Use of notifiable infectious disease surveillance data for benefit/risk monitoring of vaccines in the EU within the context of the IMI ADVANCE project

Estimating the annual burden of invasive meningococcal disease in the EU/EEA, 2011-2015

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Abstract
The Innovative Medicines Initiative Accelerated Development of VAccine beNefit-risk Collaboration in Europe (IMI ADVANCE) project aims to develop a framework for best practice methods on integrated rapid benefit/risk monitoring of vaccines in the European Union (EU). Burden of disease is one of the measures considered when estimating vaccine benefits. This study explores the use of notifiable infectious disease surveillance data for this purpose by estimating burden of invasive meningococcal disease in the EU/European Economic Area (EEA). We use the Burden of Communicable Diseases in Europe toolkit for computing disability-adjusted life years from incidence-based data retrieved from the European Surveillance System (TESSy) held at the European Centre for Disease Prevention and Control.

Invasive meningococcal is a common cause of meningitis and septicaemia, with high case-fatality (~10%) and sequelae. We found that the median annual burden of invasive meningococcal disease in the EU/EEA, 2011-2015, was 3.87 DALYs per 100 000 total population (95% UI: 3.79-3.95). Children below one year of age and children below five years of age were at greatest risk of invasive meningococcal disease serogroup B with 89.15 DALYs per 100 000 stratum specific population (95% UI: 83.11-95.02) and 22.57 DALYs per 100 000 stratum specific population (95% UI: 21.03-24.12), respectively. We found that the distribution of burden of invasive meningococcal disease serogroup B differs widely between countries in the EU/EEA and consequently confirm that national assessment of the new infant meningococcal B vaccine is highly relevant.

Keywords
IMI ADVANCE, vaccine benefit/risk monitoring, burden of disease, disability-adjusted life years, infectious disease epidemiology, infectious disease surveillance data

Abbreviations
EU – European Union
EEA – European Economic Area
ECDC – European Centre for Disease Prevention and Control
IMI – Innovative Medicines Initiative
ADVANCE – Accelerated Development of VAccine beNefit-risk Collaboration in Europe
IMD – Invasive meningococcal disease
IMD SgB – Invasive meningococcal disease serogroup B
DALY – Disability-adjusted life year
YLD – Years lost due to disability
YLL – Years of life lost due to premature mortality
TESSy – The European Surveillance System
BCoDE – Burden of Communicable Diseases in Europe
SMPH – Summary measure of population health
Introduction

Ever since Edward Jenner discovered the smallpox vaccine in 1796, vaccination have been one of our most powerful weapons in the human fight against infectious diseases. Millions of lives are saved every year, smallpox has been eradicated and polio is close to eradication. In fact, many vaccine-preventable diseases have become so rare that most of the general population in Europe never encounters these diseases any longer. Consequently, people tend to forget how severe some of the diseases are and the perceived risk of contracting them is considered very low. Since vaccines are generally given to healthy people, the acceptance of adverse events following immunization is extremely low. A combination of these factors along with increased media attention to vaccination issues has led to an urgent problem of public vaccine hesitancy. Public distrust in immunization programmes is currently contributing to reduced general vaccine coverage and herd immunity and can result in outbreaks of vaccine-preventable diseases (1-3). In addition, new vaccines are being introduced to the market every year and consequently the immunisation programmes have expanded and become more and more complex. Post marketing monitoring of vaccines is therefore highly important in order to optimize immunization programs, deal with possible concerns for adverse effects and to maintain public trust in vaccinations (2-5).

It has been shown that there is enormous potential and need to improve methods for vaccine benefit/risk monitoring in Europe (4-6). Today, studies of vaccine risks and benefits are planned and performed by different institutions and groups of researchers, using heterogeneous methods and data sources, which makes them difficult to assess jointly. The Innovative Medicines Initiative Accelerated Development of VAccine beNefit-risk Collaboration in Europe (IMI ADVANCE) project (7) is an EU-wide collaboration between the European Centre for Disease Prevention and Control (ECDC), the European Medicines Agency (EMA), national public health institutes, regulatory bodies, vaccine manufacturers and academic experts. By developing methods and guidelines, the project aims to establish a validated and tested best practice framework for rapid delivery of transparent and robust data on benefit/risk monitoring of vaccines in the EU (4-7).

