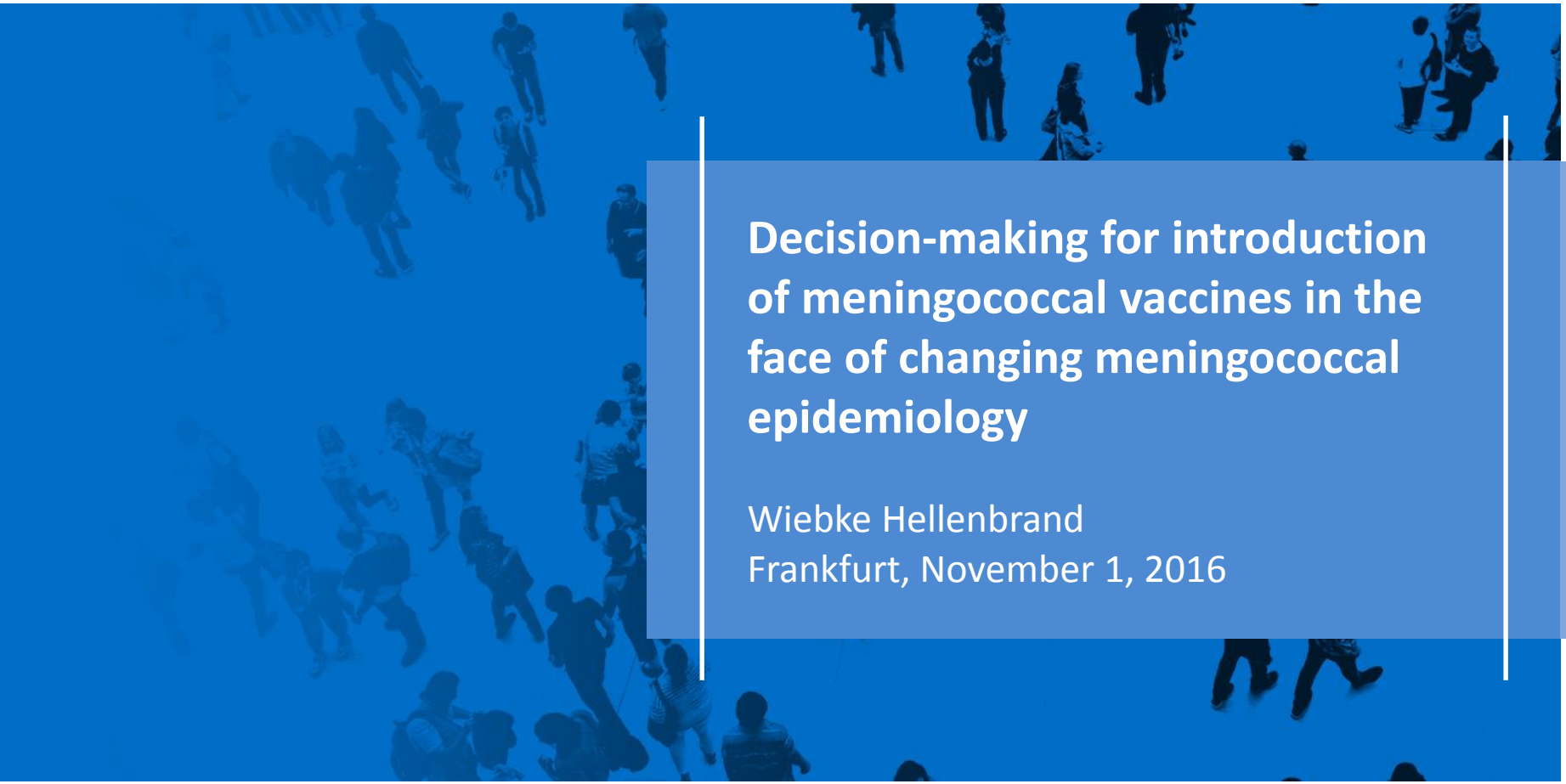
GESUNDHEIT SCHÜTZEN
RISIKEN ERFORSCHEN
DAS PUBLIC HEALTH INSTITUT 125

ROBERT KOCH INSTITUT

EMGM
The European Meningococcal and Haemophilus Disease Society

NRZM



Decision-making for introduction of meningococcal vaccines in the face of changing meningococcal epidemiology

Wiebke Hellenbrand

Frankfurt, November 1, 2016

Evidence-based approach to vaccination recommendations used by German vaccination committee (STIKO) since 2011

- Decision-making requires review of data on
  - Pathogen characteristics
  - Age-specific disease burden

