Temporal associations between national outbreaks of meningococcal serogroup W and C disease in the Netherlands and England: an observational cohort study

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Summary

Background Since 2009, the incidence of meningococcal serogroup W disease has increased rapidly in the UK because of a single strain (the so-called original UK strain) belonging to the hypervirulent sequence type-11 clonal complex (cc11), with a variant outbreak strain (the so-called 2013 strain) emerging in 2013. Subsequently, the Netherlands has had an increase in the incidence of meningococcal serogroup W disease. We assessed the temporal and phylogenetic associations between the serogroup W outbreaks in the Netherlands and England, and the historical serogroup C outbreaks in both countries.

Methods For this observational cohort study, we used national surveillance data for meningococcal serogroup W and serogroup C disease in the Netherlands and England for the epidemiological years (July to June) 1992–93 to 2015–16. We also did whole genome sequencing and core genome multilocus sequence typing (1546 loci) on serogroup W disease isolates from both countries for surveillance years 2008–09 to 2015–16. We used Poisson regression to compare the annual relative increase in the incidence of serogroup W and serogroup C between both countries.

Findings In the Netherlands, the incidence of meningococcal serogroup W disease increased substantially in 2015–16 compared with 2014–15, with an incidence rate ratio of 5·2 (95% CI 2·0–13·5) and 11% case fatality. In England, the incidence increased substantially in 2012–13 compared with 2011–12, with an incidence rate ratio of 1·8 (1·2–2·8). The relative increase in the Netherlands from 2014–15 to 2015–16 was 418% (95% CI 99–1248), which was significantly higher than the annual relative increase of 79% (61–99) per year in England from 2011–12 to 2014–15 (p=0·03). Cases due to meningococcal serogroup W cc11 (MenW:cc11) emerged in 2012–13 in the Netherlands. Of 29 MenW:cc11 cases found up to 2015–16, 26 (90%) were caused by the 2013 strain. For both the current serogroup W outbreak and the historical serogroup C outbreak, the increase in incidence started several years later in the Netherlands than in England, the rate of increase was higher in the Netherlands, and age distributions were similar in both countries.

Interpretation Given the historical similarities of meningococcal serogroup W with meningococcal serogroup C emergence, the rapid expansion of the MenW:cc11 2013 strain in the Netherlands, its high case fatality, and the availability of a safe and effective vaccine, urgent consideration is needed for public health interventions in the Netherlands and other affected countries to prevent further serogroup W cases and deaths.

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Introduction

Meningococcal disease is caused by the Gram-negative bacterium *Neisseria meningitidis* and can cause severe disease including septicaemia and meningitis. Because meningococcal disease progresses rapidly, often presenting initially with non-specific symptoms, it is not always recognised in time, which contributes to the high case fatality and devastating long-term consequences for survivors.[1] Lifelong severe sequelae occur in 6% of survivors of meningococcal disease, and include deafness, limb amputation, and brain damage.[1] In a study from the Netherlands, 32% of children who survived bacterial meningitis (caused by various pathogens including *N meningitidis*) had cognitive limitations, behavioural limitations, or both.[2] Different meningococcal serogroups can be discerned on the basis of differences in the polysaccharide capsule, of which serogroups A, B, C, W, Y, and X cause most meningococcal disease worldwide.[3]

In England and Wales, the occurrence of invasive meningococcal disease was fairly stable in the early 1990s, with around 1200 laboratory-confirmed cases and an incidence of approximately 2·3 cases per 100 000 population reported each year up to 1994–95.[4] However, from 1995–96, the incidence of laboratory-confirmed disease increased, peaking at 5·4 cases per 100 000 population in 1998–99. This increase was mostly attributable to an increase in

Research in context

Evidence before this study

On Feb 14, 2017, we searched MEDLINE, Embase, SciSearch, and BIOSIS Previews for reports of meningococcal serogroup W disease in Europe, published since Jan 1, 2010, with no language restrictions. We did this literature search using terms for meningococcal serogroup W disease in combination with search terms for European countries. We identified 185 reports, including 19 with information on the incidence of meningococcal serogroup W disease in a European country since 2010. Of these 19 reports, ten were from the UK, six were from other European countries (Austria, Spain, and two publications each from the Czech Republic and Poland), and three included data from multiple countries, including Sweden. The reports from the UK showed that since 2009, the meningococcal serogroup W cc11 (MenW:cc11) South American strain sublineage has diversified with the emergence of a related strain, which expanded to cause an outbreak of serogroup W disease that is still ongoing in the UK. This outbreak has been accompanied by the rapid expansion of an emergent substrain in the UK since 2013. In response to the serogroup W outbreaks, quadrivalent conjugate meningococcal vaccination (MenACWY) programmes were implemented in the UK. Also in Europe, increasing incidence of serogroup W disease has been reported in Spain and Sweden. Reports from Austria and Poland did not include data for years since 2012. The increase in serogroup W disease in Spain and Sweden was attributed to the emergence of a strain with a similar typing profile as the MenW:cc11 South American strain and other MenW:cc11 sublineages (W:P1.5,2:ST-11).

Added value of this study

Our results show the emergence of the MenW:cc11 outbreak strain in the Netherlands, particularly the variant that emerged in the UK in 2013. The increase in incidence of meningococcal serogroup W disease in the Netherlands started 3 years after the increase in serogroup W incidence in England, and the rate of increase was higher in the Netherlands. This pattern resembles the historical outbreak of serogroup C disease around 2000, in which the increase in the Netherlands also started several years after the increase in England and the rate of increase was also higher in the Netherlands. Additionally, the age distributions of the serogroup W cases belonging to the MenW:cc11 outbreak strain were similar between the Netherlands and England.