The IMI ADVANCE project defines four types of data that can be used for benefit/risk monitoring of vaccines: (I) vaccine effectiveness, (II) vaccine safety (III) vaccination coverage and (IV) burden of disease. The data sources used to estimate the fourth element (burden of disease), identified so far within the project, are mostly administrative data from health care databases and clinical routine care. The use of notifiable infectious disease surveillance data in this context has not yet been explored. ECDC collects notifiable infectious disease surveillance data on 52 communicable diseases from 30 EU/EEA Member States and stores the information in the database called The European Surveillance System (TESSy). ECDC has also developed a stand-alone software application called the Burden of Communicable Diseases in Europe (BCoDE) toolkit, which allows calculation of disability-adjusted life years (DALYs) from incidence-based data (8, 9). We hypothesize that, in addition to previously used databases and methods, the use of notifiable infectious disease surveillance data and a composite health measure such as DALYs could be of value for benefit/risk monitoring of vaccines in the EU. In this approach, the burden of a vaccine-preventable disease, and the burden of adverse events following vaccination, can both be expressed using the same summary (composite) measure of population health, like the DALY. Using such common measure would facilitate the benefit-risk comparison and enable computation of benefit-risk indices based on benefit-risk difference or ratio.

By conducting an analysis on burden of invasive meningococcal disease in Europe, this thesis explores the use of DALYs as a composite health measure for estimating burden of a vaccine-preventable disease and exemplifies how notifiable infectious disease surveillance data can be used within the context of the IMI ADVANCE project.
Burden of disease and vaccine benefit studies
The concept of burden of disease was developed in order to quantify population health and to better understand the size and impact of diseases, infections and other health problems (10). Burden of disease studies have enabled comparison of different health problems and facilitated public health policy making and resource allocation. In the field of infectious diseases, burden of disease can also be used to estimate the potential benefits of proposed measures such as vaccines. (10-12)

In the past, measures of population health have mostly been based on mortality statistics and/or incidence/prevalence statistics. These measures are simple and straightforward to calculate but have limitations. Measures based on mortality statistics do not include information on non-fatals outcomes and thus underestimate the burden of diseases that cause significant morbidity but low mortality. Measures based on disease incidence or prevalence do not take into account sequelae that can follow the acute disease. Summary health measures of population health (SMPHs) address these limitations and nowadays are more commonly used to estimate disease burden. SMPHs usually consist of a single numeric index composed of information from both mortality and morbidity, including long-term disability. (13, 14)

Disability adjusted life years (DALYs) are a summary measure of population health that consists of the sum of years of life lost (YLL) due to premature mortality and years of healthy life lost due to disability (YLD). One DALY equals to one year of healthy life lost (15). By computing DALYs for invasive meningococcal disease, we can provide a more comprehensive and appropriate measure of burden of disease than evaluating incidence or mortality rates alone. The burden of disease prevented by the vaccine can then be compared with burden of adverse events following immunization to generate estimates of vaccination benefits. This approach has been briefly explored but not fully developed within the IMI ADVANCE project.

Invasive meningococcal disease
Invasive meningococcal disease (IMD) is a severe bacterial infection with acute onset that can lead to serious complications and death. IMD is a common cause of meningitis and septicaemia, which are both life-threatening conditions. It can also cause focal disease such as arthritis and pneumonia (16). A considerable proportion of the patients with invasive meningococcal disease suffer from long-term sequelae such as hearing loss, visual disturbance, neurological problems and cognitive difficulties (17). Around 3 000-4 000 cases of IMD are reported to TESSy every year and IMD has a case fatality rate of 9% (18). Thus, invasive meningococcal disease is a serious public health risk and accounts for a considerable amount of mortality and morbidity in the EU/EEA.

The causative agent is the Gram-negative bacterium Neisseria meningitidis. It is related to some non-pathogenic species of Neisseria, including e.g. Neisseria lactamica. N.meningitidis has an outer membrane with several important protein structures surrounded by a polysaccharide capsule. The capsule protects the bacteria from opsonophagocytosis and complement-mediated lysis and is therefore a pathogenicity marker. The bacteria can be classified into serogroups based on their capsular polysaccharide components by which A, B, C, W, X and Y are the most common. The distribution of capsular serotypes depends on geography, age, and other factors. The incidence rates of IMD vary widely between countries in the EU/EEA, for reasons that are not yet fully understood (19). Humans are the only reservoir and around ten percent of adults are asymptomatic carriers of N. meningitidis. The bacteria colonize the nasopharynx and are transmitted person-to-person through close contact via secretions or aerosols. Carriage of N. meningitidis is often associated with non-pathogenic strains and most carriers develop systemic protective antibody responses. However, virulent strains of N. meningitidis can penetrate the mucosa of the nasopharynx, enter the bloodstream and cause a systemic infection (20).
In about 50% of the patients with IMD, the bacteria cross the blood-brain barrier, reach the cerebrospinal fluid and cause meningitis, with typical clinical presentation of stiff neck, fever, headache, nausea and altered mental status. The incubation period of IMD is commonly 3 to 4 days, but can vary between 2-10 days. The symptoms often have a sudden onset and all suspected cases of IMD should immediately be treated with antibiotics.