  → **(Semi-) systematic reviews, primary data analyses**

  - Vaccine characteristics
    - Efficacy (VE)
      - Including duration of protection
    - Safety from published RCTs
    - Strain coverage

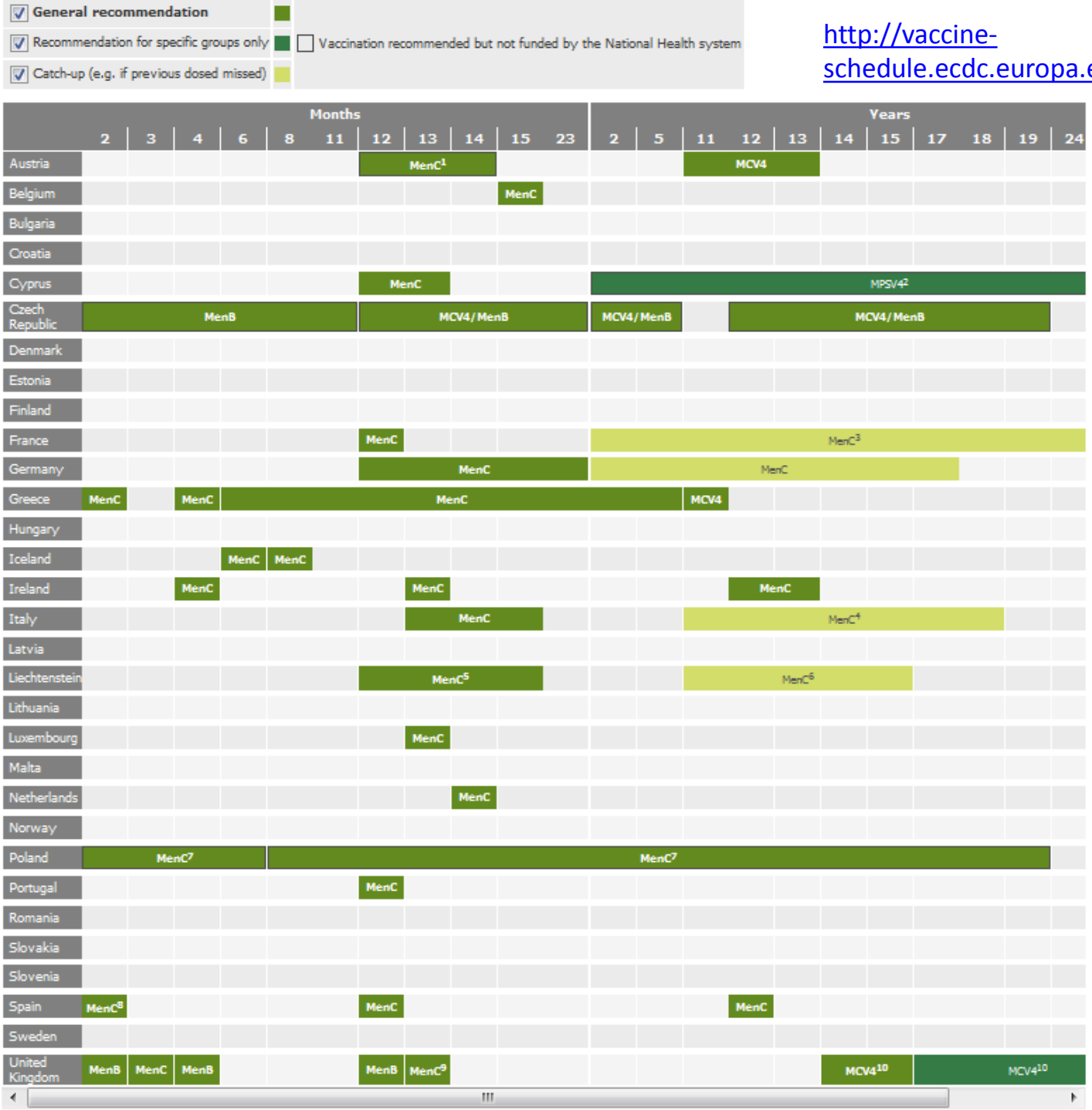
    → **GRADE***

  - Impact of vaccine on disease burden
    - Including indirect effects such as herd immunity, replacement
  - Cost-effectiveness

    → **Modelling**

  - Implementability & acceptance → **Surveys, literature**
  - Ability to evaluate vaccination programme if implemented