Implications of all the available evidence

Given the rapid expansion of the MenW:cc11 strain causing meningococcal disease in the UK, the Netherlands, and several other European countries, close monitoring is needed in all European countries, along with early considerations for public health interventions, including vaccination.

meningococcal serogroup C disease; between 1994–95 and 1995–96, the number of cases of serogroup C disease more than doubled and the proportion of meningococcal disease cases caused by serogroup C infection increased from 25% to 36%.[4] This increase led to accelerated clinical trial programmes for meningococcal conjugate vaccines in the UK, resulting in the introduction of a routine serogroup C meningococcal (MenC) vaccination programme for infants and a catch-up campaign for all other children up to the age of 18 years from November, 1999.

The Netherlands also had an increase in the incidence of meningococcal serogroup C disease, from 0·5 cases per 100 000 population per year during 1993–99 to 0·7 per 100 000 population in 2000 and 1·7 per 100 000 population in 2001.[5] Consequently, a serogroup C conjugate vaccine was introduced into the national immunisation programme in September, 2002, for 14-month-old children, and a catch-up campaign was implemented for children aged 14 months to 18 years. In both the UK and the Netherlands, the vaccination programmes led to rapid and sustained control of serogroup C disease.[6,7]

Currently, the UK has an ongoing national outbreak of meningococcal serogroup W disease, with the number of cases increasing from 19 in 2008–09 to 176 in 2014–15.[8,9] Most patients with serogroup W disease were previously healthy (81%) and the case fatality rate of 12% is significantly higher than that reported for serogroup B disease (<5%).[9] Because of the continuing rapid increase in serogroup W disease, the UK replaced the adolescent MenC conjugate vaccine for 13–14 year olds and new university entrants with the quadrivalent conjugate meningococcal vaccination (MenACWY) in the autumn of 2015.[8,10,11] Additionally, catch-up campaigns are being implemented to offer the MenACWY vaccine to all 13–18 year olds during 2015 to 2017.

The increase in meningococcal serogroup W disease in the UK was initially due to the rapid expansion of a single strain of sequence type (ST)-11 clonal complex (cc11).[9] Previous genomic analyses of geotemporally diverse meningococcal cc11 strains of various serogroups showed that most meningococcal serogroup W cc11 (MenW:cc11) isolates belonged to cc11 lineage 11.1, following what is believed to be a single capsular switching event that occurred prior to 1970.[12,13] There are two main divergent serogroup W-associated sublineages of lineage 11.1: the Hajj strain sublineage and the South American strain sublineage.[12] The Hajj strain sublineage includes the Hajj strains that caused local and national outbreaks in different parts of the world during the early 2000s. The South American strain sublineage includes the South American strain that emerged in 2003 in southern Brazil, then spread to Argentina and Chile. A descendent of the South American strain, the so-called original UK strain, emerged in the UK in 2009. Genomic analyses revealed the expansion of a further descendent strain in the UK, the 2013 strain (so called to

reflect its year of emergence). Genetic differences between the original UK strain and the 2013 strain included four point mutations and three putative recombination events.[14] In the Netherlands, serogroup W disease was rare up to 2014, but its incidence increased in 2015 and 2016.[15]

The aim of our study was to describe the current outbreak of meningococcal serogroup W disease in the Netherlands and to compare its epidemiology and phylogeny with the serogroup W outbreak in England. To provide context for this comparison, we also analysed historical data from the national serogroup C outbreaks (also due to cc11) that occurred around 1998–2001 in both countries. Although serogroup B disease is a major contributor to meningococcal disease in the Netherlands and England, we did not include it in this study because serogroup B disease has been declining for the past 20 years in both countries and is rarely associated with cc11. The aim of the analysis was to gain insight into how the Dutch serogroup W outbreak is evolving, to inform vaccine policy in the Netherlands and beyond.

Methods

Surveillance data

In this observational cohort study, we used data from the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM), which receives *N meningitidis* isolates from blood and cerebrospinal fluid (CSF) from all microbiological laboratories in the Netherlands on a voluntary basis. Serogroup is assessed by Ouchterlony gel diffusion.[16] From 1985 to 2005, serosubtyping based on differences in outer membrane proteins PorB and PorA was done.[17] Fine typing has been based on sequencing of PorA since 2001 and sequencing of FetA protein since 2005.[18] In addition to *N meningitidis* isolates, laboratories can also submit PCR-positive samples from invasive sites to the NRLBM; the capsular group is then determined by real-time (rt) PCR with group-specific probes. Briefly, serogroup W was detected in CSF and blood by use of rtPCR with a Lightcycler 480 (Roche LifeScience, Mannheim, Germany). Primers were NMFW135 (CAGAAAGTGAGGGATTTCCATA) and NMRW135 (CACAACCATTTTCATTATAGTTACTGT), and the probe was NMPW135 (6FAM-TGGAAGGCATGGTGTATGATATTC-BHQ1). Whole-genome sequencing[19] has been done on all serogroup W isolates received from 2008–09 to 2015–16. Meningococcal disease has been a notifiable disease in the Netherlands since 1905. Since 2003, data from the laboratory surveillance and the notification system have been linked through date of birth, sex, postal code, and (approximate) date of diagnosis. If a case is missing in one of the sources, we actively request that the case is officially notified or that the material is sent to the NRLBM, as appropriate. Serogrouping is done by the NRLBM and not by local laboratories. Therefore, if material has not been sent to the NRLBM, the serogroup is not known and we did not include these cases in this analysis of serogroup W and serogroup C. The percentage of cases notified for which material has been sent to the NRLBM is 90–95%.

