Saudi Arabia (SA) experienced two large invasive meningococcal disease (IMD) outbreaks during the 2000 and 2001 Hajj pilgrimages. In 2002, polysaccharide quadrivalent ACWY vaccines became mandatory for Mecca and Medina pilgrims/residents older than two years. This study aimed to analyse IMD surveillance data among citizens, residents and pilgrims in SA from 1995 to 2011, focusing on changes before and after the new vaccination policy. For all laboratory-confirmed IMD cases in the national surveillance database from 1995 to 2011, serogroup and age were retrieved. The cases’ seasonal distribution as well as the case fatality ratios (CFR) were obtained. For Saudi citizens/residents and Hajj pilgrims, annual rates were calculated using mid-year population estimates. The Student’s t-test was used to compare means between the pre-epidemic (1995–1999) and post-epidemic (2002–2011) periods, excluding outbreak years. From 1995 to 2011, laboratories notified 1,103 cases. Between the pre- and post-epidemic periods, mean annual IMD rates decreased from 0.20 (standard deviation (SD): 0.1) to 0.06 cases/100,000 (SD: 0.06; p=0.02), mean numbers of Hajj-related cases from 13 (SD: 9.3) to 2 cases/year (SD: 2.3; p=0.02) and the mean age from 31 (SD: 1.3) to 18 years (SD: 1.4; p<0.01). The CFR in Saudi citizens (10.4) was lower than among foreign pilgrims (28.9) and decreased from 19.3% (SD: 1.8) in the pre-epidemic to 11.4% (SD: 7.0; p=0.04) in the post-epidemic phase. The decrease of annual IMD rates, CFR and Hajj-related cases between the pre- and post-vaccine era suggests a possible positive effect of the mandatory ACWY vaccination for pilgrims/residents in Mecca and Medina. Regular surveillance with an annual data analysis is necessary to monitor trends and circulating serotypes and to implement appropriate public health measures to avoid new IMD epidemics during upcoming Hajj seasons.

Introduction
Invasive meningococcal disease (IMD) is caused by the gram-negative coccoid bacterium Neisseria meningitidis [1,2]. Transmission via respiratory droplets can lead to bacterial meningitis and septicaemia in the persons who get infected. Six serogroups (A, B, C, W135, X and Y) differentiated by their polysaccharide capsule, account for the majority of IMD cases [3]. IMD primarily affects children below five years of age, causing an estimated 500,000 cases and 50,000 deaths annually worldwide [4]. Polysaccharide and conjugated vaccines are available for serogroups A, C, W135 and Y [5]. One vaccine for serogroup B has been licensed in Europe in January 2013 and other serogroup B vaccines have been used in New Zealand, Cuba and France to control epidemics [6].

In Saudi Arabia (SA), the annual Hajj and the year-round Umrah pilgrimage lead to a particular high risk of outbreaks with invasive N. meningitidis. The Hajj pilgrimage is held on every 12th month of the Islamic calendar (2011 attendance: 2.9 million pilgrims, including 1.8 million from >140 foreign countries), making it one of the largest mass gathering events worldwide [7-9]. About 45,000 pilgrims arrive from the European Union each year [7]. Compared to the Hajj, the Umrah pilgrimage includes slightly different rituals and can be undertaken at any time of the year. Foreign pilgrims generally arrive by air in the city of Jeddah and continue to the pilgrimage sites in Mecca, Mina, Mount Arafat and Muzdalifah. Many end the journey with a visit to the holy sites in Medina [7]. Extreme congestion with populations from diverse geographical areas appears to promote a high prevalence of asymptomatic N. meningitidis carriage, with up to 80% reported for Mecca pilgrims [10,11]. In comparison carriage prevalence between 3% and 30% has been shown for the
African meningitis belt and in a Norwegian randomised study, 9.6% of Norwegian volunteers harboured *N. meningitidis* [12,13]. The United States (US) Centers for Disease Control reported five to 10% of adults as asymptomatic nasopharyngeal carriers [14].

Following an outbreak of serogroup A IMD among pilgrims in 1987, Saudi Arabian health authorities implemented three interventions: (i) the compulsory vaccination before entering SA with bivalent AC vaccine for all Hajj pilgrims, (ii) annual vaccination campaigns for all residents in the proximity of pilgramage sites and (iii) compulsory oral ciprofloxacin upon entering SA to pilgrims from sub-Saharan Africa to eradicate nasal carriage [11,15,16].