Grading of Recommendations, Assessment, Development and Evaluations



http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx

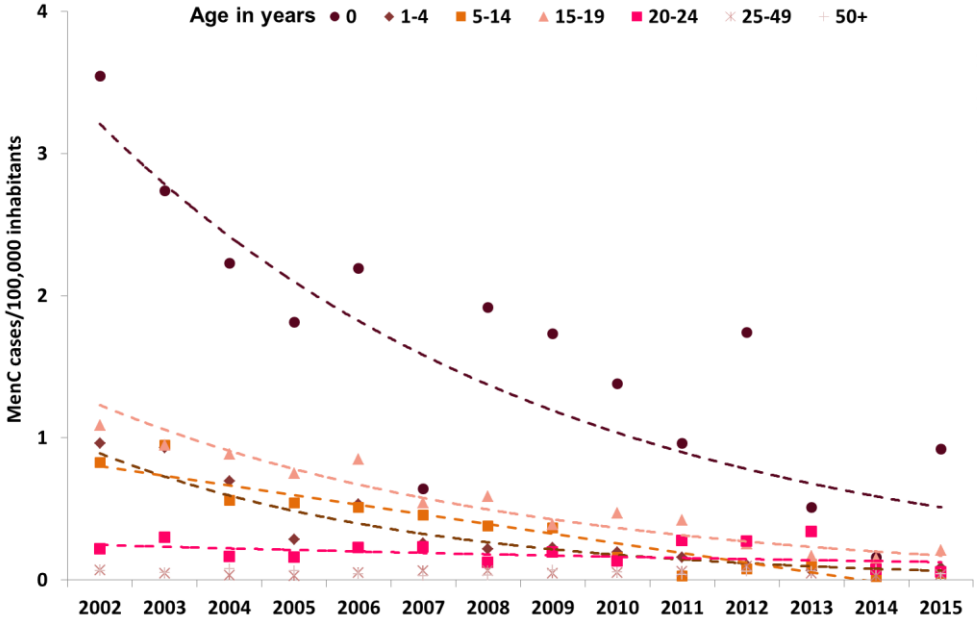
- **Vaccination in infancy**
  - 6 countries MenC
- **Vaccination in toddlers**
  - 15 countries MenC
  - 1 MenACWY
- **Adolescent booster**
  - 4 countries MenACWY
  - 3 countries MenC

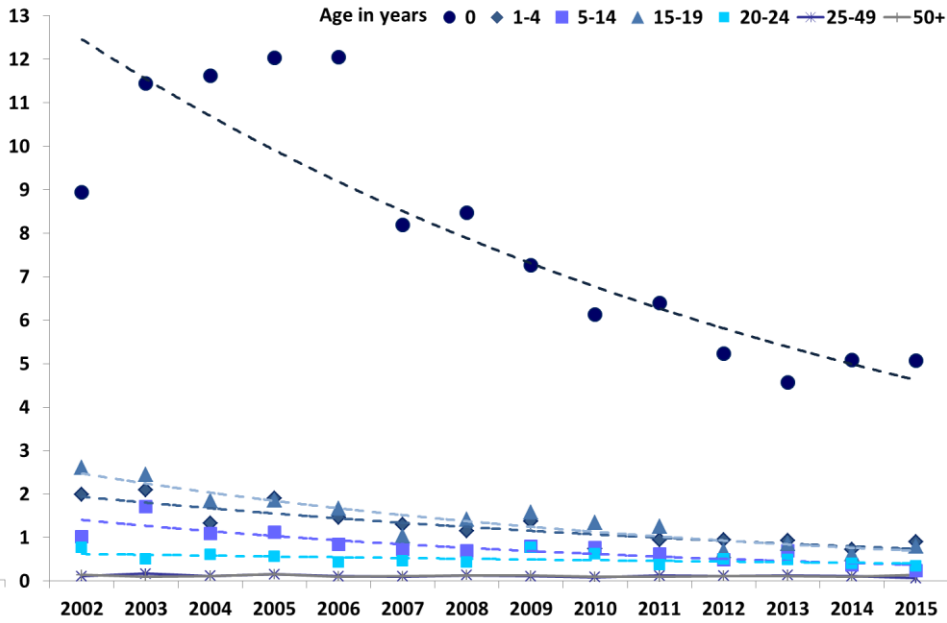
Meningococcal Vaccination in Germany

- MenC vaccination recommended in 2nd year of life since 2006
  - Catch-up campaign not considered feasible or justified due to low disease burden (2002-2005: 0.2 cases/100,000 inhabitants)
    - MenC vaccine nonetheless reimbursed by health insurance up to age 17
- MenACWY and MenB vaccination recommended for risk groups
- MenC vaccination coverage
  - 80% in toddlers[1]
  - 89% at school entry[2]
  - ≈40-50% in 15-17 year olds
- Both MenC and MenB incidence show overall decreasing trend
  - 0.07 MenC cases/100,000 inhabitants in 2015 ► 65% decrease since 2002
  - 0.26 MenB cases /100,000 inhabitants in 2015 ► 55% decrease since 2002
  - Comparison of age-specific trends suggest very little herd immunity using German approach
    - Slight increase in MenC case numbers in 2016, primarily in adults

