CAN CURRENT HEALTH ECONOMIC MODELING FRAMEWORKS CAPTURE THE UNPREDICTABILITY OF INVASIVE MENINGOCOCCAL DISEASE?

Liping Huang, Paul Balmer, Ray Farkouh
Pfizer Inc, Collegeville, PA, United States

BACKGROUND

- Overall incidence of invasive meningococcal disease (IMD) is low; serogroup-specific incidence can be erratic and unpredictable. Even with appropriate treatment, IMD still causes substantial mortality and morbidity.
- To introduce new vaccines into national immunization programs, many countries have instituted health technology assessments that require a cost-effectiveness analysis (CEA).
- The health economic model used in these evaluations typically requires an assumption of endemic disease epidemiology, which thus far has been incompatible with variable and unpredictable IMD.

OBJECTIVE

To review and assess disease incidence and CEA methodology and their influence on predicting vaccine impact.

METHODS

- A targeted review of published or presented IMD vaccine CEAs was conducted using PubMed and desktop research.
- Inclusion criteria:
  - IMD
  - Any serogroup or combination of serogroups (e.g., serogroup B, C, ACWY, or CWXY)
  - CEA
  - Published between 2000 and 2018
- Identified articles that met inclusion criteria were reviewed, and data were extracted regarding:
  - Country of analysis, model structure, and time horizon
  - Incidence:
    - Number of years of historical IMD incidence used for base-case CEA inputs
    - Stochasticity of epidemiology inputs considered
    - Sensitivity analysis considered and how

RESULTS

- 24 articles or conference presentations were reviewed. Of these, 3 CEAs evaluated MenC, 10 evaluated Men B, 10 evaluated MenACWY and 1 evaluated MenCWYX (Table 1).
- Median historical incidence rates considered in calculating base-case epidemiological inputs were 5 years (mean = 5.95 and SD = 4.01), and only approximately one-fourth of models considered incidence rates occurring in more than 10 years of the time period in the past (Figure 2).
- Approximately two-thirds of models were developed based on a static approach in which the dynamics of IMD (susceptible, infected, and recovered) were not captured (Figure 1).
- Four interval cycle models were developed based on assumptions of a certain number of cases over a period of time in which probability of endemic episode or outbreak was taken into consideration and follows a fixed pattern, whereas the average incidence rate over the modeling time horizon would not change (Table 1 and Figure 1)
- All models conducted sensitivity analyses based on epidemiological inputs. One model considered various scenarios of total numbers of cases from outbreaks as epidemiological inputs, whereas others either used observed incidence rates from different years or considered expert opinions as epidemiological inputs to conduct sensitivity analyses.
- No models considered the potential for emerging serogroups (Table 1).