In response to two large IMD outbreaks caused by *N. meningitidis* serogroup W135 in the 2000 and 2001 Hajj seasons [15,17], the SA Ministry of Health (MoH) adjusted their vaccination policy. In 2002, they required a polysaccharide quadrivalent non-conjugated ACWY meningococcal vaccine for (i) children and adults aged above two years living in Mecca and Medina, (ii) Hajj pilgrims aged above two years from within and outside of SA, (iii) healthcare workers in SA and (iv) government personnel serving the pilgrims [18]. Since 2010, a conjugated polysaccharide quadrivalent ACWY meningococcal vaccine is given to the same target groups aged from above two to 55 years. The vaccines are administered during annual vaccination campaigns in Mecca and Medina in a single dose with boosters every three years. As of 2013 no meningococcal vaccines are included in the Saudi national childhood immunisation schedule (NCIS). This study aims to describe the epidemiology of IMD in Saudi Arabia for the years 1995 to 2011, with a focus on changes in incidence and case fatality ratio (CFR) after the introduction of the polysaccharide quadrivalent ACWY vaccine in 2002, in order to evaluate the effect of this Hajj vaccination policy change.

Methods

A confirmed IMD case was defined as either isolation of *N. meningitidis* from cerebrospinal fluid (CSF) or blood or detection of capsular antigen in CSF by latex agglutination assay [19]. An IMD surveillance system was started in 1994 in SA based on recommendations of the World Health Organization (WHO) [20]. Since then, the Preventive Medicine Directorate at the MoH requires laboratories from all 20 health regions in SA to anonymously report confirmed IMD cases. The case-based reporting form collects information on age, sex, nationality, SA residency status, vaccination status, date of onset of symptoms (by Gregorian and Islamic calendar), clinical status and place of laboratory confirmation (health region). Information on the capsular groups, determined by latex agglutination, is also collected on the reporting form.

For the purposes of this study, all IMD cases in the surveillance database from 1 January 1995 to 31 December 2011 were extracted. This included cases among Saudi citizens and residents, foreign pilgrims and illegal immigrants. A citizen was considered a person in possession of the Saudi Arabian nationality, and a resident a person originating from outside SA but residing and working in SA. A foreign pilgrim was defined as a person holding a special visa for the Hajj or Umrah pilgrimage, whereas an illegal immigrant was an unregistered person devoid of any valid entry permit for SA. Hajj-related cases were specified as IMD cases with dates of disease onset during the Hajj season in the cities of Mecca or Medina.

Statistical analysis

Age group-, sex- and region-specific annual and cumulative disease incidences were calculated for IMD cases among Saudi citizens or residents. Age group- (0–4; 5–14; 15–64; >65 years of age) and year-specific population denominators were obtained from the United Nations Development Programme (UNDP) website [21]. To calculate the cumulative incidence over several years, mid-period population estimates were used as a denominator. The Ministry of Hajj, Saudi Arabia [22] provided the numbers of foreign and domestic Hajj pilgrims. For foreign Hajj pilgrims, no age or sex specific incidences have been calculated, as no age or sex specific Hajj pilgrim numbers were available. In the absence of a population register to calculate rates, illegal immigrants were excluded from any incidence calculations.

From all cases, regardless of citizenship and nationality, numbers of Hajj-related IMD cases as well as year, age and region specific CFRs were calculated. Relative risks for death from IMD were identified by calculating ratios of case-fatalities and their 95% confidence intervals (95% CIs) for the residence status, seasons, age groups and sex. The Student’s t-test was used to compare means (age, CFRs and number of cases) between the pre-epidemic (1995–1999) and post-epidemic (2002–2011) periods, excluding the outbreak years (years 2000, 2001), and linear regression models were fitted to describe trends. A p-value <0.05 was considered statistically significant. Surveillance data were computerised using Excel programme (Microsoft, USA) and statistical analysis was performed with Stata 12 (Statacorp, Texas, USA) software.

Results

Study population

During the study period, the population of SA rose from 18,491,845 in 1995 to 27,448,000 persons in 2011, the latter of which comprises 68% SA citizens and 32% residents of foreign origin [21]. In 2011, children less than five years-old and adults above 65 years of age accounted for 10%, and 3% of the population, respectively. The largest population increase has been recorded for the 15 to 64 years age group, which comprised 66.7% of the population in 2011 (compared to 56.1 in 1995). Forty-five percent of the population were
There were 1,936,124 and 1,858,490 persons registered in the health districts of Mecca and Medina in 2011 respectively, representing 14% of the population in SA. During the study period the number of Hajj pilgrims increased by 57% from 1,865,234 (1,080,465 from outside SA) in 1995 to 2,927,717 (1,828,195 from outside SA) in 2011 [22].

