 years in certain high-risk groups; and routine immunization of adolescents in jurisdictions where local epidemiology warrants it [8].

The unpredictable nature of IMD outbreaks and its rapidly progressing symptoms create significant public concern as well as disease management challenges. Moreover, herd immunity is thought to be important in *Nm* epidemiology [6] and routine and outbreak interventions are costly, meaning decision-makers must consider competing healthcare priorities. Under these circumstances, dynamic models can help us understand the complexity of *Nm* epidemiology and the impact of policy decisions regarding meningococcal vaccines.

Several seminal dynamic models have enhanced our understanding of *Nm* disease dynamics [2,3,9,10]. However, multi-strain *Nm* transmission models, as needed to predict strain replacement, are rare [3]. Here, we develop a dynamic model to study the potential impact of a quadrivalent ACWY vaccine compared to a monovalent C vaccine. The Canadian setting was selected based on availability of data to calibrate the model.

2. Methods

2.1. Model

Our stochastic two-strain model allows us to capture the effect of meningococcal vaccination on *Nm* epidemiology in a heterogeneous bacterial population where infection confers partial cross-protection. The model aggregates multiple serogroups into two larger groups: one contains A, W135, and Y ('AWY'), while the other contains B, C, and all other serogroups ('Other'). Aggregating kept the number of model equations at a manageable level, which is particularly important when natural immunity and cross-protection are included. We explored the impact of grouping using sensitivity analysis.

The population is subdivided into discrete age classes (<1 year, 1 year, 2 years, 3 years,. . ., 19 years, 20–29 years, 30–39 years,. . ., 50–59 years, 60+ years). The first twenty age classes are individual birth cohorts and the last 5 age classes are aggregates of ten consecutive birth cohorts. At the end of each year, individuals in the first twenty age classes move to the next highest age class, whereas one-tenth of individuals in each of the five aggregated age classes move to the next highest age class. Newly born individuals enter the <1 age class. Individuals are removed each year according to age-specific all-cause mortality rates.

The model incorporates disease transmission mechanisms, including age-specific contact rates. In the model diagram (Fig. 1), compartment S is the number of susceptible individuals, C_{AWY} is the number infected by (carrying) serogroups A, W135, or Y ('AWY'), C_O is the number carrying 'Other' serogroups, and X_{AWY} and X_O are the number of individuals with invasive meningococcal

disease (IMD) attributable to 'AWY' or 'Other' respectively. 'AWY' and 'Other' compete for the same pool of susceptible hosts, creating the potential for strain replacement once immunization is introduced. We assumed that carriage of one group fully protects against co-infection by the other group [3].

Many individuals who clear *Nm* infection appear to have some degree of natural immunity [5]. Therefore we define R_{AWY} and R_O as the number of individuals who have cleared infection and have natural immunity to 'AWY' and 'Other' respectively. We moreover assumed that natural immunity to one group reduces susceptibility to future infection by the other group, due to partial cross-protection [5,11,12]; σ_{AWY} is the relative susceptibility to 'AWY' infection for an individual with natural immunity to 'Other' due to previous infection by 'Other'. Thus, $\sigma_{AWY} = 1$ corresponds to complete cross-immunity, whereas $\sigma_{AWY} = 0$ corresponds to none. σ_O is defined similarly.

$C_{O|AWY}$ and $C_{AWY|O}$ are the number of individuals carrying 'Other' (respectively, 'AWY') who previously cleared infection by 'AWY' (respectively, 'Other'), and R_{AWYO} is the number of individuals who have cleared infection and have natural immunity to both groups of strains. We assume the duration of carriage is constant across serogroup and age.

V_{mono} is the number of individuals with vaccine-generated immunity to infection by 'Other' (due to C vaccine) and V_{quad} is the number of individuals with vaccine-generated immunity to infection by 'Other' or 'AWY' (due to the ACWY vaccine). We assume vaccine immunity works in all-or-none fashion; the vaccine provides no additional protection against IMD, above and beyond protection against infection; in other words, for a vaccine efficacy of 97%, 97% of those vaccinated will not contract IMD or carry the pathogen, but 3% of those vaccinated are as likely to develop IMD upon infection as an unvaccinated person. We also assumed that natural and vaccine-induced immunity affect carriage acquisition but not its duration.