The best preventive measure against IMD is vaccination. The first IMD vaccine was developed in the 1940s and was a polysaccharide meningococcal C vaccine. Polysaccharides are long polymeric carbohydrate molecules present on the outer surface of the bacterial capsule. They are one of the principal antigens in most pathogenic bacteria. Polysaccharides are T-cell independent type 2 antigens, which means that they only activate mature B cells to produce antibodies and that the elicited immune response is rather weak. This makes it especially difficult to induce immunity in infants, as their majority of B-cells are still immature. Polysaccharide vaccines were also shown to have poor effect on nasopharynx carriage of the bacterium, and thereby minor effect on herd immunity. Due to the poor immunogenicity of polysaccharide vaccines, conjugate meningococcal vaccines were developed and introduced in the late 1990s. These vaccines consist of capsular polysaccharides conjugated to protein carriers e.g. diphtheria or tetanus toxoid. Vaccination with conjugate polysaccharide vaccines elicit a T-cell dependent response and results in immunological memory, thereby making them far more effective than the polysaccharide vaccines. Today, there are several conjugate vaccines on the market that are either monovalent, containing one type of polysaccharide or tetravalent, containing four types (A, C, Y, and W) (16, 21). As of 2015, 14 European countries had introduced a meningococcal C vaccine into their national routine immunization programme (18).

The development of a vaccine against meningococcal serogroup B has been challenged by the cross-reactivity of the group B capsular components and human glycoproteins present in neural tissue. The meningococcal B vaccines available today are therefore instead composed of recombinant outer membrane proteins. (21-23) The first meningococcal B vaccine was licensed in Europe in 2013 and since then three countries have introduced it into their national routine immunization programme: The United Kingdom (September 2015), Ireland (October 2016) and Italy (January 2017) (24). Some of the European countries recommend the vaccine without covering its costs while other countries recommend it to risk groups only. Several countries still have the vaccine under assessment or have planned to assess it in the near future (24).

ECDC published an expert opinion on the introduction of the meningococcal B vaccine in the EU/EEA in December 2017 (24). One of the major considerations for introduction of the vaccine in the EU/EEA Member States was the country specific burden of SgB IMD. In the Expert Opinion report, burden of disease is expressed as incidence/notification rates. We hypothesize that expressing burden of disease in DALYs could provide a more comprehensive picture of disease burden in this context. We also investigated the serogroup specific burden of IMD since this would be valuable when assessing the benefits of serogroup specific vaccines. Due to the ongoing discussion and assessment of the new meningococcal B vaccine, we decided to focus on serogroup B in this study.

As far as we know, this is the first study to estimate serogroup and country specific DALYs for invasive meningococcal disease in Europe.
Aim
The primary aim of this study was to do an epidemiological description of the age- and country specific burden of invasive meningococcal disease in the EU/EE, expressed in DALYs, with focus on meningococcal disease caused by serogroup B of \textit{N. meningitidis}.

The secondary aim of this project is to explore the use of notifiable infectious disease surveillance for vaccine benefit monitoring within the context of the IMI ADVANCE project.

Specific objectives of the project:
- To investigate the total and serogroup specific burden of IMD in the EU/EEA, 2011-2015
- To explore which age groups that are in greatest risk of IMD by investigating the stratum specific burden of IMD
- To describe the distribution of IMD and IMD serogroup B in the EU/EEA by country specific analyses

Method

Data assessment

Data source and ethics statement
The analyses were conducted using data from The European Surveillance System (TESSy), 2011-2015. The data are notified to ECDC by the EU/EEA Member States, based on Decision 1082 of the European Parliament and of the Council (25). Case based data are coded automatically and no personal identifiers can be linked to the data. No informed consent or ethical permission is therefore needed.

EU/EEA Member States included
All European/EEA Member States were included with the exception of Liechtenstein, Bulgaria and Croatia. The decision to exclude these countries was based on data availability (Liechtenstein did not report during the observation period) and type of reported data (Bulgaria and Croatia only reported aggregated data). In summary, of the 30 European/EEA Member States that report IMD cases to ECDC, 28 countries were included in the analysis.