Annual and cumulative invasive meningococcal disease incidences

Between 1995 and 2011, 1,103 cases of IMD were reported to the MoH in SA (Table 1). Of those, 645 cases were Saudi citizens/residents and 299 were foreign Hajj pilgrims. Of the remaining cases, 82 were illegal immigrants (not included in incidence calculations), 73 were foreign Umrah pilgrims and four had unknown identity (combined cumulative incidence of IMD among citizens, residents and foreign Hajj pilgrims: 3.92/100,000 population). Between 1995 and 1999, the mean annual incidence was 0.20/100,000, ranging from 0.25/100,000 in 1995 to 0.06/100,000 in 1999 (Figure 1A). In the two outbreak years of 2000 and 2001, the annual incidence increased to 1.42 and 1.32/100,000, respectively. In the post-epidemic period, the mean annual incidence did not exceed 0.06/100,000, ranging from 0.21/100,000 in 2002 to 0.01/100,000 in 2010, a significant decrease compared to the pre-epidemic period (p=0.02) (Figure 1A).

Age, sex and region specific incidence for Saudi Arabia citizens and residents

For SA citizens and residents, in the study period, the age group including less than four year-olds had the highest cumulative incidence, with both sexes equally affected (12.3 cases/100,000; Figure 2). Above four years of age, males had a higher cumulative incidence. Among those between 15 and 64 years of age, cumulative incidence among males (1.8 cases/100,000) was three times higher than among females (0.6 cases/100,000).

In an analysis restricted to SA citizens and residents, the cumulative incidence between 1995 and 2011 (2.85 cases/100,000) was lower compared to rates including Hajj pilgrims. Outside the outbreak periods the annual incidence followed the same trend described above (Figure 1A).

<table>
<thead>
<tr>
<th>Confirmed IMD cases</th>
<th>Residency status</th>
<th>Citizen</th>
<th>Resident</th>
<th>Visa-holding Hajj pilgrim</th>
<th>Visa-holding Umrah pilgrim</th>
<th>Illegal</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td></td>
<td>227/149</td>
<td>181/88</td>
<td>136/163</td>
<td>54/19</td>
<td>78/4</td>
<td>3/1</td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td></td>
<td>9.6 (0.8)</td>
<td>14.4 (1.0)</td>
<td>48.9 (0.9)</td>
<td>51.4 (2.1)</td>
<td>29.5 (1.2)</td>
<td>35 (2.9)</td>
</tr>
<tr>
<td>Number of deaths</td>
<td></td>
<td>39</td>
<td>28</td>
<td>111</td>
<td>14</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Time period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1995–1999</td>
<td></td>
<td>78</td>
<td>61</td>
<td>60</td>
<td>46</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>2000–2001</td>
<td></td>
<td>193</td>
<td>179</td>
<td>223</td>
<td>26</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>2002–2011</td>
<td></td>
<td>105</td>
<td>29</td>
<td>16</td>
<td>1</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Serogroup</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Serogroup A</td>
<td></td>
<td>36</td>
<td>45</td>
<td>63</td>
<td>30</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Serogroup B</td>
<td></td>
<td>33</td>
<td>7</td>
<td>22</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Serogroup C</td>
<td></td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Serogroup W135</td>
<td></td>
<td>153</td>
<td>99</td>
<td>110</td>
<td>4</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Other serogroups</td>
<td></td>
<td>11</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unknown serogroups</td>
<td></td>
<td>138</td>
<td>115</td>
<td>104</td>
<td>35</td>
<td>52</td>
<td>3</td>
</tr>
<tr>
<td>Total confirmed IMD cases</td>
<td></td>
<td>376</td>
<td>269</td>
<td>299</td>
<td>73</td>
<td>82</td>
<td>4</td>
</tr>
<tr>
<td>Mid-period population estimates (1995–2011)</td>
<td></td>
<td>22,652,297</td>
<td>1,452,978</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

IMD: invasive meningococcal disease; SD: standard deviation.

a Unless otherwise specified.

b For the period considered, only the number of citizens and residents combined are available. No reliable numbers for Umrah pilgrims and persons with illegal residency status are available.
Hajj-related cases

In the 2000 and 2001 outbreak years, IMD cases from Mecca and Medina during the Hajj accounted for 49% and 31% of all notified annual IMD cases, respectively (Figure 1B). In contrast, between 2002 and 2011, only a mean annual 8.1% (standard deviation (SD): 10.1) of all IMD cases were reported from Mecca or Medina during the Hajj season. Since 2006, during Hajj seasons, Medina reported only one case of IMD. The mean numbers of Hajj-related cases was higher (13.4 cases/year; SD: 9.3) during the pre-epidemic than during the post-epidemic years (1.7 cases/year; SD: 2.3; p=0.02).