Public Health England (PHE) routinely conducts national surveillance of meningococcal disease using a combination of clinical and laboratory reporting schemes.[4] PHE's Meningococcal Reference Unit (MRU) establishes the serogroup, serotype, and serosubtype of all invasive *N meningitidis* isolates and offers a free, national PCR service for patients with suspected meningococcal disease to confirm the diagnosis and establish the capsular group. Ascertainment of cases on the basis of laboratory confirmation by the PHE MRU is very high.[20,21] Since July, 2010, all invasive isolates received by the MRU have

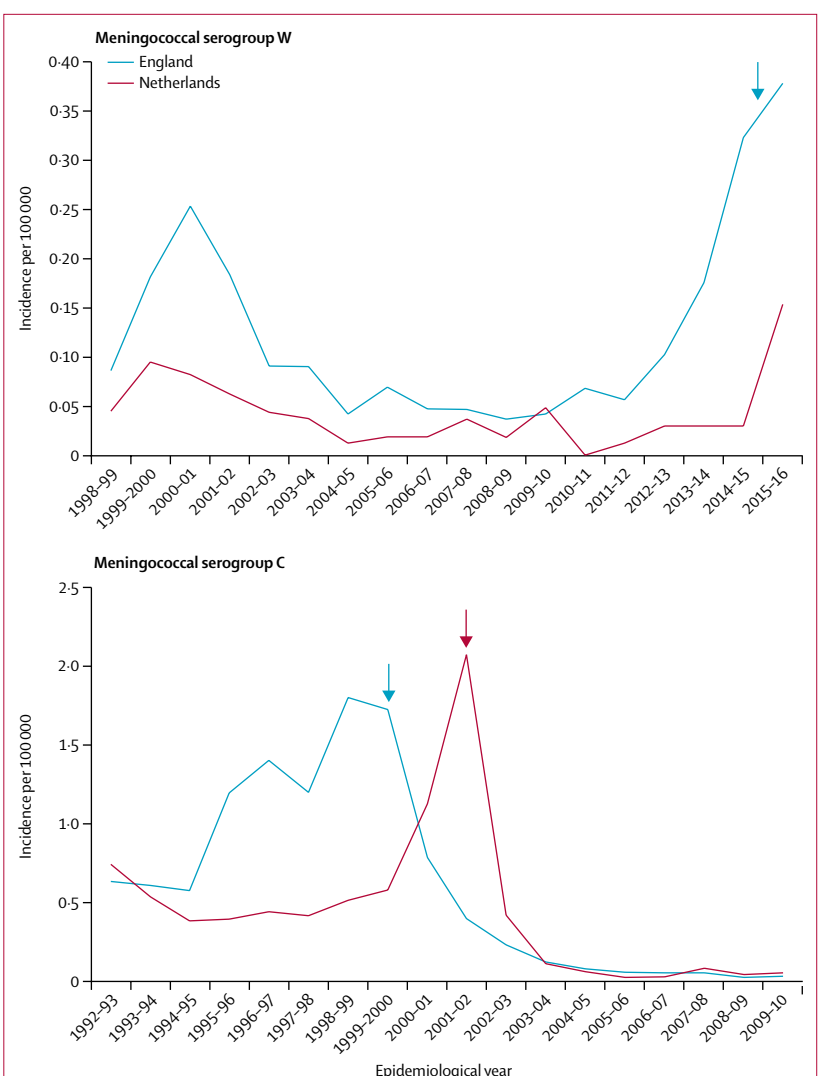

Figure 1: **Incidence of invasive meningococcal disease in the Netherlands and England**
Incidence of meningococcal serogroup W and serogroup C disease by epidemiological year (July to June). Arrows show the start of implementation of quadrivalent conjugate meningococcal vaccine (MenACWY) in the UK in 2015, and meningococcal serogroup C vaccination in the UK in 1999 and the Netherlands in 2002.