Inclusion criteria for cases and serogroups
As of 2015, most countries in the EU/EEA use a comprehensive, passive surveillance system with national coverage to report cases of IMD (18). Most Member States use either the European Commission 2012 case definition (26) or the case definition from 2008. Only confirmed cases in 2011-2015 were included in the analyses. This report focuses on serogroups that accounts for 5% or more of the total number of reported cases in the EU/EEA, 2011-2015. These serogroups are B (62%), C (14%), Y (8%) and W (5%). The other serogroups (A, X, Z, 29E) and cases with unknown serogroup (“not under surveillance”, “not groupable”, “other” and “unknown”) are referred to as “Other”.
Data quality
Completeness of data for invasive meningococcal disease varies between countries and years (2011-2015). The confirmed IMD cases reported to TESSy in 2011-2015, had an overall completeness of 90.6% for serogroup, 99.2% for sex and 99.2% for age. Cases with unknown sex and/or age were distributed according to the known distribution seen in the dataset. Cases with unknown serogroup were referred to as "unknown".

Model

Estimation of the annual number of IMD cases
To estimate the mean annual number of IMD cases in Europe, i.e. to account for fluctuations in yearly number of cases, all confirmed cases of IMD reported to TESSy in 2011-2015 were averaged. However, most national notifiable surveillance systems have some degree of underestimation of cases, which needs to be considered. Underestimation can be caused by underascertainment and underreporting. Underascertainment occurs at the community-level and represents the number of cases that for some reason do not attend healthcare. Underascertainment is more common for infections that are asymptomatic or infections that causes mild symptoms. Underreporting occurs on healthcare level and represents the cases that seek healthcare but are not captured by the surveillance system. This could be due to difficulties in diagnosis or limitations in the reporting system. Underreporting is less common for infections with mandatory reporting status. (27)

To adjust for underestimation a multiplication factor were applied, which multiplies the number of notified cases with a factor to give an estimate of the real incidence. There are different methods to define proper multiplication factors for certain infections and they can differ between surveillance systems (27). We applied the multiplication factor previously evaluated and used in the study of the burden of communicable diseases in Europe 2009-2013 (28). The multiplication factor was initially retrieved from the literature (29-31). The same range of multiplication factors, 1.01-1.14, were applied for all cases in the EU/EEA.

Age- and sex specific demographics and population data were retrieved from the Eurostat database 2014 (32).

Disease progression pathway
To compute the analyses the Burden of Communicable Diseases in Europe (BCoDE) toolkit were used. The BCoDE toolkit was developed by ECDC in 2015 to facilitate the calculation of DALYs from incidence-based data for 32 different infectious diseases and six healthcare-associated infections in Europe. (8, 9)

As input data, the estimated mean annual number of IMD cases in Europe by age, sex, serogroup and country were used. The toolkit uses a disease progression pathway that describes the progression of disease over time, from acute infection to death, resolution or long-term sequelae. The disease progression pathway is illustrated in a disease outcome tree (Figure 1). Each health outcome is given a disability weight, reflecting its severity (33). The risk of transitioning from acute infection to each health outcome is described using age- and sex dependent transition probabilities (34). YLLs and YLDs are then calculated in relation to the overall remaining life expectancy retrieved from the standard reference life table used in the Global Burden of Disease Study 2010 (35).
The duration of symptomatic invasive meningococcal disease is based on Tunkel et al 2014 (36) assuming antibiotic treatment. The likelihood of developing meningitis from an acute infection and the case fatality proportion (transition probability for death) are based on TESSy data for EU/EEA countries in 2011 (37). Disability weights are taken from Haagsma et al 2015 (33) and the transition probabilities are based on Edmond et al 2010 (34). All these measures are provided in the BCoDE toolkit.

Data analysis
Separate models were created in the BCoDE toolkit: One for all cases of IMD in the EU/EEA, one for each serogroup in the EU/EEA and two models for each country (one for all cases of IMD and one for IMD SgB). All variables except country specific population data and age- and sex-specific incidence data were kept static and inserted into the BCoDE software. The multiplication factors (1.01-1.14) was kept static for all cases, independent of age, sex and country. The models were run using Monte Carlo simulations at 1 000 iterations, without time discounting and age-weighting, to produce uncertainty intervals. The results were expressed as median DALYs per 100 000 total population or stratum specific population with 95% uncertainty intervals (UI).