Distribution of mean age

In the period between 1995 and 2011, among Saudi citizens and residents, the age group comprising those younger than four years had the highest disease incidence. However, the mean age of all IMD cases, including pilgrims, between 1995 and 2011 was 31.6 years (SD: 1.9) in the pre-epidemic period to 18 years (SD: 1.4) in the post-epidemic period (p<0.01; b coefficient -1.27, Figure 3).

The mean age of IMD cases during the Hajj season (37.0 years; SD: 1.0) was higher (p<0.01) than among cases outside this season (17.4 years; SD: 0.8). Similarly, the mean age of IMD cases among foreign Hajj and Umrah pilgrims (48.9 years (SD: 0.9); 51.4 years (SD: 2.1), respectively) was higher (p<0.01) than among Saudi residents cases (14.4 years; SD: 1.0) or citizens (9.6 years; SD: 0.8). Finally, cases in Mecca (33.9 years; SD: 1.2) and Medina (31.4 years; SD: 1.8) had a higher mean age than in other health regions (16.7 years; SD: 0.8) (p<0.01).

Serogroup distribution

Serogroup results were available for 59% (656/1,103) of all cases reported between 1995 and 2011. In 33% (369/1,103) the serogroup could not be determined and in 7% (78/1,103) no information was submitted (Table 2). In one isolate, serogroups A and C and in nine isolates serogroups A, C, W135 and Y were not further subtyped. Of all serogrouped isolates, 89% (587/656) belonged to the vaccine preventable serogroups A, C, W135 and Y. From 1995 to 1999, the predominant serogroup was A, accounting for 49% (77/158) of all typed isolates, followed by B with 26% (41/158) and serogroup W135 with 20% (31/158) of isolates (Table 2). During the 2000 and 2001 outbreak years, the emerging serogroup W135 predominated, accounting for 78% (298/383) of typed isolates, while during the post-epidemic period between 2002 and 2011, serogroups A and W135 were almost equally distributed (36% (41/115) and 40% (46/115), respectively), while serogroup B accounted for 17% (19/115) of typed isolates.

The age group below one year is dominated by isolates of serogroup B (19% (14/74)) and serogroup W135 (70% (52/74)). In those aged one through four years, serogroup W135 is by far the most common serogroup (78%
The black line can be expressed by the equation \( y = 34.108 - 1.2747x \); \( R^2 = 0.54 \).

The mean age of invasive meningococcal disease cases was 31 years (standard deviation (SD): 1.3) in the pre-epidemic period (1995–1999) and 18 years (SD: 1.4) in the post-epidemic period (2002–2011).
(112/143)) among typed isolates. Above four years of age, serogroups A and W135 comprise 87% (385/439) of all typed isolates in those age groups. Serogroups other than A, B and W135 contribute only marginally to the IMD burden in SA (Table 2).

Case fatality
Between 1995 and 2011, the overall reported CFR was 18.0% (198/1,103), with a decrease from an annual mean of 19.3% (SD: 1.8) in the pre-epidemic years to 11.4% (SD: 7.0) in the post-epidemic years (p=0.04). The CFR increased with age, from 6.8% in the <1 year-olds to 32.6% in the >45 years age group (Table 3). When stratified by age groups, no significant changes in the CFR for the <5 years group between pre-epidemic (13.6%; 95% CI: 0.0–39.6), epidemic (6.3%; 95% CI: 0.0–40.6) and post-epidemic years (12.4%; 95% CI: 3.2–21.6) were observed (Table 4). For cases >5 years of age, the CFR decreased significantly between the pre-epidemic (20.72%; 95% CI: 18.2–23.2) and post-epidemic period (8.72%; 95% CI: 2.6–14.8). During the epidemic the CFR for cases above five years-old was significantly elevated (25.6; 95% CI: 24.9–26.2). The CFR was similar for the most common serogroups (A: 21.8%; B: 21.2%; C: 20.0%; W135: 19.7%). Among Hajj or Umrah pilgrims from foreign countries the CFR was 2.8 times higher than Saudi citizens/residents (Table 3). In addition, the CFR during the Hajj season (28.6%) was 2.9 times higher than outside the season (10.0%).

Discussion
According to the present study and confirming previous reports, the Hajj season constitutes a special opportunity that is very favourable to IMD epidemics [7,9,10]. The high morbidity and fatality for pilgrims during the Hajj season might be largely explained by epidemiologically unfavourable conditions (e.g. crowding, delayed clinical and laboratory diagnosis). Our study indicates that the incidence of IMD decreased in SA following the introduction of the ACWY vaccine in 2002. More specifically, Hajj-related IMD cases declined after the introduction of the vaccine compared to pre-epidemic years. The results suggest that the compulsory use of the ACWY vaccine for pilgrims and residents of Mecca and Medina may have played a role in reducing not only Hajj-related IMD cases, but also the overall disease incidence in SA.

