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Epidemiology of invasive meningococcal disease in Germany, 2002—2010, and impact of vaccination with meningococcal C conjugate vaccine

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Summary *Objectives:* To analyse serogroup (Sg)- and finetype-specific invasive meningococcal disease burden (IMD) in Germany, 2002—2010, with emphasis on effects of vaccination with conjugate SgC vaccines targeting one-year old children since 2006, including individual-based catch-up to 17 years of age.
Methods: Serogroup- and age-specific IMD incidence and trends were calculated using statutory surveillance data. The national reference laboratory performed genetic finetyping. Vaccination uptake data were obtained from school entry surveys and prescription monitoring.
Results: In persons <25 years, SgB and SgC IMD incidence decreased significantly from 0.63 to 0.32/100,000 and 0.26 to 0.10/100,000, respectively. The decline was significantly steeper for SgC than SgB in 1—5 year-olds, the primary vaccination target group, but not other ages. The slope of the SgC incidence curves was similar before and after vaccination implementation in all age groups; however, the decrease in incidence was steeper in states with higher vaccination uptake. Declining SgC incidence was associated with decreased SgC finetype diversity. An increase in SgY incidence was limited to adults.
Conclusions: Results suggest effects of the German SgC vaccination strategy are limited, although interpretation is complicated by already low and decreasing incidence before vaccination. More effective use of vaccination resources might be achieved by rigorously targeting adolescents in addition to 1-year-olds.
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Introduction

While the overall incidence of invasive meningococcal disease (IMD), caused by *Neisseria meningitidis*, is relatively low in Europe (0.1—3.4 cases/100,000 inhabitants), case-fatality remains high at 7—9%.[1;2] Compared to other European countries, incidence in Germany (81.8 million inhabitants) is low.[1;3] Surveillance is based on statutory notification according to the German Protection Against Infection Act (IfSG) since 2001, with linkage to typing performed at the National Reference Laboratory for Meningococci (NRLM).

In 2006, the German Standing Committee on Vaccination (STIKO) recommended routine meningococcal serogroup C (SgC) vaccination in the second year of life. Previously, SgC conjugate vaccines were recommended only for risk groups, except in the federal state of Saxony (4.1 million inhabitants), where SgC vaccination was recommended from 2 months of age in July 2003.[4] STIKO recommended catch-up vaccination for all children and adolescents $<$18 years on an individual basis,[5;6] but a catch-up campaign was not undertaken.

Here, we analyse IMD burden and secular trends in Germany from 2002 to 2010, including analysis of vaccination effects.

Materials and methods

SgC vaccination coverage

Vaccination coverage with conjugate SgC vaccines is ascertained routinely by local health authorities (LHA) from children at school entry and provided to the Robert Koch Institute (RKI) annually in aggregate form. Furthermore, the number of prescribed conjugate SgC vaccine doses from 2006 to 2010 was analysed based on data purchased by RKI from Insight Health (http://www.insight-health.de/), which collects data on all prescriptions for $>$99% of persons insured by the statutory health insurance (SHI) in Germany from pharmacy data processing centres. SHI covers $\sim$85% of the German population.[7] We calculated the number of prescribed vaccine doses per 1000 one-year-old children, as these comprised the primary vaccination target group, for each state. We used the median value to categorize states as having high or low vaccination uptake.

Surveillance

According to IfSG, notification of IMD to LHA is required of physicians and laboratories. LHA verify notified cases according to the national case definition. Clinical criteria include at least one of fever, meningeal signs, skin lesions (maculopapular rash, petechiae, or ecchymoses), signs of increased intracranial pressure or circulatory collapse. Laboratory confirmation requires detection of *N. meningitidis* in blood, cerebrospinal fluid (CSF), skin biopsy of hemorrhagic infiltrates, or clinical specimens from a normally sterile site by culture, nucleic acid detection, microscopic detection of gram-negative diplococci or detection of capsular antigen (CSF only). Cases fulfilling clinical and either laboratory or epidemiological criteria (contact to laboratory-confirmed case) are considered confirmed, and transmitted from LHA to RKI via the state level in anonymized form together with data on vaccination status, clinical presentation (meningitis, sepsis, Waterhouse-Friderichsen Syndrome (WHF)), hospitalization, and outcome (survived/died).

Laboratory methods

NRLM routinely receives isolates or samples from IMD patients from peripheral laboratories and performs antigen sequence typing.[8] A finetype is defined as the combination of serogroup, antigen sequence type of two variable regions (VR) of the outer membrane protein PorA and of one VR of FetA, resulting in the formula "Sg:PorA VR1,VR2:FetA VR".[9] Since 2004, all NRLM results are reported directly to LHA in addition to primary laboratories. NRLM cases were matched to notified cases using an automated algorithm requiring identical sex, month/year of birth, county and state of residence, $\leq$7 days between date of illness onset and date sample taken and a unique match. A manual search was performed for potential further matches fulfilling fewer criteria. These were verified at the level of the local health authority using personalized data not available at the national level.

Data analysis

IMD incidence was calculated using 2002—2010 notification data as of 4 July 2011 and population estimates from the Federal Statistical Office (http://www.destatis.de). Serogroup specific incidences were calculated assuming a similar serogroup distribution among cases with and without known serogroup. Proportions were compared using the Chi-squared test. Exact binomial confidence intervals were calculated for case-fatality estimates. Temporal trends were estimated using poisson and negative binomial regression analysis. Confidence bands (CI) were obtained using delta method.

Finetype diversity D according to serogroup was calculated as

$$D = \left(\sum_{j}^{s} nj(nj-1) \right) \Big/ N*(N-1)$$

where s = total number of finetypes, n_j = number of strains belonging to the j th finetype and N = total number of cases in the serogroup under consideration.[10] Confidence intervals (CI) were calculated according to Grundmann et al.[11]

Statistical analyses were performed using PASW SPSS 18 and STATA 11.0/IC.

Results

SgC vaccination coverage

Based on data from 92% of children entering school in 13 of 16 federal states (4—6-year-old children presenting with vaccination records, n = 494,455), SgC vaccination coverage in 2010 was 69,8% (range: 52.8%—89.5%) (Table 1). In 2009, coverage was 55.9% (range in 13 states: 9.1%—79.5%).[12] These children would have been one year

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