The C vaccine only protects against infection (both carriage and IMD) by serogroup C. Hence, vaccine efficacy against infection by 'Other' was assumed to be partial, and was determined by weighting the vaccine efficacy against C by the relative proportion of IMD caused by C, B and other non-groupable *Nm* bacteria. This left a proportion of individuals in the susceptible compartment to account for B infections. Vaccine efficacy for ACWY vaccine against infection (both carriage and IMD) was weighted similarly since it does not protect against infection by serogroup B. Efficacious vaccination with the C vaccine was assumed to provide no protection against infection by 'AWY', hence, those compartments were treated as fully susceptible with respect to 'AWY' infection. However, individuals efficaciously vaccinated with ACWY vaccine were protected against both 'AWY' and 'Other'.

The model was updated in discrete time steps. A description of the state transitions appears in Table S1 of the Supplementary File. Both entrance into the carriage state and acquisition of IMD were modeled as stochastic processes, with number of stochastic transitions per time step sampled from a binomial distribution [13], while all other transitions were modeled deterministically. We analyzed a variant where all transitions were stochastic to confirm that the dynamics were unchanged. The model was coded in Matlab R2011a, and the code is provided in the Supplementary Files.

2.2. Parameterization and model calibration

Parameter values were derived from epidemiological literature or calibrated, except for the duration of natural immunity for which a baseline assumption of two years was made (Supplementary File: Table S2) [1,14–26]. Each parameter value associated with the natural history of infection or vaccination was estimated from key epidemiological or review articles in the available literature between 1985 and 2011 [17,22].

Age-specific susceptibility to infection (γ_i^{AWY} and γ_i^{O}) and degree of pathogenicity (ε_O and ε_{AWY}) were estimated through model calibration to available IMD case notification and carriage prevalence data (Supplementary File: Tables S2 and S3). The total transmission rate is the product of age-specific contact rates Φ_{ij} [26], age-specific susceptibility γ_i, and a constant transmission rate coefficient β (see Supplementary File for details).

To evaluate the impact of data uncertainty, triangular distributions were assumed for the least certain parameters: the calibrated degree of pathogenicity (ε_O and ε_{AWY}), calibrated degree of susceptibility to infection (γ_i^{AWY} and γ_i^{O}), rate of loss of natural immunity (α_N^{O}, α_N^{AWY} and α_N^{AWYO}), and strength of cross-protection (σ_{AWY} and σ_O).

A large number of Monte Carlo realizations were simulated: for each realization, parameter values were drawn from these distributions and the model was simulated with these parameter values. The projected IMD incidence and prevalence of carriage due to 'Other' and 'AWY' were generated in 5-year age groups (0–4, 5–9, 10–14, 15–19 and 20+). Minimum and maximum acceptable IMD incidence and carriage prevalence due to 'Other' and 'AWY' were defined for each of these age groups. Any parameter set giving rise to projections falling outside of one or more of the 20 acceptability ranges was rejected. The 400 surviving parameter sets (out of ~40,000 tested) were used to generate model results. Acceptability ranges and triangular distribution bounds appear in Supplementary File: Tables S2 and S3.

2.3. Vaccine scenarios

Vaccination was administered under ten scenarios (Table 1). Assuming a country with a C vaccine program already in place, all scenarios used the C vaccine exclusively in the first 10 years of the program (from $t = 40$ to 49 years). At $t = 50$ years, the 'status quo' scenarios 1 and 2 continue with the same program, but scenarios 3–10 involve a change in vaccine type and/or protocol. This involved switching at least one dose from C vaccine to ACWY vaccine (scenarios 3–6, 9, 10), adding a booster dose at age 12 or 15 years (scenarios 5–10), or both (scenarios 5, 6, 9, 10). Based on recent coverage rates in Quebec [27,28], infant vaccination coverage was 90% and adolescent coverage was 80%.

Table 1
The ten vaccine scenarios examined. 'C' = monovalent C vaccine, 'ACWY' = quadrivalent ACWY vaccine.

Scenario	Simulation time at which vaccination is introduced (year) and age of vaccination	
	$t = 40$	$t = 50$
1	C at 12 months	C at 12 months
2	C at 12 years	C at 12 years
3	C at 12 months	ACWY at 12 months
4	C at 12 years	ACWY at 12 years
5	C at 12 months	ACWY at 12 months + ACWY at 12 years
6	C at 12 months	ACWY at 12 months + ACWY at 15 years
7	C at 12 months	C at 12 months + C at 12 years
8	C at 12 months	C at 12 months + C at 15 years
9	C at 12 months	C at 12 months + ACWY at 12 years
10	C at 12 months	C at 12 months + ACWY at 15 years

3. Results

Introducing either vaccine has a marked effect on *Nm* epidemiology. Introducing C vaccine at 12 months of age (scenario 1) quickly causes a decline in prevalence of carriage of 'Other' (Fig. 2a and Table 2) as well as IMD incidence due to 'Other' serogroups (Fig. 2b).