[1]Greiner et al. 2016; [2]RKI, 2016

Incidence of MenB and MenC disease by age, Germany, 2002-2015





Age (years)	IRR (95% CI)		p for Δ SgC/SgB
	Serogroup C	Serogroup B	
0	0.88 (0.85-0.92), p<0.0001	0.92 (0.90-0.94), p<0.0001	0.08
1-4	0.80 (0.76-0.83), p<0.0001	0.92 (0.90-0.93), p<0.0001	<0.0001
5-14	0.79 (0.75-0.83), p<0.0001	0.89 (0.87-0.92), p<0.0001	<0.0001
15-19	0.86 (0.83-0.88), p<0.0001	0.89 (0.88-0.91), p<0.0001	0.019
20-24	0.97 (0.91-1.03), p=0.32	0.97 (0.94-0.99), p=0.019	0.87
25-49	1.00 (0.98-1.02), p=0.90	0.98 (0.97-1.00), p=0.045	0.32
50+	No significant trend	No significant trend	
All ages	0.89 (0.88-0.91), p<0.0001	0.93 (0.92-0.94), p<0.0001	<0.0001

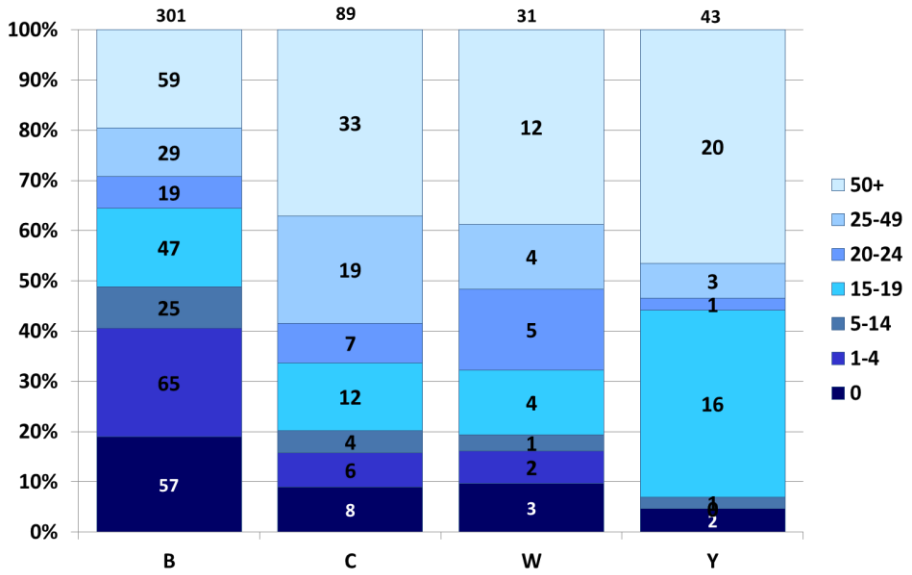
Need for MenC-booster vaccination? Considerations in Germany

- Toddlers first vaccinated in 2006
  - Oldest cohorts currently 11-13 years of age
    - age group still at low risk for IMD
  - Current data suggest high proportion of children vaccinated as infants and toddlers no longer protected in adolescence[1-7]
    - Rationale for adolescent booster in a number of countries
    - In Germany only very small number of vaccination break-through infections
      - 11 since 2006, none 2016
  - Evidence that high MenC vaccination coverage in adolescents leads to reduction of meningococcal carriage[10] and thereby herd immunity[6]
    - And evidence in Germany that low vaccination coverage does not
  - Evidence that MenC priming in later childhood[8] and booster in adolescence[9] lead to more sustained protection