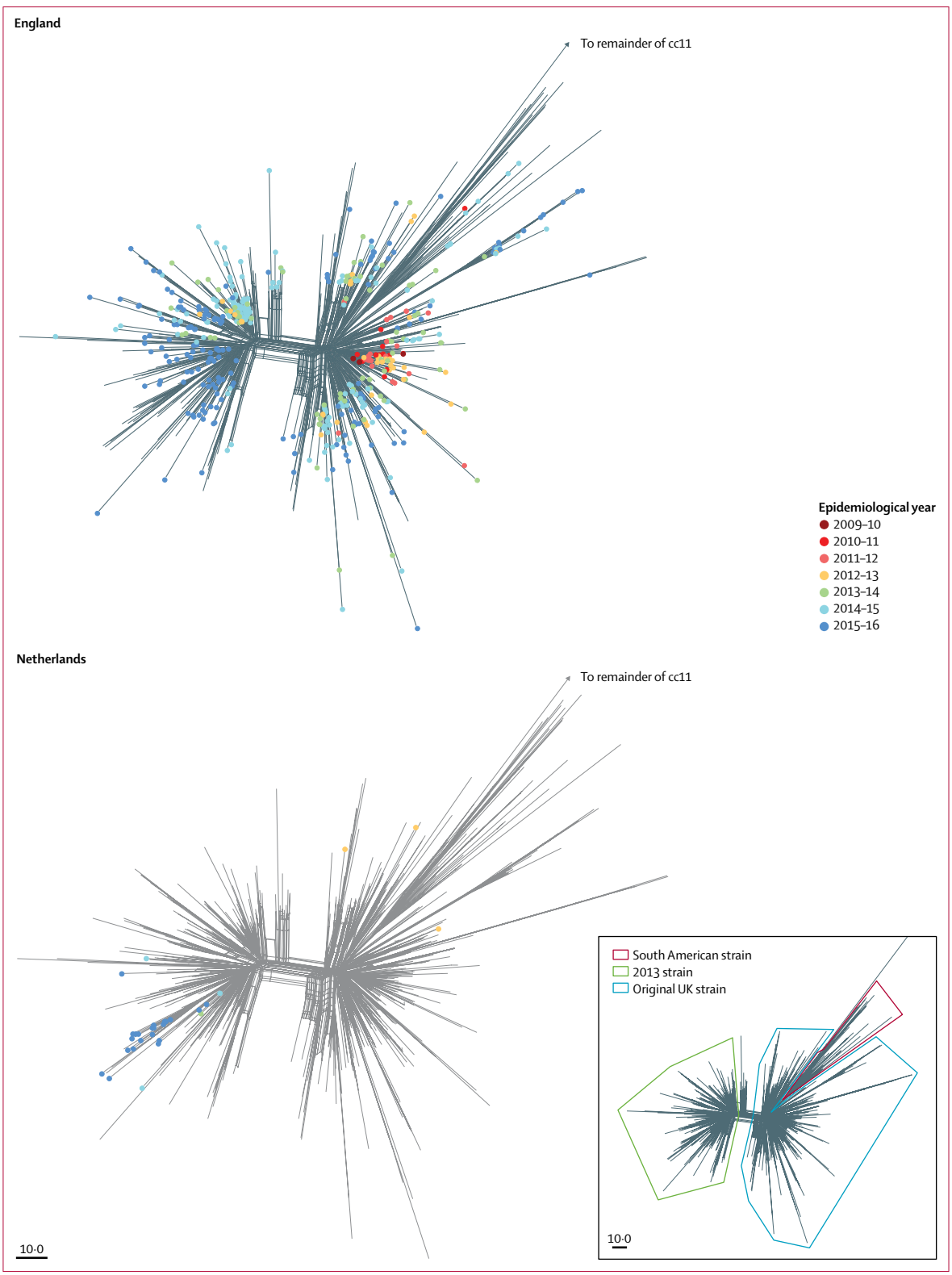

Figure 2: **Genomic analysis of the MenW:cc11 South American strain sublineage**
Neighbour-net phylogenetic network of all available genomes of MenW:cc11 South American strain sublineage isolates from England and the Netherlands, 2009–10 to 2015–16. Colours represent the epidemiological year the sample was acquired. The insert shows the position of individual strains within the South American strain sublineage. cc11=sequence type-11 clonal complex.

undergone whole genome sequencing. Genomic data for invasive MenW:cc11 isolates from 2008–09 were available as part of a specific study.[12]

Epidemiological analyses

We compared the incidence and age distribution of meningococcal serogroup W and serogroup C disease in the Netherlands and England during the epidemiological years (July to June) 1998–99 to 2015–16 for serogroup W and 1992–93 to 2003–04 for serogroup C. We used Poisson regression to estimate the annual relative increase in incidence during the outbreaks of serogroup C and serogroup W disease in the Netherlands and England. We estimated the annual relative increase from the start of the serogroup C or serogroup W outbreak (ie, the first year in which the incidence was significantly higher than that of the previous year) until the year before vaccination was introduced. We tested whether the annual relative increase differed between the Netherlands and England by including an interaction term between time and country in the model. We did these analyses using SPSS version 24.

Genomic analyses

We obtained genome sequence data for all invasive meningococcal serogroup W isolates collected in England from 2010–11 to 2015–16 (n=501) from the Meningitis Research Foundation Meningococcus Genome Library.[22] Additionally, genome sequence data for five invasive South American strain sublineage MenW:cc11 isolates collected in England from 2008–09 to 2009–10 were available from an earlier study.[12] For the Netherlands, 53 (98%) of 54 serogroup W isolates from 2008–09 to 2015–16 underwent whole genome sequencing. We extracted multilocus sequence typing (MLST) data from the PubMLST *Neisseria* database using the export dataset analysis tool.[23]

We compared genomes using the PubMLST genome comparator tool.[24] We established respective sublineages for MenW:cc11 genomes submitted to the PubMLST *Neisseria* database subsequent to previous analyses on Jan 21, 2016.[14] We did this by comparing genomes to a representative panel of isolates spanning the known diversity of cc11[14] in terms of 1546 core genes.[9] With the exception of nine genomes consisting of more than 500 contigs, we then made core genome comparisons for all South American strain sublineage genomes (n=689) on the PubMLST *Neisseria* database (accessed Nov 8, 2016) and a distant cc11 reference genome (lineage 11.1; ID 30060).[9] We visualised the resulting distance matrices with SplitsTree4 version 4.13.1.[25]

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From 1998–99 to 2015–16, 1182 cases of meningococcal serogroup W disease were reported in England and 126 cases were reported in the Netherlands. Figure 1 shows the incidence of serogroup W disease in the Netherlands and England by epidemiological year from 1998–99 to 2015–16. The increase in serogroup W disease incidence in 1999–2000 and 2000–01 in both countries was due to an outbreak associated with the Hajj to Saudi Arabia.[26] In England, the incidence of serogroup W disease increased significantly in 2012–13 compared with the previous year, from 0·06 cases per 100 000 in 2011–12 to 0·10 cases per 100 000 in 2012–13 (incidence rate ratio 1·8, 95% CI 1·2–2·8). In the Netherlands, the average incidence of serogroup W disease from 2002–03 to 2014–15 was 0·03 cases per 100 000 population per year, but in 2015–16 increased significantly to 0·15 cases per 100 000 population (incidence rate ratio 5·2 [2·0–13·5] compared with 2014–15). The relative increase in the Netherlands from 2014–15 to 2015–16 was 418% (95% CI 99–1248), which was significantly higher than the relative increase of 79% (61–99) per year in England from 2011–12 to 2014–15 (p=0·03). In 2015–16, the incidence of serogroup W disease in the Netherlands (0·15 cases per 100 000 population per year) was similar to that in England in 2013–14 (0·18 cases per 100 000 population per year). In the third and fourth quarter of 2016 (July to December) and the first quarter of 2017 (January to March), 53 cases of serogroup W disease were confirmed in the Netherlands.