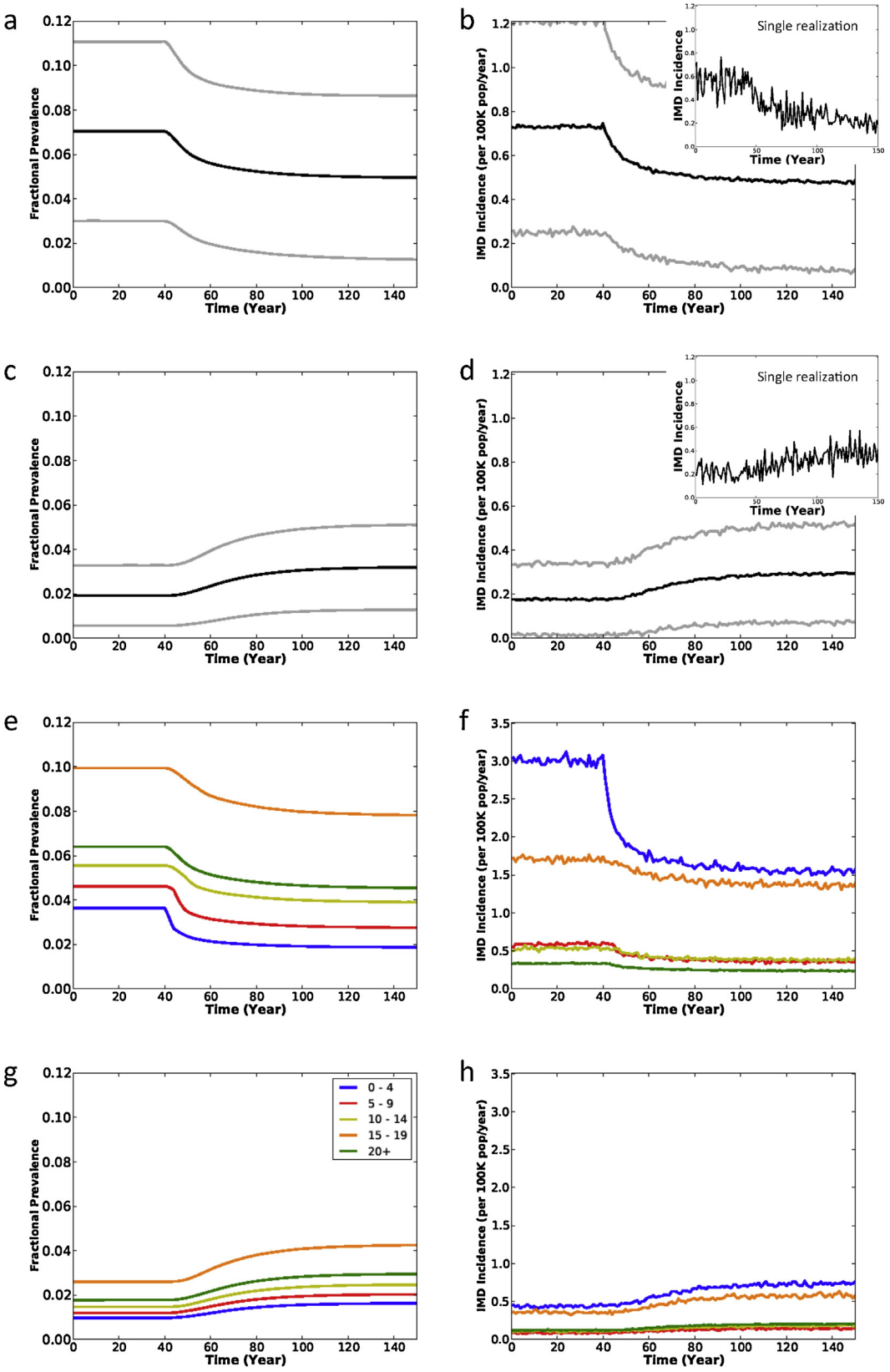

Fig. 2. Model projections for scenario 1: infant only vaccination using the C vaccine, starting at $t = 40$ years. (a) Overall prevalence of *Nm* carriage due to 'Other', (b) overall incidence of IMD due to 'Other', (c) overall prevalence of *Nm* carriage due to 'AWY', (d) overall incidence of IMD due to 'AWY', (e) age-stratified prevalence of *Nm* carriage due to 'Other', (f) age-stratified incidence of IMD due to 'Other', (g) age-stratified prevalence of *Nm* carriage due to 'AWY', (h) age-stratified incidence of IMD due to 'AWY'. For plots (a–d), black lines represent the average of 400 Monte Carlo realizations, while the gray lines bound 2 standard deviations, but insets in subpanels (b) and (d) show results for a single Monte Carlo realization. For plots (e–h), lines represent the average of 400 Monte Carlo realizations among those age 0–4 years (blue line), 5–9 years (red line), 10–14 years (yellow line), 15–19 years (orange line), and ≥20 years (green line). The carriage time series appears smooth because we present the average of many stochastic realizations.

Table 2
Projected total IMD incidence under all vaccine program scenarios and across all age classes.[a]

Scenario	$t=40$	$t=50$	$t=60$	$t=75$	$t=90$
1	0.92 (0.45, 1.4)	0.77 (0.38, 1.17)	0.77 (0.36, 1.17)	0.77 (0.36, 1.17)	0.76 (0.35, 1.17)
2	0.91 (0.45, 1.36)	0.78 (0.37, 1.19)	0.78 (0.36, 1.19)	0.79 (0.36, 1.23)	0.79 (0.35, 1.23)
3	0.9 (0.44, 1.36)	0.78 (0.37, 1.19)	0.66 (0.27, 1.05)	0.62 (0.25, 0.99)	0.6 (0.24, 0.97)
4	0.9 (0.44, 1.36)	0.78 (0.36, 1.21)	0.65 (0.26, 1.04)	0.6 (0.19, 1.01)	0.59 (0.15, 1.02)
5	0.9 (0.44, 1.36)	0.78 (0.39, 1.17)	0.46 (0.13, 0.79)	0.33 (0, 0.65)	0.3 (−0.04, 0.63)
6	0.9 (0.44, 1.36)	0.77 (0.38, 1.16)	0.39 (0.11, 0.67)	0.26 (−0.01, 0.54)	0.23 (−0.06, 0.52)