Figure 1. Invasive meningococcal disease outcome tree showing the disease progression pathway with possible outcomes of an infection including death and lifelong sequelae

Source: The Burden of Communicable Diseases in Europe toolkit (8)
Results

Between 2011 and 2015, there were 16 484 confirmed cases of IMD reported to ECDC through TESSy. This gave a mean annual number of 3 297 cases per year in the EU/EEA. The overall mean notification rate was 0.65 per 100 000 total population. After adjusting for underestimation the mean annual estimated number of cases was 3 543 (95% UI: 3 487-3 599) and the mean annual estimated number of deaths was 315 (95% UI: 310-319).

The total annual burden of all cases of IMD in the EU/EEA was estimated at 3.87 DALYs per 100 000 total population (95% UI: 3.79-3.95) (Figure 2). Of the total burden, 2.54 DALYs (95% UI: 2.48-2.60) was due to serogroup B, 0.53 DALYs (95% UI: 0.52-0.54) was due to serogroup C, 0.25 DALYs (95% UI: 0.24-0.25) to serogroup Y, 0.18 DALYs (95% UI: 0.17-0.18) to serogroup W and 0.38 DALYs (95% UI: 0.38-0.39) was due to other serogroups. In total, 66% of the total burden of IMD in the included EU/EEA countries could be attributed to meningococcal serogroup B (Figure 2).

Figure 2. Median annual serogroup-specific burden of invasive meningococcal disease in the EU/EEA*, 2011-2015

By dividing cases into age groups and using the age specific (stratum specific) population as denominator, we generated the age-specific estimates of the burden of IMD (Figure 3). The age group with the highest annual burden was children younger than one year with 89.15 DALYs per 100 000 stratum specific population (95% UI: 83.10-95.02) followed by children aged 1-4 years with 22.57 DALYs per 100 000 stratum specific population (95% UI: 21.03-24.12). The burden of IMD decreased with rising age but showed a small peak in 15-24 year olds, with 7.98 DALYs per 100 000 stratum specific population (95% UI: 5.88-8.52). The notification rate followed a similar pattern as the burden of disease with highest rates in small children and a small peak in young adults.
Figure 3. Median annual age-specific notification rate and burden of invasive meningococcal disease in the EU/EEA*, 2011-2015

95% uncertainty intervals for DALYs per 100 000 total population per year are shown with error bars. The age-specific notification rates are retrieved directly from TESSy data, 2011-2015, with no adjustment for underestimation.

*Countries included: Austria, Belgium, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom

We then computed the age-specific estimates of the burden of IMD by serogroup. All serogroups showed a similar pattern with the highest burden in small children and a small peak in 15-24 year olds. The highest burden of serogroup Y was seen in the elderly (65 years and older). However, serogroup B had the highest burden of all serogroups in all age groups (Figure 4). Disease burden related to serogroup B was highest in children younger than one year with 68.49 DALYs per 100 000 stratum specific population (95% UI: 64.22-72.89) followed by children between 1-4 years with 17.12 DALYs per 100 000 stratum specific population (95% UI: 15.99-18.26).
Figure 4. Median annual age-specific burden of invasive meningococcal disease in the EU/EEA* 2011-2015, shown by serogroup

95% uncertainty intervals for DALYs per 100 000 total population per year are shown with error bars.

*Countries included: Austria, Belgium, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom

To do country specific comparisons within EU/EEA we estimated the country specific burden of IMD and the country specific burden of IMD SgB. The countries with the highest annual burden of IMD included Lithuania with 11.77 DALYs per 100 000 total population (95% UI: 11.52-12.01), Ireland with 10.29 DALYs per 100 000 total population (95% UI: 10.03-10.52), Malta with 10.01 DALYs per 100 000 total population (95% UI: 9.77-10.23) and the United Kingdom with 8.19 DALYs per 100 000 total population (95% UI: 8.02-8.40) (Figure 5).

Ireland, Lithuania and the United Kingdom also had the highest annual burden of IMD due to serogroup B with 9.15 (95% UI: 8.92-9.39), 7.49 (95% UI: 7.34-7.63), and 6.20 (95% UI: 6.05-6.35) DALYs per 100 000 total population, respectively (Figure 5 and 6). The distribution of burden if IMD serogroup B varied widely between the countries in the EU/EEA (Figure 6).