Of the 501 meningococcal serogroup W isolates collected in England between 2010–11 and 2015–16, 443 (88%) belonged to cc11, 52 (10%) to cc22, three (1%) to cc23, one (<1%) to cc174, and two (<1%) to cc-unassigned (both ST-9316). 187 (42%) of the 443 English MenW:cc11 isolates from 2010–11 to 2015–16

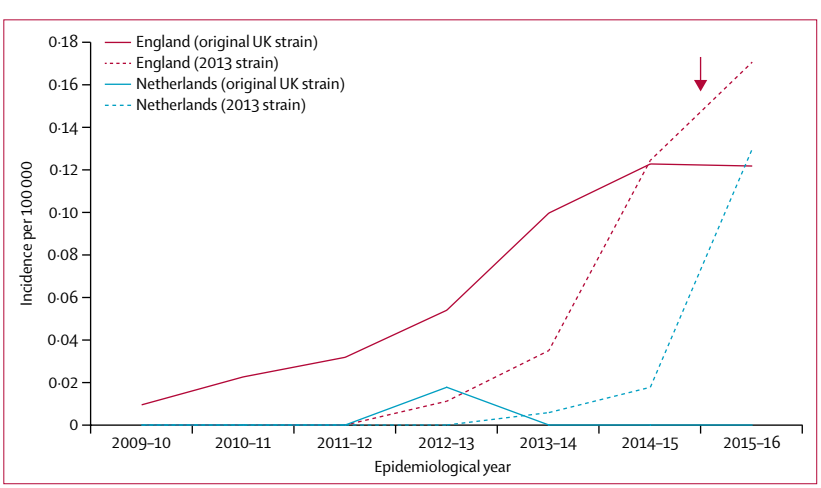

***Figure 3*: Incidence of invasive meningococcal serogroup W disease caused by the South American MenW:cc11 strain sublineage**

Incidence is for the original UK strain and the 2013 strain by epidemiological year in England and the Netherlands, 2009–10 to 2015–16. The arrow shows the start of implementation of quadrivalent conjugate meningococcal vaccine (MenACWY) vaccination in the UK in 2015. cc11=sequence type-11 clonal complex.

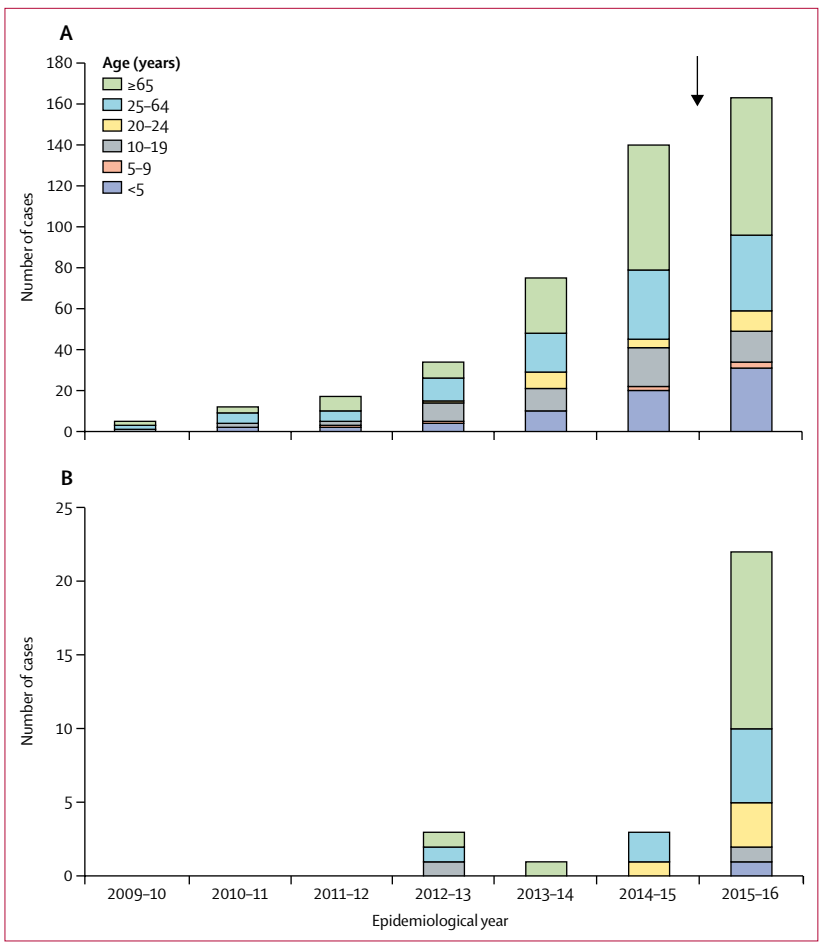

Figure 4: **Cases of invasive meningococcal serogroup W disease caused by the South American MenW:cc11 strain sublineage**

Cases are by age group and epidemiological year in England (A) and the Netherlands (B), 2009–10 to 2015–16. The arrow shows the start of implementation of quadrivalent conjugate meningococcal vaccine (MenACWY) vaccination in the UK in 2015. cc11=sequence type-11 clonal complex.

belonged to the 2013 strain. Of the 53 sequenced serogroup W strains from the Netherlands between 2008–09 and 2015–16, 29 (55%) belonged to cc11, of which 26 (90%) belonged to the 2013 strain. The remaining serogroup W strains included 19 (36%) belonging to cc22, one (2%) to cc167, and four (8%) to cc-unassigned (three ST-5436 and one ST-12348).