7	0.91 (0.45, 1.36)	0.77 (0.36, 1.17)	0.66 (0.3, 1.02)	0.67 (0.27, 1.06)	0.67 (0.29, 1.05)
8	0.9 (0.43, 1.36)	0.77 (0.37, 1.18)	0.62 (0.27, 0.97)	0.64 (0.28, 1)	0.65 (0.28, 1.03)
9	0.9 (0.43, 1.37)	0.77 (0.38, 1.16)	0.53 (0.22, 0.85)	0.44 (0.11, 0.77)	0.42 (0.05, 0.8)
10	0.9 (0.46, 1.34)	0.76 (0.38, 1.15)	0.47 (0.18, 0.76)	0.39 (0.06, 0.72)	0.37 (0.03, 0.72)

[a] IMD incidence (per 100,000 population per year) due to 'Other' or 'AWY' serogroups at $t=40$, 50, 60, 75, and 90 years, with average and ± two standard deviations of 400 stochastic realizations.

This decline is particularly strong and rapid in 0–4 year-olds, but is also observed in other ages also due to herd immunity (Fig. 2e and f).

However, C vaccine causes strain replacement: both IMD incidence and carriage prevalence due to 'AWY' increase after vaccine introduction (Fig. 2c and d and Table 3), and this occurs across all ages (Fig. 2g and h). However, the increase in 'AWY' IMD is delayed relative to the sudden decrease in 'Other' IMD: while IMD incidence due to 'Other' decreases immediately after introduction of C vaccine ($t=40$ years), IMD incidence due to 'AWY' does not begin to increase significantly until 10 years later ($t=50$ years) and it takes longer to reach equilibrium. Moreover, in a single model realization, this effect is not obvious until much later than $t=50$ years, due to the stochastic nature of IMD outbreaks (Fig. 2b and d insets). Hence, the model suggests that there will be a significant delay before we observe evidence of A, W135, or Y strain replacement in IMD case notifications (~10 years after C vaccination becomes widespread) although changes in carriage prevalence might be noticed sooner. This is consistent with Canadian data over the past ten years [6].