*[1]Borrow et al. CVI 2010; **17**: 154-9; [2]Khatami et al. CVI 2011; 18:2038-2042; [3]Ishola et al. CVI 2012; 19:1126-30; [4]Perret et al. 2010;CID 20:1601-10; [5]Stoof et al. PLoS ONE 9(6): e100651; [6]Campbell et al. CVI 2010:17:840-7;[7]de Voer et al. PLoS ONE 2010;5:e12144; [8]Snape et al. BMJ 2008; 1487-1491 [9]de Whalley et al. 2013 PIDJ 30:e203-e208; [10]Maiden et al. 2008 JID 197:737-43*

Assessing need for Men(C)WY vaccination – Disease burden

- MenWY incidence highly variable in Europe, but recent increase in some countries
  - IMD increase in one region not necessarily predictive of increase in others
- Current very low incidence in Germany (≈0.07 cases/100,000)
  - Recent increase to same magnitude as MenC incidence
  - Highest incidence in infants and adolescents (0.5 & 0.2 cases/100,000, resp.)
    - But low absolute no. of cases especially in infants
  - Highest proportion of cases in adults ≥ 25 years (52-53%)
  - High proportion of MenY in adolescents (37%)
  - Severe disease
    - High case fatality



IMD age distribution by serogroup, Germany, 01.01.2015-19.10.2016

Assessing need for Men(C)WY vaccination – Vaccine effectiveness (VE) and safety

- No data on VE for MenACWY vaccines in use in Europe
  - Immunogenicity data suggest high short-term VE with waning over time[1-3]
    - More marked in children<10 than 10-25 y.o.'s
    - Most marked for MenA component
    - Limited data suggest
      - higher GMTs after Menjugate® vs. Nimenrix®[4] in young children
      - longer persistence of MenC-SBA after monovalent MenC vs. Menveo® in infancy[5]
- No safety concerns in licensure studies or postmarketing surveillance
- More limited data on indirect effects of quadrivalent vaccines than monovalent MenC vaccines[6,7]
  - No data on possible replacement effects

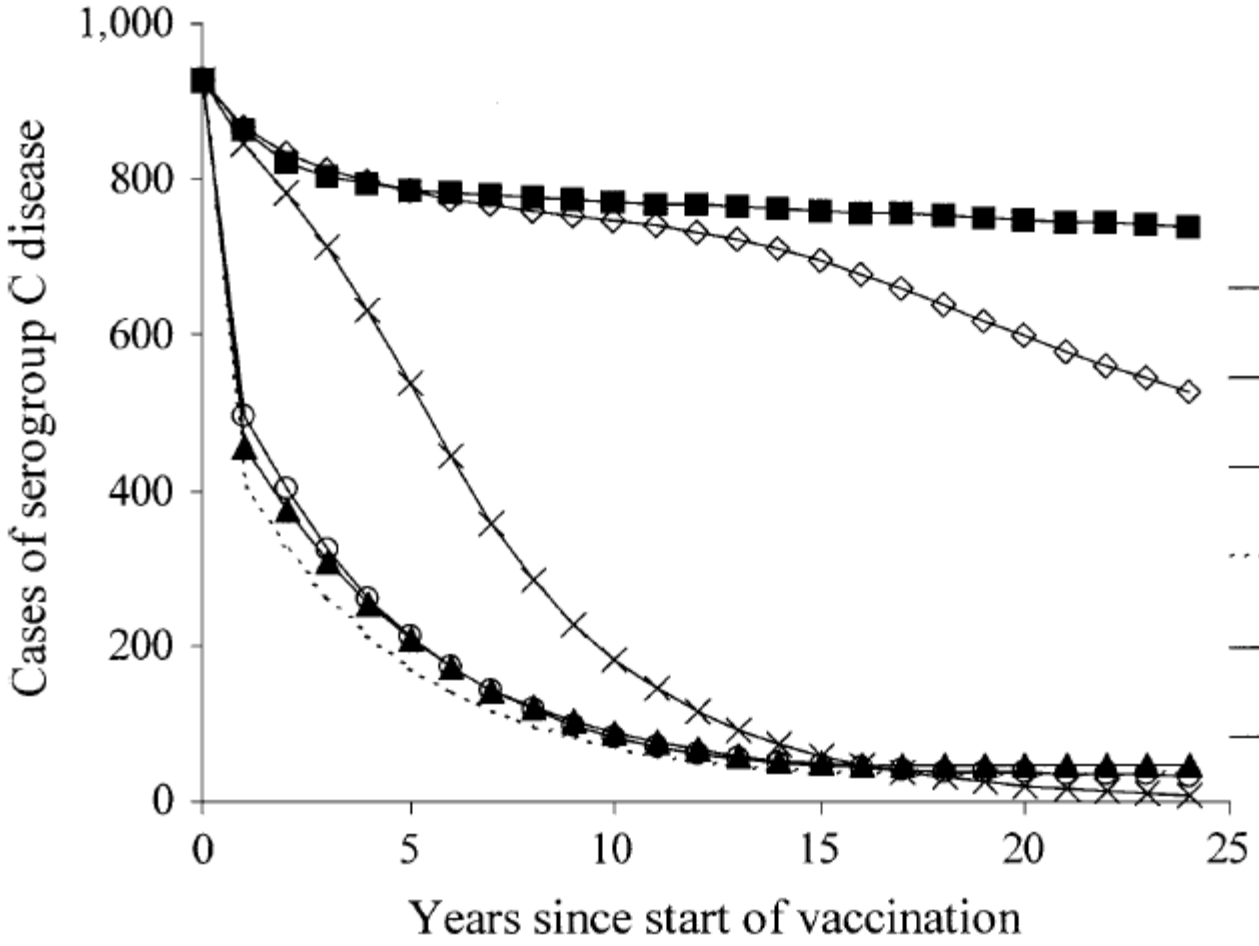
[1]Klein et al. 2016, PIDJ 35:662–672; [2]Baxter et al. 2016 Hum Vacc Immunother 12:5, 1300-10 ; [3]Bloch et al. 2015 Vaccine 33:2175-82; [4]Knuf et al. Eur J Pediatr 2013; 172:601-12 2; [5]Khatami et al. 2012 vaccine 30:2831-8; [6]Read et al. 2014 Lancet 384: 2123-31; [7]Korzeniewski et al. 2014 Adv Exp Med Biol 836:19-28.