Table 1. Summary of Reviewed Studies

Study	Country	Model Structure and Time Horizon	Baseline Incidence Inputs	Years in baseline Incidence Assumption	Outbreak/ Stochastic situation considered?	Incidence-Based Sensitivity Analysis Conducted?	Selected Study Results
MenC vaccination							
De Wals et al., 2004	Canada	Cohort model (decision tree, 24 years)	Age-specific 3 scenarios range 1.20, 12.6, and 24.1/100,000 PY	1990-1996, 1996-2000, 1999 (UK)	Various probability	Yes (7 plausible epidemiological scenarios)	Case reduction: 65%-70%
Welte et al., 2004	Netherlands	Cohort model (decision tree, 20 years)	Overall 2.28/100,000 and age-specific	1997-2001	No	Yes (25% higher or lower than baseline	Severe squelae averted: 1.14-1.21
De Soares et al., 2011	Brazil	Cohort model (decision tree, 10 years)	Age-specific (5.11-22.82/100,000)	2006	No	Yes	Case averted: 1,218-2,728
MenB Vaccination							
Christensen et al., 2013	UK	Cohort model (Markov model, 100 years) and transmission dynamic model (100 years)	Overall 3.17/100,000 and age-specific	2004/2005-2005/2006	No	Yes (1997/1998 2005-2006	Cases averted: 484-1,800
Pouwels et al., 2013	Netherlands	Cohort model (Markov model, 99 years)	Overall 1.07/100,000	2005-2009	No	Yes (3.46/100,000 from 1990-1993 and one way sensitivity	Cases averted 4.53-12.58 cases/100,000 person-years
Tu et al., 2014	Canada	Cohort model (Markov, model, lifetime)	Overall 0.19/100,000	2000-2010	No	Yes (1x-10x of base case)	Case averted: 4.6 per birth cohort
Christensen et al., 2014	UK	Transmission dynamic model (99 years)	Age-specific	2005/2006-2011/2012	No	Compared with previous model	Cases averted: No herd effect: 5,962-51,685 With herd effect: 52,152-91,304
Tirani et al., 2015	Italy	Cohort model (1 cohort followed for 100 years)	Overall 0.21/100,000 and age-specific	2007-2012	No	Yes (use min and max of each age group over 6 years	ICER: €61,076-€699,548
Izquierdo et al., 2015	Chile	One-time catch-up program for outbreak Prevention	Overall 5.9/100,000	1990-1999	Yes	No	Averted 215 cases yearly
Christensen et al., 2016	Germany	Cohort model (Markov, 100 years) and transmission dynamic model	Overall 0.34/100,000 and age-specific	2009-2012	No	Yes (0.39 and 0.27/100,000 between 2002-2012 and 2013-2014)	Case averted: No herd effect: 6%-15% With herd effect: 19%-55%
Gasparini et al., 2016	Italy	Cohort model (decision tree, lifetime)	Overall 0.23/100,000 or 3x higher	2007-2012	No	Yes (3x baseline)	Case averted: 83-249
Ginsperg et al., 2016	Israel	Cohort model (decision tree, 10 years)	Overall 0.94/100,000	2000-2013	No	Yes (1.2x baseline)	Cases averted: 148-334
Lecocq et al., 2016	France	Cohort model (Markov model, 100 years)	Overall 0.61-0.76/100,000	2003-2011	No	Yes (0.75x-1.25x baseline)	Cases averted: No herd effect: 5%-23% With herd effect: 24%-51%
MenACYW Vaccination							
Ortega-Sanchez et al., 2008	United States	Cohort model (Monte Carlo simulation, 10 years)	Age-specific (0.3-4.6/100,000)	1991-2002	No	Yes (+/- baseline based on empirical distribution)	Cases averted: 48% - 99%
De Wals et al., 2007	Canada	Cohort model (Markov model, 99 years)	Age-specific (0.2-2.3/100,000)	1995-2001	No	Yes (0.5x-2.0x baseline age)	Cases averted per 100,000: No herd effect: 2.8 With herd effect: 2.8
Hepkema et al., 2013	Netherlands	Cohort model (decision tree, 99 years)	Overall 0.15/100,000 and age-specific	2007-2011	No	Yes (incidence from 2011)	Threshold incidence/100,000 for cost effective: No herd effect: 0.65-1.53 With herd effect: 0.35-0.87
Demarteau et al., 2013	Canada	Static population model with annual cycles reproduced (100 years)	300 cases per year with a peak 350 at a 10-year interval	2013	Yes	Yes (RF 0.5 and 1 accounts for unpredictability)	Cases averted in 40 years: 4,355-4,629
Demarteau et al., 2015	Saudi Arabia	Static population model with annual cycles reproduced (100 years)	34 cases per year with a peak 300 at 15-year interval	1995 & 1999	Yes	Yes (RF 0.5 and 1 accounts for unpredictability	Cases averted: 1,539-2,493
Ceyhan et al., 2015	Turkey	Static population model with annual cycles reproduced (100 years)	900 cases per year multiplied by a random number 80% - 120%	2005-2006	Yes	Yes (RF 0.8 and 1.2 accounts for unpredictability)	Cases averted: 19,816
Christensen et al., 2016	England	Cohort model (Markov model, 100 years)	Outbreaks every 10 years (range, 5-15) with a peak 1,000 per year (range, 500-1,500) and a duration of 20 years (range, 5-30)	2011/2012-2014/2015	Yes	Yes (ranges of outbreak -15, annual case 500-1,500, and duration 5-30)	Continuing the MenACWY adolescent program in the long term was likely to be highly cost-effective
Delea et al., 2017	Canada	Cohort model (Markov model, 100 years)	Age-specific (0.036-1.306/100,000)	2007-2009	No	Yes (+/- 50% of the base case)	Additional cases averted with adolescent MCV4 program: 1,826 (252-7,031)
Kuznik et al., 2017	Africa Meningitis Belt	Cohort model (Markov model, 40 years)	50 or 150/100,000 per year	1995	No	Yes (CE threshold analysis by country)	Cases averted: 13-142/100,000
De Wals and Zhou 2017	Canada	Cohort model (Markov model, 99 years)	0.08/100,000 as low and 0.28/100,000 as high	2006-2011	No	Yes (+/- 20%)	Incidence reduction: 15.8%-100% ICER: 36,000$ CAD-452,000$ CAD
MenCYWX Vaccination							
Yaesoubi et al., 2018	Burkina Faso	Transmission dynamic model (30 years)	Age-specific	2002-2015	No	No	Cases reduction: With strain replacement: 45% (26%-62%) Without strain replacement: 43% (22%-59%)

CE=cost-effectiveness; ICER=incremental cost-effectiveness ratio; RF= random factor; UK=United Kingdom.

Figure 1. Type of Models Structure (N = 24)

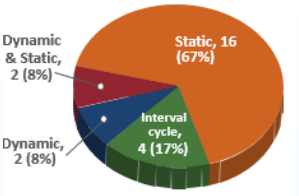
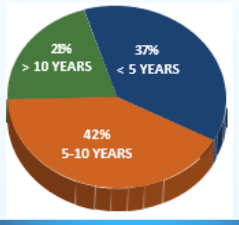


Figure 2. Proportion of Publications With Years of Historical Incidences Used in Calculating Epidemiology Inputs (N = 2 4)



CONCLUSION

- Over the past several decades, IMD has been characterized by the emergence of hyperinvasive clones expressing different polysaccharide capsules, demonstrating the highly unpredictable dynamics of this life-threatening disease.
- With constrained health care resources, health technology assessments have become necessary to interrogate whether a health care intervention is good value for money, however cost-effectiveness modeling approaches to assess meningococcal vaccination strategies have yet to develop a methodology sufficient to capture the natural fluctuations and unpredictability of IMD.
- IMD incidence is simultaneously the most sensitive and uncertain parameter in CEAs. Given the stochastic and unpredictable nature of IMD, it calls into question whether current tools for health economic assessment are sufficient to assess the value of vaccines.
- Further research is needed to determine how to best incorporate stochastic IMD incidence into health technology assessments

Selected Quotes Relevant to Epidemiology Inputs from the Review

Christensen et al. (2014): "Assumptions about disease incidence are also highly influential. **We are currently experiencing low rates of disease, which might increase in the future…."**

DeWals & Zhou (2017): "The **epidemiology of IMD is unpredictable** and outbreaks caused by serogroup A, W or Y clones may occur anywhere…. The economic value of such an insurance policy is, however, difficult to assess."

Contact information:
Liping.Huang@pfizer.com

REFERENCE

- See handout for references

Funding for this study was provided by Pfizer Inc.