Despite strain replacement, total IMD incidence is lower under a C vaccine program providing a single dose at 12 months (scenario 1). However, these declines are relatively modest: total IMD incidence declines from 0.92 to 0.76/100,000/year over the long term (Table 2). In contrast, total IMD incidence declines much more significantly when switching to ACWY vaccine at $t=50$ years and adding a second dose at 12 years of age (scenario 5): from 0.9 to 0.3/100,000/year over the long term (Table 2). Strain replacement is also prevented (Fig. 3).

As expected, strategies with multiple-scheduled vaccinations and/or CAWY vaccine were most effective. Model predictions for these strategies extend the general picture emerging from the comparison of Figs. 2 and 3 (Tables 2 and 3). Scenarios that add a booster dose at 12/15 years and switch to ACWY vaccine for adolescent immunization and possibly also infant immunization reduce total IMD incidence the most, as well as IMD incidence due to 'AWY' and 'Other' individually (scenarios 5, 6, 9, 10: Tables 2 and 3). The best overall approach is adding a booster dose at age 15 and switching to ACWY vaccine for both infants and adolescents (scenario 6). Scenarios that switch to ACWY vaccine without adding a second dose at 12/15 years (scenarios 3, 4), or continue with C vaccine but add a second dose at 12/15 years (scenarios 7, 8), moderately reduce IMD incidence. Finally, scenarios that simply continue with a single dose of C vaccine (scenarios 1, 2) are least effective. Also, scenarios continuing with C vaccine (scenarios 1, 2, 7, 8) always cause 'AWY' strain replacement in the long-term (Table 3). Scenarios that continue with a single dose but switch to ACWY vaccine (scenarios 3, 4) also cause strain replacement, but it is slight and long-term (Table 3).

Age-specific projections for 'Other' and 'AWY' IMD incidence for scenario 6 are available in Supplementary File: Table S4. Vaccine impacts are most evident in vaccinated age groups, but indirectly benefit non-vaccinated age groups due to herd immunity (see also Figs. 2 and 3).

To explore the impact of aggregating serogroups, we simulated three ACWY vaccine scenarios using the alternative grouping A, C, W135, Y ('ACWY') versus B and all other serogroups ('Other'). Predictions are qualitatively unchanged, with all programs reducing net IMD incidence, and with similar relative effectiveness (Supplementary File: Tables S5 and S6 and Fig. S1). Limited type B strain replacement occurs, but is offset by steep declines in IMD due to A, C, W135, and Y. The relative increase in B and ungroupable prevalence is small – compared to the significant relative decrease in C, A, W and Y prevalence – simply because C, A, W and Y are much less prevalent than 'Other' serogroups. Hence the ecological niche that opens up for B and ungroupable serogroups when C, A, W and Y are removed is relatively small.

4. Discussion

Our stochastic, two-strain dynamic model predicted that switching from a monovalent C vaccine to a quadrivalent ACWY vaccine while also adding a second dose to the immunization schedule at 12 or 15 years of age provides the best long-term reductions in total IMD incidence and prevents strain replacement to a greater extent than continuing with a monovalent C vaccine program.

Continuing with the current program of a single dose of C vaccine provided the smallest reductions, and also induced strain replacement of A, W135 and Y. However, this should not be observed until at least 10 years after vaccination becomes widespread. This is due to stochasticity, which masks the early effects of replacement in IMD data, though not necessarily in carriage data, which are less subject to stochasticity (Fig. 2d, inset). In recent years, there is evidence of replacement at the carriage level but not at the disease level [6,29], which is consistent with these predictions. However, we note there have been no confirmed examples of strain replacement at the time of publication.

Widespread strain replacement occurred with pneumococcal vaccines, which stimulated the inclusion of more serogroups in pneumococcal vaccines. However, the effect of pneumococcal strain replacement on disease was highly variable, being much more pronounced for some serotypes than others. Here, we did not explicitly allow serogroups to vary in their ability to cause strain replacement, although some variability naturally emerged out of the model's transmission mechanisms. It remains to be seen whether strain replacement will unfold for *Nm* vaccines, but the similar biology of *Nm* and *Streptococcus pneumonia*, together with our model projections, suggest it would not be surprising.