As seen in Figure 5, the proportion of disease burden attributed to serogroup B varied widely between countries. Countries with the highest proportional burden of serogroup B included Ireland (89%), the United Kingdom (76%), Latvia (76%), Belgium (77%), Greece (75%) and the Netherlands (76%). Other countries, including Sweden, Luxembourg and Malta had very low proportion of serogroup B, i.e. 28%, 9% and 26%, respectively. (Figure 5)
Figure 5. Median annual burden of invasive meningococcal disease and invasive meningococcal disease B in EU/EEA*, 2011-2015, shown by country

95% uncertainty intervals intervals for DALYs per 100 000 total population per year are shown with error bars.

*Countries included: Austria, Belgium, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom

Figure 6. Distribution of median annual burden of invasive meningococcal B disease in the EU/EEA*, 2011-2015

Burden of disease increases with darker colour.

*Countries included: Austria, Belgium, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom
To compare two countries with different proportions of serogroup B we calculated the annual burden of IMD by serogroup in Sweden and the United Kingdom (Figure 7). In Sweden, the total annual burden of IMD consisted of 28% related to SgB, 25% to SgC, 35% to SgY, 5% to SgW and 6% to other serotypes. In the United Kingdom, the total annual burden of IMD consisted of 76% related to SgB, 3% to SgC, 8% to SgY, 10% to SgW and 3% to others. This exemplifies the large differences in proportional serogroup distribution between countries (Figure 7).

Figure 7. Median annual burden of invasive meningococcal disease in Sweden and the UK 2011-2015, shown by serogroup

95% uncertainty intervals for DALYs per 100 000 total population per year are shown with error bars.

Discussion
This study is an epidemiological description of the annual burden of IMD in the EU/EEA, 2011-2015. We showed that the annual burden of all IMD cases in the EU/EEA during this period was 3.87 DALYs per 100 000 total population (95% UI: 3.79-3.95). Another, more general study of the burden of communicable diseases in Europe during 2009-2013 (28), showed that the total annual burden of all infectious diseases in Europe was 275 DALYs per 100 000 overall population. Influenza has a high annual burden of disease with around 80 DALYs per 100 000 total population and very rare diseases such as rabies has low burden with around 0.01 DALYs per 100 000 total population (28). When ranking infectious diseases according to the annual burden of disease per 100 000 total population, IMD is placed in the middle with a low to moderate burden. However, when using age-specific population data as denominator we can determine the annual burden of disease per age group and thereby identify the age group at risk for the specific disease. In this study, we show that the annual burden of IMD is considerably high in children younger than one year and in 1-4 year olds. This implies that children below five years of age is the age group at greatest risk of invasive meningococcal disease. In addition, we showed that there is a small but considerable peak of burden of disease in young adults (15-24 year olds).
The reason why children below five years are at greatest risk of IMD is not yet completely understood. As for many other infectious diseases, the immature immune system of infants and young children may play an important part in the risk of contracting the infection (21). IMD is mainly spread by close contact between people and crowded living conditions is believed to be a risk factor (20). Outbreaks of IMD have been seen in young adults living in University student dormitories and corridors and this could be one explanation to the small peak of burden of IMD seen in young adults (15-24 year olds) (20, 21).

The notification rate of IMD in the EU/EEA has decreased during the last years (38) for reasons are not yet fully understood. It could be due to natural fluctuations in the incidence of the disease, increased living conditions (limited spread of disease), or a consequence of increased vaccination coverage (21, 39). The Burden of Communicable Diseases in EU/EEA study, 2009-2013 (28), showed an annual burden of 4.78 DALYs per 100 000 total population (95% UI: 4.68–4.88), indicating a similar decreasing trend of the burden of IMD. The annual burden also varies widely between countries in the EU/EEA.

Some EU/EEA Member States provide general recommendation for vaccination with meningococcal disease C/ACWY (40). In a few countries, the vaccination is funded by the national health system. So far, three countries have introduced the meningococcal B vaccine into their national immunization programme: The United Kingdom (September 2015), Ireland (October 2016) and Italy (January 2017) (24). Data on vaccination coverage are collected using different methods. The WHO Centralized Information System for Infectious Diseases (CISID) project collects vaccination coverage data using a joint reporting form developed by WHO and United Nations Childrens Fund (UNICEF) (41). The European New Integrated Collaboration Effort (VENICE) project, sponsored by EC-DG SANCO and funded by ECDC, collects data on vaccination coverage from EU/EEA Member States through the European VAccination COverage Collection System (EVACO) (42). The quality and availability of the coverage data varies between vaccines/diseases and countries. Unfortunately, there are limited data on meningococcal vaccination coverage in the EU/EEA and therefore, no association studies on burden of disease and vaccination coverage could be done within this study.