Children under five, predominantly affected by serogroup B and W135 infections, suffered the highest age-specific incidence of IMD throughout the study period. This is consistent with experience from the United Kingdom (UK), the US and Germany, where B is the most prevalent serogroup in children below five years [23-25]. The mean age of cases decreased during the study period. Two factors may explain this evolution. First, there could have been a decrease in IMD in adolescent or adult Hajj pilgrims since 2002 because of the vaccine introduction for all Hajj pilgrims. Second,
no meningococcal vaccines are yet given to children below three years-old according to the Hajj vaccination policy from 2002.

The CFR of IMD was highest among older age groups, as reported elsewhere [23,26]. Our data indicate that one third of deaths occurred among persons ≥45 years of age. Following introduction of ACWY meningococcal vaccine, both the IMD morbidity and the CFR for above four-year-olds decreased among the SA population including Hajj pilgrims. A number of factors could be responsible for this finding. First, the reduced number of cases among pilgrims during the Hajj season in recent years contribute to a lower CFR, as clinical and laboratory diagnosis might be delayed during the Hajj and pilgrims seek medical care too late while being on the pilgrimage. Second, the reduction in the mean age of cases might contribute to the decreased CFR and third, there might have been increased awareness after the two outbreak years 2000 and 2001 leading to a more rapid diagnosis and therefore improved healthcare measures. The reported CFR outside of the Hajj season (10%, and 11% for the whole post-vaccination period) were comparable to reports from non-endemic European countries. Austria, France, Germany, UK reported CFRs ranging from 8.2 to 12.5% [24,25,27-29].

The majority of outbreak-related cases were caused by N. meningitidis serogroup W135. The responsible clone was later found to belong to the ST-11/ET-37 complex [34]. Genetic analysis of the clone suggested that a capsular switch from serogroup C to serogroup W135 may have occurred years before the onset of the outbreak [34]. The same hypervirulent clone caused serogroup C disease in Belgium, Iceland, Ireland, the Netherlands, Portugal and the UK in the late 1990s and early 2000s [10]. Concerns had been raised that mass immunisation with vaccines that do not protect against all serogroups could lead to an increase in incidence of meningococcal disease due to strains not included in the vaccine [35,36]. Following the introduction of ACWY vaccines, this phenomenon of serotype replacement, or a major emergence of non-vaccine serotypes, has not been reported in Mecca and Medina, or elsewhere.

Vaccine coverage data are needed to determine whether the vaccine contributed to reduced morbidity. While no coverage data are available for foreign Hajj pilgrims, the entry requirement that is enforced through border checks suggest that coverage should be high. In comparison, compliance among Saudi pilgrims may be poorer, since Saudi citizens do not have to provide proof of vaccination at border controls or check points. In 2006, a study of 134 British and 109 Saudi Hajj pilgrims reported that vaccine coverage was lower among local residents (64%) than among British pilgrims (100%) [37]. According to this study, 50% of local pilgrims residing in Mecca and Jeddah had been

### Table 4

<table>
<thead>
<tr>
<th>Age group</th>
<th>Mean of the annual CFR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 years-old</td>
<td>13.64 (0.00–39.56)</td>
</tr>
</tbody>
</table>

95% CI: 95% confidence interval.

* CFR = (Number of deaths /Number of confirmed IMD cases) in each category.
vaccinated, compared with 71% from the rest of the country. Overall, a larger vaccine coverage study would obviously help interpret results of IMD surveillance data.

Conclusion

Saudi-Arabian IMD surveillance data highlight the shift from Hajj-related cases towards non-Hajj related ones, following the introduction of the ACYW vaccine in 2002. The number of cases and the CFR also declined, suggesting a potential positive effect of the current Hajj vaccination policy, among other factors. On the basis of our investigations, we can formulate a number of recommendations. First, regular monitoring of vaccination coverage would help interpret trends of IMD. Second, the surveillance system could be improved through notification of clinically suspected and epidemiologically-linked cases as well as including more sensitive molecular biology based diagnostic methods. Third, inclusion of information on possible links to the Hajj could be considered for the surveillance form. Continued surveillance with annual data analysis remains necessary to drive adapted public health measures and avoid future IMD epidemics during the Hajj seasons of the coming years.

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Conflict of interest

None declared.

Authors’ contribution

All authors contributed to the drafting, writing, and reviewing of the manuscript.

References