Both vaccines are predicted to provide significant herd immunity, despite short-lived vaccine immunity. Under the alternative grouping A, C, W, Y versus B, ungroupable types, the ACWY vaccine reduced ACWY IMD incidence to almost zero (Fig. S1) and results

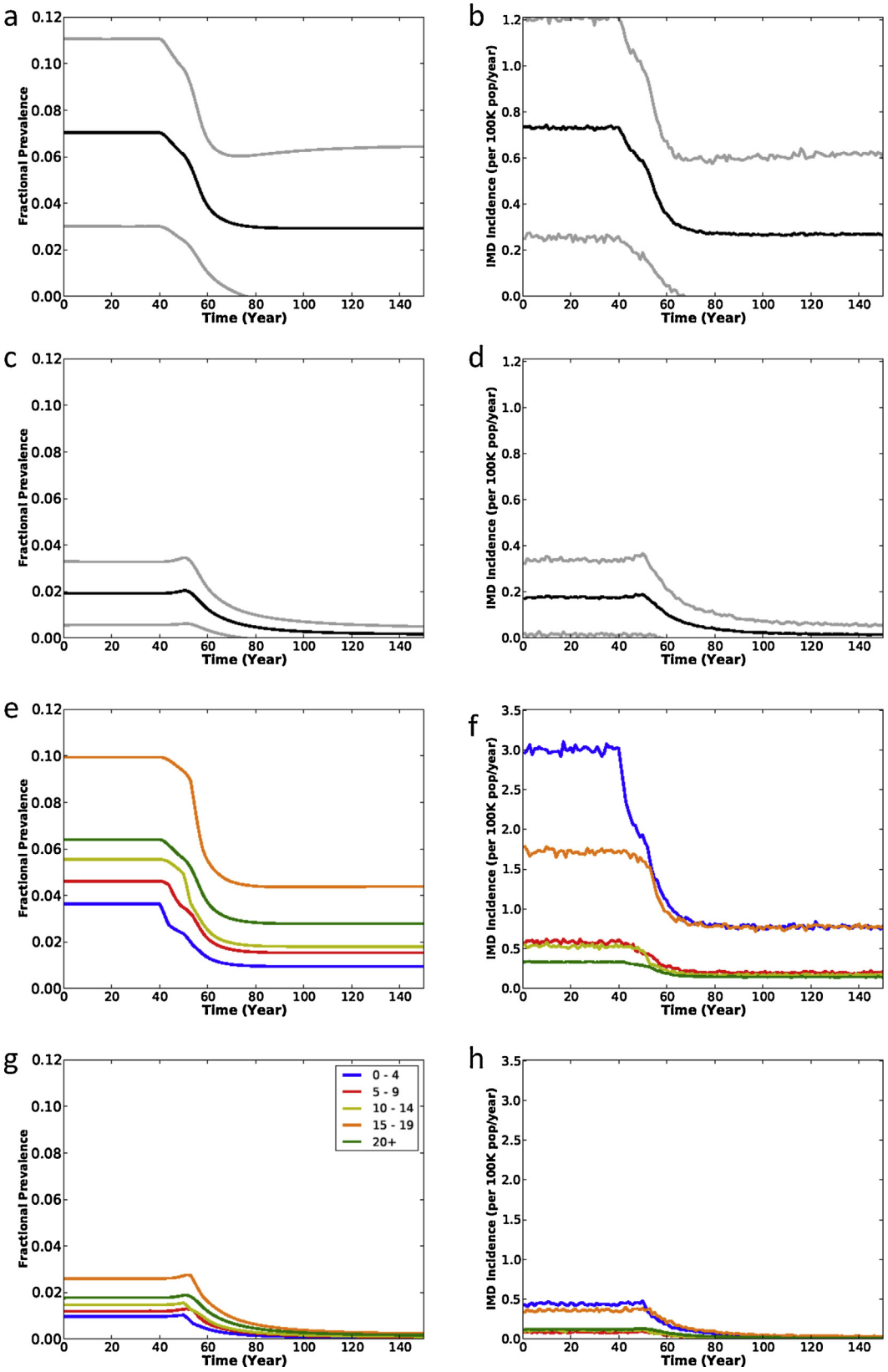

Fig. 3. Model projections for scenario 5: vaccination of infants at 12 months, using the C vaccine (at $t = 40–49$ years), then infant vaccination with adolescent booster at 12 years using the ACWY vaccine (at $t = 50$ years). (a) Overall prevalence of *Nm* carriage due to 'Other', (b) overall incidence of IMD due to 'Other', (c) overall prevalence of *Nm* carriage due to 'AWY', (d) overall incidence of IMD due to 'AWY', (e) age-stratified prevalence of *Nm* carriage due to 'Other', (f) age-stratified incidence of IMD due to 'Other', (g) age-stratified prevalence of *Nm* carriage due to 'AWY', (h) age-stratified incidence of IMD due to 'AWY'. For plots (a–d), black lines represent the average of 400 Monte Carlo realizations, while the gray lines bound 2 standard deviations. For age-stratified plots (e–h), lines represent the average of 400 Monte Carlo realizations among those age 0–4 years (blue line), 5–9 years (red line), 10–14 years (yellow line), 15–19 years (orange line), and ≥20 years (green line). The carriage time series appears smooth because we present the average of many stochastic realizations.