In England, the South American strain sublineage emerged in 2009–10 (the original UK strain) and, from 2013, an increasing number of cases belonged to the new 2013 strain (figures 2, 3). In the Netherlands, the original UK strain emerged in 2012–13 and was responsible for three cases of meningococcal serogroup W disease; no cases due to the original UK strain were detected in subsequent years. The 2013 strain, which was first identified in the Netherlands in 2013–14, became established and is now responsible for most MenW:cc11 cases (figures 2, 3). Within this outbreak of the 2013 strain, we identified a distinct genetic cluster among 16 isolates causing disease in 2015–16 (figure 2). Notably, the incidence of strains not belonging to cc11 remained stable over the study period.

Figure 4 shows the age distribution of meningococcal serogroup W cases belonging to the South American MenW:cc11 strain sublineage in the Netherlands and England. In England, an increase first occurred in people aged 25–64 in 2010–11 and in people aged 65 years and older in 2011–12. Subsequently, in 2012–13, cases increased in children and adolescents aged 10–19 years followed by an increase in cases among children younger than 5 years in 2013–14 and 2014–15.[8] In the Netherlands, the outbreak started in 2015–16, mainly among people aged 65 years and older, with an increase among 10–19 year olds from July to September, 2016 (data not shown). The age distribution of cases due to MenW:cc11 in the Netherlands in 2015–16 was similar to the age distribution in England in 2013–14, although, in the Netherlands, there were more cases in people aged 65 years and older than in England (12 [55%] of 22 patients in the Netherlands *vs* 27 [36%] of 75 patients in England).

Of the 79 patients in the Netherlands diagnosed with meningococcal serogroup W disease between July, 2015, and March, 2017, inclusive, six (8%) were aged 0–4 years (all aged <2 years), one (1%) was aged 5–9 years, 12 (15%) were aged 10–19 years, five (6%) were aged 20–24 years, 25 (32%) were aged 25–64 years, and 30 (38%) were aged 65 years or older. Nine patients died (11% case fatality). The clinical manifestation was known for 71 cases: 32 (45%) patients had septicaemia, 14 (20%) had meningitis, and seven (10%) had both septicaemia and meningitis. The other 18 (25%) patients had atypical clinical manifestations, including bacteraemic pneumonia (12 patients), septic arthritis (four patients), pericarditis (one patient), and necrotising fasciitis (one patient[15]). The cases were not geographically clustered and none were epidemiologically related.

From 1992–93 to 2009–10, 5377 cases of meningococcal serogroup C disease were reported in England and 1270 were reported in the Netherlands. Similar to the current serogroup W outbreak, the increase in serogroup C incidence in the Netherlands started several years after the increase in incidence in England (figure 1). Additionally, the incidence of serogroup C disease increased more gradually in England, with an annual relative increase of 22% (95% CI 19–26) during 1994–95 to 1998–99, whereas in the Netherlands, a sudden increase occurred, with an annual relative increase of 88% (69–109) during 1999–2000 to 2001–02. The difference in the annual relative increase between England and the Netherlands was significant ($p<0·001$). The age distribution of patients during the current serogroup W outbreak is different from that of the serogroup C outbreak, in which 0–4 year olds and 10–19 year olds were the most affected age groups. However, the age distributions of the patients with serogroup C disease were similar between outbreaks in England and the Netherlands (figure 5).