Assessing need for Men(C)WY vaccination – Possible vaccination strategies and their potential impact

In context of age-specific disease burden and existing vaccination programs

- Introduction of/replacement of MenC-vaccination with MenACWY
  - In infancy and/or toddlers
    - Very high NNV unless disease burden substantially higher than in most European countries
    - No or very little herd immunity
  - In adolescents
    - High NNV unless disease burden substantially higher than in most European countries
    - Potential for herd immunity with high vaccination coverage
      - Prevention of high proportion of cases in other age groups
  - Combination of above
    - Depending on disease burden in infants and toddlers

Model of the effect of different MenC vaccination strategies on MenC incidence in England and Wales



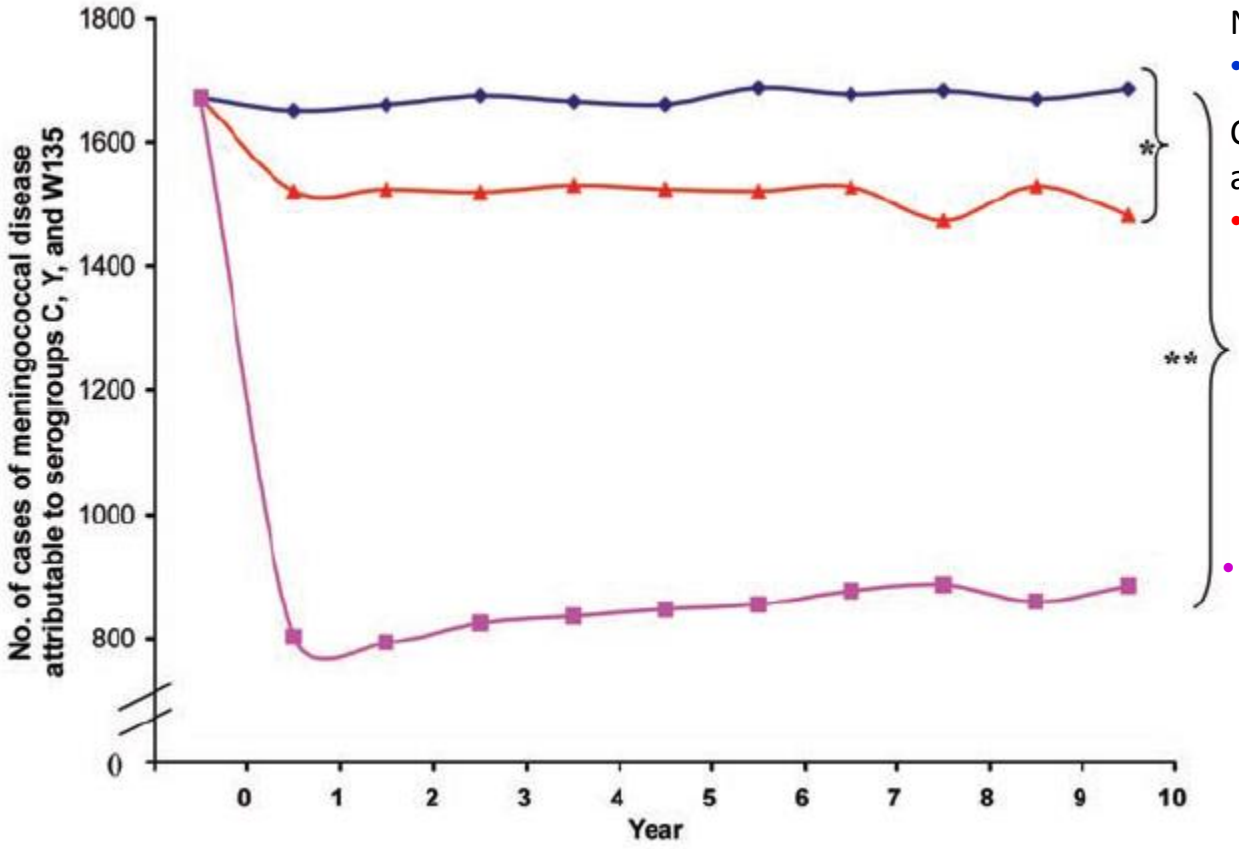
Vaccination at

- 2,3,4 months, no catch-up
- 12 months
- 2,3,4 months, catch-up < 18 years
