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Characteristics and changes in invasive meningococcal disease epidemiology in France, 2006—2015

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Summary *Objectives:* This work aimed to describe the epidemiology of invasive meningococcal disease (IMD) in France, 2006—2015, including group- and genotype-specific disease burden, incidence trends before and after introduction of meningococcal C conjugate vaccines (MCCV) in 2010, and factors influencing the case fatality rate.
Methods: Mandatory notification data on incidence and IMD case characteristics were used. Genotyping of invasive strains and whole genome sequencing were performed by the French National Reference Center. Vaccination coverage was estimated from the National Health Insurance Information System's reimbursement data.
Results: The decrease in annual IMD incidence rates (per 100,000 inhabitants) from 1.23 in 2006 to 0.78 in 2016 was mainly related to the decrease in group B IMD. Group C incidence decreased from 0.29 in 2006 to 0.13 in 2010 but increased thereafter in age groups not targeted by MCCV. From 2010 onwards, MCCV coverage gradually increased but remained below 25% in 15—19 year-olds in 2015. Age, clinical presentation and, to a lesser extent, clonal complex 11 were the most significant factors determining mortality.
Conclusions: The limited impact of vaccination on group C IMD incidence may be explained by the emergence of a new epidemic cycle in 2011 and the low vaccination coverage rates among adolescents and young adults.

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Introduction

Invasive meningococcal disease (IMD) is an acute and severe infection caused by the bacterium *Neisseria meningitidis (meningococcus)*. It is characterized by its sudden onset and by one or more clinical presentations including meningitis, sepsis, and less commonly, pneumonia and arthritis.[1] The most severe form is fulminant meningococcemia (*purpura fulminans*), characterized by progressive cutaneous hemorrhage and necrosis, as a result of dermal vascular thrombosis and disseminated intravascular coagulation. Pathogenicity and virulence are strongly related to capsular polysaccharides which are classified into 12 groups, groups A, B, C, W, Y and X being the most frequent among invasive strains.[2] The majority of IMD cases are sporadic and outbreaks are usually caused by closely related strains of meningococci. In 2012, a report based on data from various countries showed that the incidence of IMD in Europe was relatively low, between 0.11 and 1.76 cases/100,000 inhabitants.[3] The case fatality rate varied between 4.5% and 9.7%. Half of the cases occurred in children under 15-years-old. Sg B and C represented 85% of all cases.[4] In France, routine vaccination with meningococcal C conjugate vaccines (MCCV) was introduced into the immunization schedule in early 2010 for infants aged 12 months of age and a catch-up until 24-years-old (one dose of MCCV).[5] The protection of infants less than 1-year-old is expected through herd immunity, achieved by high vaccine coverage in individuals up to 24 years according the French recommendation.[5] Epidemiological and microbiological surveillance of IMD is aimed at detecting outbreaks and at tracking the incidence and the characteristics of the disease over time, in order to adapt prevention and control strategies. Here, we analysed IMD data from 2006 to 2015, including the impact of serogroup C vaccination and factors influencing the case fatality rate.

Materials and methods

Surveillance

Notification of IMD cases by physicians and laboratories to the regional health agencies (RHA) is mandatory. RHA verify cases according to the French case definition and have to implement prophylaxis for cases' close contacts in accordance with the national recommendation from the Ministry of Health.[6] Case notification forms are sent to Santé publique France — the French national public health agency (SpF) — for data entry and analysis. A case of IMD was previously defined as the presence of at least one of the following notification criteria: isolation of *N. meningitidis* or testing PCR positive[7] in blood, cerebrospinal fluid (CSF), other sterile sites (e.g., joint, pleural, peritoneal or pericardial fluid) or purpuric skin lesions; detection of Gram-negative stained diplococcus in CSF; purulent CSF associated with purpuric skin lesions or with the detection of *N. meningitidis* antigens in blood, urine or CSF; *purpura fulminans* (severe sepsis with extensive hemorrhagic and necrotic skin lesions). The case definition was modified in 2014: the eye anterior chamber was added to the list of sterile sites and the detection of meningococci antigens was no longer considered as a criterion for lab-confirmation. All the cases meeting the case definition criteria applicable at the time of disease onset were included in the present analysis. Cases notified on Mayotte island — an overseas administrative region that was attached to France in 2010 (8 cases) or cases exclusively notified with criteria added or removed in 2014 (8 cases) were excluded from historical comparisons. The following hierarchical classification of criteria, based on biological confirmation sites or clinical presentation, was used to classify a single syndrome for cases: *purpura fulminans*, meningitis associated with bacteremia, isolated meningitis, isolated bacteremia, and other localizations.

Laboratory methods

The French National Reference Centre for Meningococci (NRCM) routinely received isolates, DNA and positive samples from patients from all the country's hospital laboratories. Since 2008, phenotyping (serotyping and serosubtyping) results have been transmitted monthly to SpF and matched to notified cases. In addition to phenotyping, the NRCM has been performing systematic sequence typing since 2011. The genotypic formula is defined as the combination of i) group, ii) an antigen sequence type of two variable regions (VR1 and VR2) of the outer membrane protein PorA, and iii) of one VR of the protein FetA, as well as iv) clonal complex (cc) determined by MLST (multilocus sequence typing). It is expressed as « SG:P1.PorA-VR1,PorA-VR2:FetA:cc ». Additional sequencing is performed in case of clusters, outbreaks and other specific epidemiological situations (*penA* and *fHbp*. Wwhole genome sequencing, WGS was also implemented since 2013.[8–11] WGS data is analyzed using a "gene-by-gene" approach available through the PubMLST Genome Comparator tool.[12] SplitsTree4 (version 4.13.1) is used to visualise the resulting distance matrices as Neighbour-net networks.[13]

Data analysis

IMD incidence rates were calculated using the notification data 2006–2015 and population estimates from the French National Institute of Statistics and economic studies (INSEE). National incidence rates were corrected for under-reporting, which was estimated at 9% by capture-recapture analyses performed in 2005[14] and 2011 (unpublished data). Proportions were compared using a chi-square test. Factors associated with death were analyzed for cases notified between 2008 and 2015 and matched with NRCM cases (clonal complex available since 2008). Variables with a p-value <0.05 were considered significant. Variables were selected through univariate analysis ($p < 0.05$) and then assessed using multivariable Poisson regression with robust variance. Results were expressed as prevalence ratios with 95% confidence intervals. We used Poisson regression to determine the temporal trends in group C IMD incidence as incidence rate ratios (IRR). The analysis was stratified by 4 age groups (<1 year, 1–14 years, 15–24 years and ≥ 25 years) and two periods: 2005–2009 (pre-vaccine introduction) and 2010–2015 (post-vaccine introduction). Statistical analyses