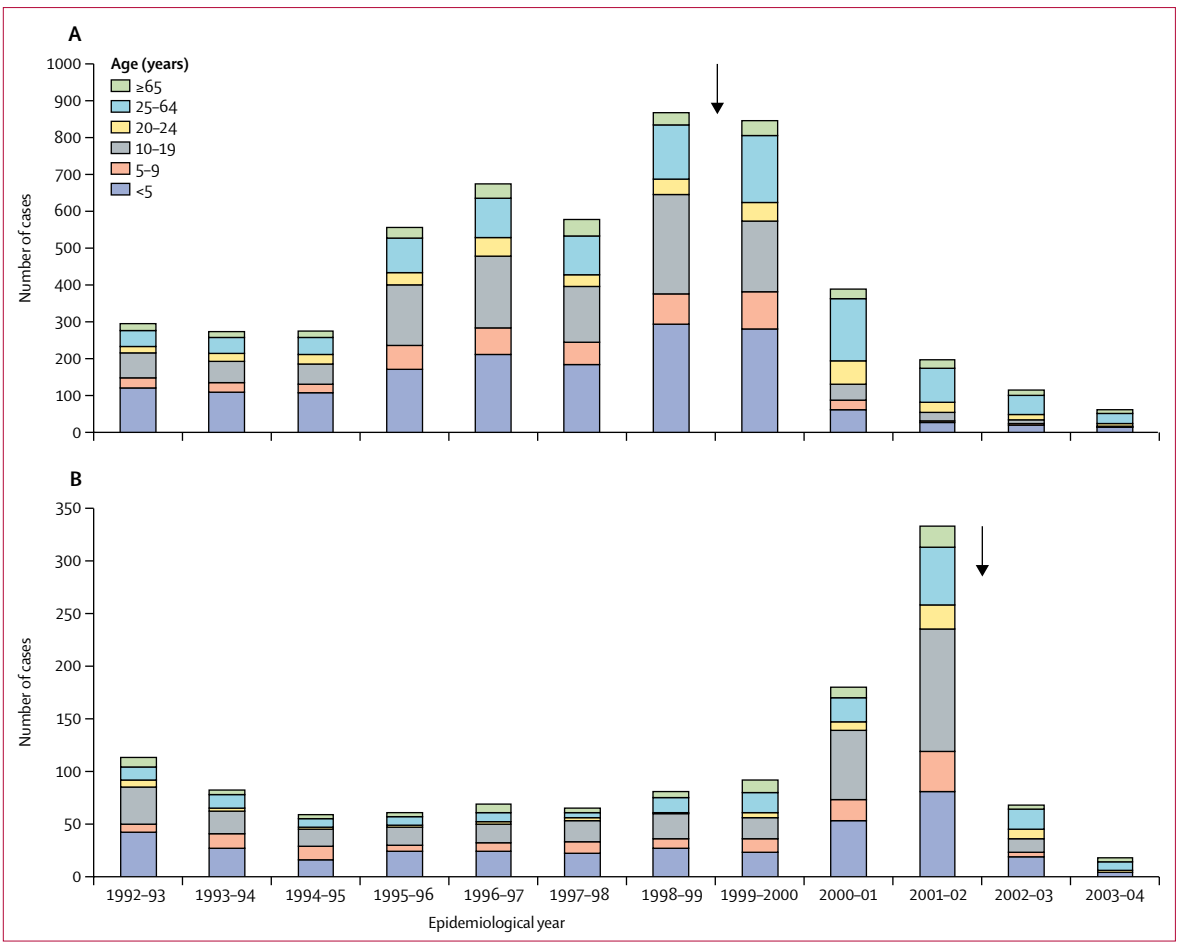

Figure 5: **Cases of invasive meningococcal serogroup C disease**
Cases are by age group and epidemiological year in England (A) and the Netherlands (B), 1992–93 to 2003–04. The arrows show the start of implementation of meningococcal serogroup C vaccination in the UK in 1999 (A) and the Netherlands in 2002 (B).

Discussion

The rapidly evolving outbreak of meningococcal serogroup W disease in the Netherlands is caused by a MenW:cc11 outbreak strain, which emerged in England in 2013. We found notable similarities when comparing the current serogroup W outbreaks and the historical serogroup C outbreak between the Netherlands and England. In both outbreaks, the increase in incidence started several years later in the Netherlands than in England and the rate of increase was higher in the Netherlands than in England. Our genomic analysis showed that the Dutch serogroup W isolates were closely related to the English serogroup W isolates, with almost all belonging to the 2013 strain. Furthermore, the age distributions of patients with serogroup W disease due to the MenW:cc11 South American strain sublineage were similar between the Netherlands and England, although patients aged 65 years and older were more commonly affected in the Netherlands. The age distribution of patients with serogroup W disease, with a relatively large number of patients older than 25 years, is not typical of meningococcal disease; for example, the incidence of serogroup B disease is highest in children younger than 5 years and adolescents.[10] The similarities in epidemiology between the Dutch and English outbreaks of serogroup W and serogroup C disease suggest that disease trends in England might predict the evolution of the serogroup W outbreak in the Netherlands. However, since the UK implemented a nationwide vaccination programme against meningococcal serogroup W disease for adolescents in the summer of 2015, future trends in disease epidemiology in the Netherlands can no longer be extrapolated from the situation in England.

Other characteristics of the meningococcal serogroup W disease outbreak in the UK, including the high case fatality rate and the high proportion of patients with an atypical clinical manifestation,[8] have also been seen in the Netherlands. The case fatality rate of 11% for serogroup W disease in the Netherlands was higher than the 3% reported for serogroup B disease during the past 2 years. The proportion of patients with serogroup W

disease who had atypical clinical manifestations (25%) was also higher than the proportion of patients with serogroup B disease who had atypical clinical manifestations (3–5% in the Netherlands during the past 2 years). In a case review of teenagers in the UK diagnosed with serogroup W disease between July, 2015, and January, 2016, seven of 15 teenagers presented predominantly with an acute history of gastrointestinal symptoms and five of these seven patients died.[27] This clinical presentation with predominantly gastrointestinal symptoms is rare and seems to be associated with the current outbreak strain in both the UK and Chile.[28] In the Netherlands, three patients with septicaemia, one of whom died, presented predominantly with gastrointestinal symptoms.[15] No geographical clustering or epidemiologically linked cases were found in the Netherlands, and in the UK, there have only been a few clusters.[14,29]

A strong argument supporting the emergency introduction of the serogroup W meningococcal vaccination programme in the UK was the rapid acceleration of the spread of MenW:cc11 cases across all age groups, with a real possibility that disease rates could mirror the MenC:cc11 outbreak in the 1990s.[30] For the first time in more than a decade, in addition to the rapidly increasing number of cases, serogroup W-related deaths were reported in infants, toddlers, and adolescents. Identification of the responsible MenW:cc11 strain as genetically related to the South American strain also raised concerns because of the high case fatality rate in Chile.[28] The implementation of the serogroup W vaccination programme in the UK involved replacing the booster dose of the MenC vaccine given at 13–14 years of age with a MenACWY conjugate vaccine, which was accompanied by a catch-up campaign targeting older teenagers. In the Netherlands, seroepidemiological data also suggest that a MenC vaccine booster in adolescence might be needed because of waning immunity after infant vaccination,[31] with most adolescents in the Netherlands no longer being protected against this serogroup. Nevertheless, because of continued herd protection, cases of serogroup C disease have so far been extremely rare in Dutch adolescents since the introduction of the vaccination programme in 2002. In the UK, seroepidemiological data and modelling predictions[7,32] were the basis for introducing a teenage MenC vaccine booster, and a pre-emptive precautionary approach was taken to maintain herd protection.[33] The serogroup W outbreak provides an additional and urgent impetus for a comprehensive review of the potential benefit of meningococcal vaccination in adolescence in the Netherlands.