Invasive meningococcal disease is found all around the world, but the highest incidence is seen in the so-called “meningitis belt” of Sub-Saharan Africa. This area has a high endemic burden of IMD and epidemic outbreaks are common during dry seasons (16, 21). Vaccination has been an important measure in order to control and limit these outbreaks. In Europe, small outbreaks of IMD can be seen occasionally. However, even small outbreaks in countries with small population size can have a considerable impact on the annual burden of disease. In addition, there could be heterogeneity in national surveillance systems, case definitions and methods of data reporting. Therefore, conclusions from the country specific analysis should be drawn with caution.

We showed that 66% of the total annual burden of IMD in the EU could be attributed to serogroup B and that the burden of serogroup B was proportionally highest of all serogroups in all age groups. Furthermore, we showed that the distribution and proportion of serogroup B varied widely between countries in the EU/EEA. It has been previously known that the serogroup distribution of IMD varies in different parts of the world. In Europe, we have had a history of proportionally high incidence of meningococcal C whereas meningococcal A has been responsible for most of the outbreaks in Africa (16, 21, 39). The reasons for the country specific differences in serogroup distributions within EU/EEA are not known. It could possibly be a result of different vaccination programmes and serogroup replacement (21). However, these questions need to be further investigated.
Country specific studies on burden of serogroup B was one important factor considered when assessing the need for introduction of the new meningococcal B vaccine in the EU/EEA Member States (24). As mentioned, this study shows the relevance of performing age-specific analyses of burden of disease in order to identify the age groups at risk when assessing the need for introduction of a vaccine. The meningococcal B vaccine under assessment is a childhood vaccine that can be introduced in the national immunization programs starting at two months of age (22, 23, 43). Country specific evaluations are ongoing or planned by some EU/EEA Member States. This study provides a comprehensive EU-wide overview of the burden of meningococcal disease B.

We wanted to compare two countries with different proportional burden of serogroup B and decided to use Sweden, with low proportional burden of serogroup B (28%), and the United Kingdom with high proportional burden of serogroup B (76%). The total burden of invasive meningococcal disease in these two countries also differs significantly. The United Kingdom had a total annual burden of 8.18 (95% UI: 8.02-8.40) DALYs per 100 000 total population whereas Sweden had a total annual burden of 3.29 (95% UI: 3.22-3.39) DALYs per 100 000 total population.

The United Kingdom introduced the meningococcal C vaccine into their routine immunization programme in 1999 and since then, the incidence rates for meningococcal disease C have decreased steadily (44). The United Kingdom is one of the three countries that have introduced the new meningococcal B vaccine into their publicly funded immunization programme. The vaccine was introduced in September 2015 after careful investigation of the possible health benefits as well as the cost effectiveness (17, 45-47).

Due to the low national burden of invasive meningococcal disease, Sweden has not included meningococcal vaccines into their routine immunization programme (48). Vaccination against meningococcal disease is only recommended for certain risk groups, such as people with certain types of immunodeficiency and some travellers. Since meningococcal disease serogroup B only represents 28% of the total annual burden of IMD in Sweden, there are no plans to assess the IMD SgB vaccine in the near future (48). As seen in Figure 7, Sweden had a relatively large proportion of serogroup Y (35%). This is surprising since the proportion of serogroup Y of the total annual burden in EU/EEA is very low (6%) (Figure 1). However, this large proportion seen in Sweden can be explained by an increased incidence of serogroup Y in the elderly during 2012 (49). In summary, Sweden have had a low annual incidence of IMD since the 1980s and the trend is decreasing (48). As mentioned, the specific reasons for why the annual burden and serogroup distribution differs considerably between countries such as Sweden and the UK need to be further investigated.

Strengths and limitations

The limitations of this study are mainly due to its modelling assumptions. The same range of multiplication factors are used for all computations, although underestimation can (and probably does) differ by country. On the other hand, the invasive nature of the disease limits the risk of underestimation due to underascertainment, which is reflected in the low multiplication factor of choice (1.01-1.14).