Table 3
Projected total IMD Incidence due to 'Other' and 'AWY' infections, under all vaccine program scenarios and across all age classes.[a]

Scenario	$t=40$	$t=50$	$t=60$	$t=75$	$t=90$
Other					
1	0.74 (0.24, 1.25)	0.58 (0.18, 0.99)	0.55 (0.14, 0.95)	0.51 (0.11, 0.91)	0.49 (0.89, 0.09)
2	0.73 (0.26, 1.21)	0.58 (0.18, 0.99)	0.53 (0.12, 0.94)	0.5 (0.09, 0.9)	0.47 (0.07, 0.86)
3	0.72 (0.24, 1.21)	0.59 (0.17, 1.01)	0.5 (0.12, 0.89)	0.49 (0.11, 0.88)	0.5 (0.12, 0.88)
4	0.73 (0.26, 1.2)	0.59 (0.17, 1.01)	0.5 (0.12, 0.88)	0.49 (0.09, 0.89)	0.5 (0.07, 0.93)
5	0.73 (0.26, 1.2)	0.59 (0.19, 0.99)	0.36 (0.04, 0.67)	0.28 (−0.04, 0.59)	0.27 (−0.06, 0.6)
6	0.73 (0.25, 1.21)	0.58 (0.19, 0.98)	0.3 (0.03, 0.58)	0.22 (−0.05, 0.49)	0.2 (−0.08, 0.48)
7	0.73 (0.26, 1.2)	0.58 (0.17, 1)	0.42 (0.08, 0.75)	0.32 (−0.01, 0.65)	0.27 (−0.03, 0.56)
8	0.73 (0.24, 1.21)	0.59 (0.17, 1)	0.37 (0.06, 0.68)	0.26 (−0.02, 0.55)	0.22 (−0.05, 0.49)
9	0.73 (0.24, 1.22)	0.58 (0.19, 0.97)	0.38 (0.08, 0.67)	0.3 (−0.01, 0.62)	0.29 (−0.05, 0.62)
10	0.72 (0.27, 1.18)	0.58 (0.18, 0.99)	0.33 (0.05, 0.61)	0.26 (−0.04, 0.56)	0.23 (−0.07, 0.54)
AWY					
1	0.18 (0.01, 0.34)	0.19 (0.02, 0.36)	0.22 (0.03, 0.41)	0.25 (0.05, 0.45)	0.27 (0.05, 0.49)
2	0.17 (0.02, 0.33)	0.19 (0.02, 0.37)	0.24 (0.05, 0.44)	0.3 (0.08, 0.52)	0.32 (0.1, 0.54)
3	0.18 (0.01, 0.34)	0.19 (0.03, 0.35)	0.15 (0.01, 0.3)	0.13 (−0.01, 0.26)	0.1 (−0.03, 0.24)
4	0.17 (0.02, 0.33)	0.2 (0.02, 0.37)	0.15 (0.01, 0.3)	0.11 (−0.01, 0.23)	0.08 (−0.03, 0.2)
5	0.17 (0.01, 0.33)	0.19 (0.01, 0.37)	0.1 (0, 0.21)	0.05 (−0.02, 0.12)	0.03 (−0.03, 0.08)
6	0.17 (0.01, 0.34)	0.19 (0.02, 0.35)	0.09 (−0.01, 0.19)	0.04 (−0.03, 0.11)	0.02 (−0.03, 0.08)
7	0.18 (0.02, 0.34)	0.18 (0.01, 0.35)	0.24 (0.04, 0.44)	0.35 (0.1, 0.6)	0.4 (0.13, 0.67)
8	0.17 (0.02, 0.33)	0.19 (0.02, 0.35)	0.25 (0.04, 0.46)	0.38 (0.12, 0.64)	0.43 (0.16, 0.71)
9	0.17 (0.02, 0.33)	0.19 (0.02, 0.36)	0.16 (0.01, 0.3)	0.14 (−0.01, 0.28)	0.14 (−0.03, 0.3)
10	0.18 (0.02, 0.34)	0.18 (0.02, 0.35)	0.14 (0.01, 0.27)	0.13 (−0.03, 0.3)	0.14 (−0.05, 0.33)

[a] IMD incidence (per 100,000 population per year) due to 'Other' serogroups at $t=40$, 50, 60, 75, and 90 years, with average and ± two standard deviations of 400 stochastic realizations.

are similar with a monovalent C vaccine. This is consistent with the Canadian experience of significant reductions in IMD due to serogroup C after expanding vaccination coverage with a C vaccine [6].