The number of cases of meningococcal serogroup W disease in England continued to increase in 2015–16, although the number is no longer doubling compared with previous years. School leavers (aged 17–18 years) were offered the MenACWY vaccine mostly through invitation by their general practitioners. In 2015 and 2016 uptake has been disappointing at 38% and 30%, respectively, by the end of October 2016.[34] Data on school leavers showed that, despite the low vaccination uptake, there have been 69% fewer cases of serogroup W disease in this group than was predicted by trend analysis and no cases have occurred among vaccinated teenagers.[35] The UK introduced the serogroup B meningococcal (MenB) vaccine into the national immunisation programme in September, 2015, as a three-dose schedule at 2, 4, and 12 months of age,[10] which might also provide some protection against serogroup W disease in infants.[35,36] Uptake of the MenACWY vaccine in children immunised in schools was much higher than in school leavers, at 77·2% for those born from Sept 1, 2000, to Aug 31, 2001, and 84·1% for those born from Sept 1, 2001, to Aug 31, 2002.[37] It is unknown what the vaccination uptake would be in the Netherlands if the MenACWY vaccine were offered to, for example, adolescents. Vaccination uptake during the MenC vaccine catch-up campaign in 2002 was high. The overall uptake was 94%,[38] but coverage was somewhat lower at 89% in the 15–18-year age group. Coverage of the routine MenC vaccine at 14 months has been 95–96% since the start of the programme.[39] We presume that acceptance or uptake of MenACWY vaccination will be similar to that of the MenC vaccine, because the vaccines are very similar with respect to immunogenicity, safety, and targeted disease.[40,41]

We noted some important differences in the progress of the outbreaks of meningococcal serogroup W disease between England and the Netherlands. For example, in England, cases of serogroup W disease appeared to increase more gradually over time (with cases eventually doubling in more recent years) than in the Netherlands, where the incidence increased by five times within 1 year, albeit with small numbers of cases. An explanation for the more rapid increase in the Netherlands could be that the MenW:cc11 cases in the Netherlands mostly belonged to the 2013 strain, which seems to have a greater propensity to spread rapidly than that of previous strains, with several European countries now also reporting cases of meningococcal disease due to this strain.[14] It has been proposed that genetic differences defining the 2013 strain, such as specific virulence factor variants, might make it more efficient in establishing carriage and causing invasive disease.[14] We also found a more rapid increase in cases of serogroup C disease in the Netherlands than in England. Possibly, a similar mechanism might also have occurred for these outbreaks, whereby a more virulent strain evolved in England, which might have spread to the Netherlands. However, the absence of sequence data for the historical serogroup C isolates precludes an analysis to investigate this possibility. Alternatively, the susceptibility to invasive meningococcal disease might differ between the populations of England and the Netherlands. However, there is no evidence to suggest this is the case. Additionally, the overall incidence of meningococcal disease has been

higher in the UK than in the Netherlands for a long time.[42]

Information from public health institutes suggests that the incidence of meningococcal serogroup W disease is increasing in several other countries in Europe, including Belgium, Denmark, France, Germany, Norway, Spain, and Sweden, albeit with small numbers of cases (personal communication between Dec 12, 2016, and Feb 9, 2017, with Bertrand S, Public Health Institute of Belgium; Hoffmann S, Valentiner-Branth P, Public Health Institute of Denmark; Barret A S, Public Health Institute of France; Hellenbrand W, Public Health Institute of Germany; Vestrheim D, Public Health Institute of Norway; and Roth A, Public Health Institute of Sweden).[43,44] An increase was also reported in the incidence of serogroup W disease due to the South American strain sublineage in Australia in 2015.[45] Notably, during the serogroup C outbreak around the year 2000, serogroup C incidence did not increase in the Scandinavian countries and, consequently, the MenC vaccine is not included in the national immunisation programmes of these countries, except for Iceland. A possible explanation for the larger increase in cases of serogroup W disease in the Netherlands than in other European countries could be the close connection between the UK and the Netherlands in terms of the short distance and high levels of travel between the countries. Another explanation might be population density which, of the countries in Europe (except for Malta), is highest in the Netherlands.[46]

A potential limitation of this study is that we might have missed a small number of cases of meningococcal disease. However, both England and the Netherlands have robust surveillance systems for meningococcal disease that are based on clinical and laboratory notifications. It is very unlikely that clinicians are selectively over-reporting or under-reporting cases of serogroup W disease compared with other strains, because serogrouping is performed at national reference laboratories in both countries; the serogroup is, therefore, not known at the time of notification. It is, however, possible that atypical presentations are less likely to be investigated for meningococcal disease and, therefore, if a capsular group is associated with atypical disease in a specific age group (such as pneumonia in elderly people or gastrointestinal symptoms in young adults, for example), then there might be some bias in the surveillance.

We describe the emergence in the Netherlands of a hypervirulent MenW:cc11 strain, which has been associated with outbreaks of meningococcal disease in South America since 2003 and the UK since 2009. We found substantial similarities between the Netherlands and England during both the current outbreaks of meningococcal serogroup W disease and historical serogroup C outbreaks. Given the rapid expansion of the MenW:cc11 2013 strain, the high case fatality rate, and the availability of a safe and effective vaccine, urgent consideration is needed for potential public health actions, including vaccination, in the Netherlands and other countries affected by the outbreak of meningococcal serogroup W to prevent further cases and deaths.

Contributors

MJK, SJMH, and AvdE designed the study. SJG, RB, JL, and AvdE were involved in data collection. MJK, JL, and HC did the data analysis. MJK and JL made the figures. MJK drafted the manuscript. All authors interpreted the data, critically reviewed the manuscript, and approved the final version.

Declaration of interests

We declare no competing interests.

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For the **Neisseria Multi Locus Sequence Typing website** see http://pubmlst.org/neisseria

For the **Meningitis Research Foundation Meningococcus Genome Library** see http://www.meningitis.org/research/genome

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