- 2,3,4 months, catch-up <25 years
- 12 months, catch up <18 years
- 12 months & 12 years

- Age-specific VC mostly > 80%, 60-70% in older adolescents
- 67% carriage reduction
- VE: age-specific: 85-100%

Trotter et al. 2005 Am J Epidemiol 2005;162:89-100

Probabilistic model of effects of adolescent-only MenACWY vaccination in the US[1]



No vaccination (blue line)

- MenCWY incidence 0.8/100,000

Catch-up vaccination in 11-17 y.o.'s, annual vaccination 11 y.o.'s

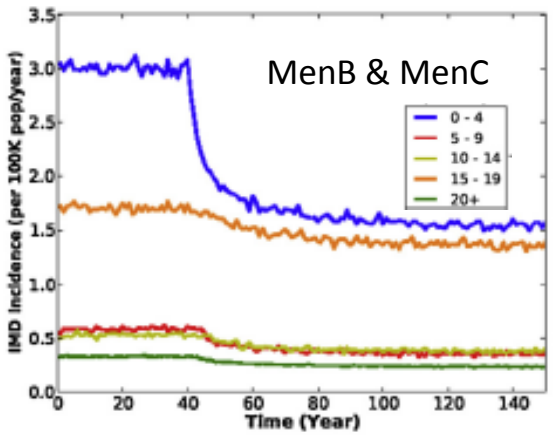
- Red line: 70% VC; 93% VE; no herd immunity
  - MenCWY incidence: 0.72/100,000 - 156 cases averted annually
- Purple line: 70% VC; 93% VE; herd immunity based on UK MenC results
  - MenCWY incidence: 0.42/100,000, 825 cases averted annually

[1]*Ortega-Sanchez 2008 CIE 2008; 46:1-13*

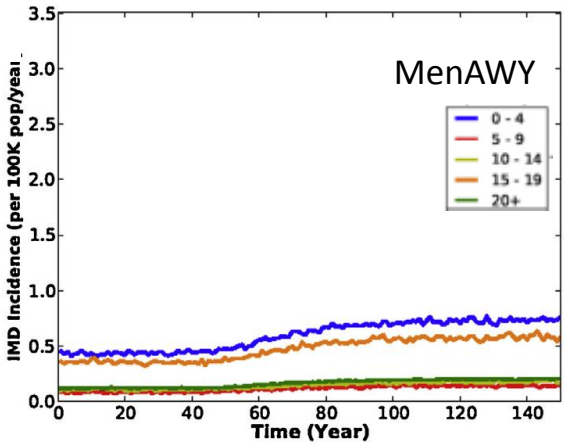
Potential impact of MenC versus MenACWY vaccine programs: stochastic dynamic model based on Canadian data