We also assumed the same transition probabilities and case fatality ratios in the disease progression pathway for all serogroups. We found weak indications of differences in case fatality ratios for the different serogroup, although we had too small a sample size on serogroup specific data to find any significant differences. Further serogroup specific research needs to be conducted in order to clarify these differences.
We have not modelled the impact of immunization on the burden of IMD, as the availability and quality of vaccination coverage data was poor. To conduct such a modelling exercise within the BCoDE framework, one needs to run the toolkit according to several scenarios: a baseline scenario using current vaccine coverage, and other hypothetical scenarios with increasing coverage, and compare the resulting burden estimates. Alternatively, country-specific burden estimates may be examined against country-specific vaccine coverage to see if there is a correlation (50). These approaches remain to be addressed and would be valuable to investigate with future research.

We want to emphasize that this model, like any disease model, is a simplification of the real world setting. However, the BCoDE toolkit methodology and the use of TESSy, enables comparison of data on an EU-wide level and provides a unique opportunity to summarize EU-data in a comprehensive way.

**Conclusions**

By estimating burden of disease in DALYs we have exemplified how to use surveillance data for benefit/risk monitoring of vaccines in the EU within the context of the IMI ADVANCE project. We have shown that the total mean annual burden of IMD in the EU/EEA 2011-2015 is low to moderate with 3.87 DALYs per 100 000 total population (95% UI: 3.79-3.95).

We have also shown that serogroup B is accountable for 66% of the mean total burden of IMD in the EU/EEA and has the highest serogroup specific burden in all age groups. By computing country specific analyses, we showed that the distribution and proportional burden of serogroup B differs significantly between countries. This was exemplified in a broader analysis of the serogroup specific burden of IMD in the UK and Sweden.

Furthermore, we showed that the highest stratum specific burden of IMD SgB, was seen in children under one year of age with 68.49 DALYs per 100 000 stratum specific population (95% UI: 64.23-72.98), followed by children between 1-4 years of age with 17.12 DALYs per 100 000 stratum specific population (95% UI: 15.99-18.26). This finding shows that children under five years of age are at the greatest risk of IMD SgB, and confirm that national assessment of the new infant meningococcal B vaccine is highly relevant.

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**Annex A – Popular scientific summary**

**Small children are at highest risk of bacterial meningitis**¹

It has been more than 200 years since the first vaccine was developed and since then, vaccination has been one of our most powerful weapons in the fight against infectious diseases. Even though immunization programmes successfully eradicated smallpox, and have almost eliminated the spread of polio-virus, we are still facing challenges to convince the public of the great value of vaccination.

One way to address the vaccine hesitancy is to provide scientific evidence on vaccine benefits and risks. This evidence is also needed in order to facilitate evidence-based policymaking. What vaccines should be used, when, where and for whom?

Even though all vaccines go through careful safety and efficacy testing before being released on the market, monitoring of their effects does not stop when they become widely used but needs to continue. This is called “post-marketing monitoring” and answer the following questions: Does the vaccine provide the expected protection? Are there any side effect we did not know of? What are the actual benefits?

After the flu pandemic of 2009, the European Medicine Agency called for improved post-marketing monitoring of vaccines in the EU. An EU-wide project called “IMI ADVANCE” were initiated to fulfil this task. The project found out that an important part of such monitoring of vaccines is the investigation of burden of disease, against the vaccines protect us. This means finding out how much suffering and death is caused by a vaccine-preventable disease, and can be circumvented using vaccination?

As an example, in 2013, a new vaccine against one common type of meningitis was licensed in the EU and many EU Member States began to assess the need for introducing this vaccine.

Meningitis, like many other infectious diseases, does not only account for many deaths but do also causes life-long disabilities in the patients who survive. Such disabilities include limb amputations, deafness, cognitive difficulties and neurological problems. When we want to estimate the burden of a vaccine-preventable disease, it is therefore important to include both the number of cases and deaths but also the amount of suffering caused by long term disabilities.

To include both elements in our analysis, we used a dedicated software tool, called “BCoDE”. It helped us discover that children below five years of age had the highest burden of meningitis and that they are at the greatest risk of the disease. This means that infants and small children should be the primary target for potential vaccination.

When we looked at country specific data, we could see that there were big differences between the countries in terms of the burden of meningitis. This may mean that the countries may consider various strategies of vaccinating against the disease.

The study of burden of disease is one part of a complex system used for post-marketing monitoring of vaccines. When technology improves, we will have access to larger datasets and even more complex information systems. As we enter an era of “big data” we need to improve our methods for collecting, analysing and comparing data and determine how to best provide evidence on the benefits and risks of vaccines. This project shows how this can be done.

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¹ Meningitis is an inflammation of membranes covering and protecting the brain.