Our model makes several simplifying assumptions that warrant discussion. For instance, almost all models of multivalent vaccines assume some level of aggregation of different strains [30,31]. Our model combined B and ungroupable serogroups in the 'Other' category. Hence, the baseline model could not capture potential serogroup B strain replacement caused by C and ACWY vaccines. However, our sensitivity analysis using the alternative grouping explored this, finding no qualitative change in our prediction of ACWY vaccine impact. The robustness of our results to aggregation may be rooted in the fact that serogroup B tends to be less pathogenic on average than A, C, W135 and Y (Supplementary File: Fig. S2). Hence, using an ACWY vaccine replaces more pathogenic serogroups with a less pathogenic serogroup, which should always result in net reductions in IMD incidence.

Aggregating tends to create an artificial 'superbug' that is harder to eradicate in model simulations that the real-world individual serogroups would be [32]. Also, we included short-lived natural immunity, which lessens the predicted impact of vaccines compared neglecting natural immunity [33]. Hence, our results may be conservative with respect to vaccine impact. Finally, we assumed the vaccine provides high protection against carriage. However, less is known about meningococcal vaccine efficacy against carriage, in contrast to the vaccine's demonstrated efficacy against IMD. Another interesting aspect that we did not explore in this paper is population attitudes toward meningococcal vaccines and how they influence vaccine uptake.

Our model is stochastic, allowing it to capture the intermittent, outbreak nature of IMD. Future research may support model validation by testing the model against IMD outbreak data. This would also allow including outbreak control costs in future economic analyses, which have largely been ignored to date.

The epidemiology of meningococcal disease is characterized by endemicity associated with a large variety of different clones, and outbreaks of variable duration caused by a virulent clone. Environmental factors may play a role in these features, or this may occur due to endogenous epidemiological effects [3]. In either case, such factors may need to be accounted for in any model focusing specifically on the nature of IMD outbreaks.

Currently, only meningococcal conjugate vaccines against serogroup C are in widespread use, although ACWY adolescent vaccination is being adopted in many provinces. Our results suggest that immunization programs employing quadrivalent ACWY meningococcal vaccines instead may have a much greater impact on IMD incidence. Additionally, epidemiologic simulations should be followed by economic evaluations, which are required for decision-making regarding new vaccination programs [34].

5. Conclusion

Switching from a monovalent C vaccine to a quadrivalent ACWY vaccine in infants while also adding a second dose of ACWY vaccine at 12 or 15 years of age is predicted to provide the best long-term reductions in total IMD incidence, and prevents strain replacement to a greater extent than continuing with a monovalent C vaccine program.

Conflict of interest

DV was an employee of Pythagoras Consulting. AA is a former employee of GlaxoSmithKline group of companies. PDW has received research grants, honoraria and reimbursement of travel expenses from the GlaxoSmithKline group of companies, Novartis, Pfizer, Merck and Sanofi Pasteur. ND is an employee of the GlaxoSmithKline group of companies and has stock option in the GlaxoSmithKline group of companies. CTB has received consulting and research contracts from GlaxoSmithKline Biologicals SA. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Authorship contribution

All authors contributed to conception and design of the study, or acquisition of data, or analysis and interpretation of data; and drafting the article or revising it critically for important intellectual

content. All authors saw and approved the submitted version of the manuscript.

Acknowledgements

This work was supported by a research contract from GlaxoSmithKline Biologicals SA to Pythagoras Consulting (CTB). The funders had no role in the research. We thank Cédric Laloyaux (Business & Decision Life Sciences on behalf of GlaxoSmithKline Vaccines) for managing the publication and Yuan Tian and Keith Poore for assistance with computer programming. This work was undertaken while AA was a GlaxoSmithKline Vaccines employee; she is now employed by Abbott Laboratories, Diagnostics Division, Abbott Park, IL, USA.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.09.034.

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