ROBERT KOCH INSTITUT

a



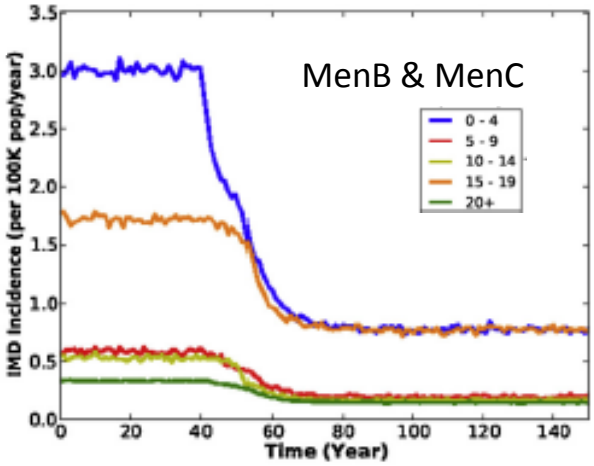
b



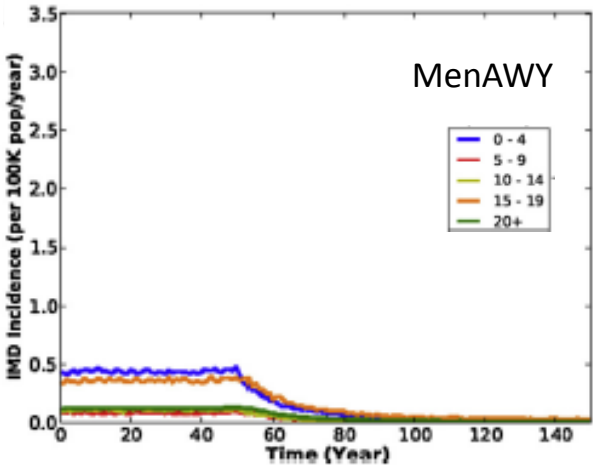
Infant VC:90%,

Effect of MenC-vaccination at 12 months of age on age-specific incidence of MenB & C and on MenAWY

c



d



Infant VC:90%,
adolescent VC: 80%

Effect of MenC-vaccination at 12 months of age followed by adolescent MenACWY booster at 12 years of age on age-specific incidence of MenB & C and on MenAWY

Vickers et al. Vaccine 2015;33:268-75

Assessing need for Men(C)WY vaccination – Cost-effectiveness and implementability

- Potential cost-effectiveness will depend on
  - Vaccination strategy chosen in relation to current strategy
    - Cost of vaccination; difference in cost/dose of MenACWY vs. MenC vaccine
    - Degree of herd immunity achievable
      - Influenced by level of vaccination coverage in adolescents
      - Available models assumed high coverage
  - Costs related to disease
    - MenCWY disease burden – determines maximal no. of preventable cases
      - Treatment costs for acute disease and sequelae/QoL loss
- Implementability
  - In infancy: challenging due to already very busy vaccination schedule
  - In toddlers: easiest
  - In adolescents: Poor track record in Germany and some other countries
- Acceptance for vaccine likely to be high

Should be modelled taking into account country-specific epidemiology and health care & vaccination costs[1,2]

Hepkema et al. 2013 PLoS ONE 8(5): e65036; de Wals et al. 2007 Vaccine 25:5433–5440

Conclusions

- Review of evidence for decision on possible implementation of MenACWY vaccines
  - Country-specific
    - Disease burden - increasing in some European countries
    - Current vaccination programme
    - Cost of treatment, sequelae and vaccination
    - Implementability & acceptance
      - ➢ Degree of vaccine uptake in adolescents → level of herd immunity
  - Vaccine-specific
    - Possibly slightly lower MenC VE compared to monovalent MenC vaccines
      - Likely negligible if used as booster
    - Limited data on carriage effects
      - Possibly lower than with monovalent MenC vaccines
- Further epidemiologic/CE models for various scenarios in Europe would be useful
  - Need for more complete data to inform input parameters regarding serogroup-specific VE and indirect effects of quadrivalent vaccines

Thank you for your attention!

- **Thanks also to my colleagues at the**
  - National Reference Laboratory for Meningococci and *Haemophilus influenzae*
    - Heike Claus
    - Ulrich Vogel
  - RKI Immunization Unit, especially
    - Judith Koch
    - Raskit Lachmann
    - Thorsten Rieck
    - Ole Wichmann

How does GRADE work

- Recommendations made according to
  - Balance between benefits versus risks, burden, and cost
  - Degree of confidence in estimated benefits, risks, burden
  - Taking into account societal values and preferences
- Evidence rated **across** studies for each relevant **clinical** outcome, specifically assessing
  - Methodological flaws within the component studies
  - Consistency of results across studies
  - Generalisability of results to the wider patient base
  - Effectiveness and harms of interventions
- Overall rating of quality of evidence
  - Lowest quality of evidence among critical outcomes