**TITLE**

Risk of invasive meningococcal disease in university students in England and optimal strategies for protection using MenACWY vaccine.

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**ABSTRACT**

**Purpose**

In August 2015, in response to increasing group W invasive meningococcal disease (IMD) nationally, a MenACWY vaccine programme was introduced in the UK for 13-18 year olds. We reviewed the epidemiology of IMD in young adults and university-associated cases in England during 2014-15 academic year and assessed the potential impact of different immunisation strategies.

**Methods**

Public Health England national enhanced surveillance data were used to describe the epidemiology of IMD cases in 15-24 year olds in England during 2014/15. Relative risks for IMD were calculated overall and by capsular group in students compared with non- student peers for 2014 and 2013 school leavers. Assuming stable future incidence and vaccine efficacy of 90% for five years, we estimated cases averted and numbers needed to vaccinate (NNV) for different MenACWY immunisation programmes: school-based adolescent, GP-based school leaver, and targeting freshers.

**Results**

Between July 2014 and June 2015, 112 IMD cases were diagnosed in those born between 01/09/1991 and 31/08/2001 (~15-24 year-olds). During the 2014/15 academic year (September to June), 49 IMD cases were reported among students attending English universities, including 22 among 2014 school leavers. In this cohort, the relative risk of IMD was higher among students compared to non-students for all capsular groups (RR 11.6; 95% CI 4.7-28.7) and for groups A/C/W/Y (RR 14.8; 95% CI, 4.3-51.5). A school-based programme could potentially have averted 14 cases in 2014/15 and 24 cases over five years with a lower NNV (18,000) than other programmes.

**Conclusions**

University students, particularly first years entering direct from school, are at higher risk for IMD than non-students. With high vaccine coverage and timely completion, an adolescent school-based MenACWY programme has the greatest potential to prevent cases with the lowest NNV, but population impact through indirect (herd) protection could take longer.

**HIGHLIGHTS**

School leaver freshers have a fifteen times greater risk of group ACWY meningococcal disease compared to non-students peers.

An adolescent school-based MenACWY vaccination programme could prevent more cases with a lower NNV than other strategies.

Our findings support UK’s introduction of a MenACWY adolescent programme, prioritising school leavers.

**Introduction**

In the United Kingdom, the meningococcal C conjugate (MenC) vaccination programme since 1999 has led to a rapid and sustained decline in group C meningococcal disease across all age groups [1]. Consequently, capsular groups B, W and Y are responsible for nearly all invasive meningococcal disease (IMD) cases in England [2]. In 2013, to maintain long-term population control of group C IMD, a routine adolescent MenC vaccine programme was introduced for 13-14 year-olds. Temporary catch-up MenC vaccination was also offered to freshers starting university in September 2013 and again in 2014.

Since the 2009/10 epidemiological year (running from 1 July to 30 June), England has experienced a marked increase in capsular group W (MenW) IMD with a high proportion of cases in young adults [2,3]. In August 2015, as an emergency public health response to this increase, a meningococcal A,C,W,Y conjugate (MenACWY) vaccine directly replaced the existing MenC school-based vaccine programme for adolescents and the GP-based programme for freshers. A phased catch-up programme was also launched for 13-18 year olds, starting with 17-18 year olds who left school in the summer of 2015 (those born between 01/09/1996 and 31/08/1997) [4]. This group was considered a priority and could realistically only be offered timely vaccination through their GP.

We reviewed the epidemiology of IMD cases in young adults in England during the 2014/15 epidemiological year, prior to the emergency introduction of the MenACWY immunisation programme. To assess the relative contribution of age and university status among IMD cases in the 2014/15 academic year (1 September 2014 to 30 June 2015), we calculated the relative risk of IMD among two school leaver cohorts (summer of 2014 and summer of 2013) compared to their non-university peers. We also estimated the potential number of cases averted using three different strategies of MenACWY immunisation; replacing the school-based MenC programme in 13-14 year olds with MenACWY vaccine, offering MenACWY vaccination to school leavers through primary care during the summer, or targeting freshers with MenACWY vaccine upon entry to university.

**MATERIALS AND METHODS**

Public Health England (PHE) conducts enhanced national surveillance of IMD using clinical and laboratory reporting systems. PHE’s Meningococcal Reference Unit (MRU) provides a national service for characterisation of all invasive *Neisseria meningitidis* isolates, as well as polymerase chain reaction (PCR) testing of clinical specimens submitted by hospitals in England. Isolates are grouped using monoclonal and polyclonal antibodies for A, B, C, E, W, X, Y, Z as previously described [5]; those negative for these groups are classified as non-groupable. Samples undergo an initial PCR screen which includes a specific assay for group B; screen negative and group B negative samples are then tested on specific PCR assays for C, W, Y (and A if indicated); those negative on these assays are classified as ungrouped [5].

PHE also receives statutory notifications of clinically diagnosed cases from physicians and electronic reports of IMD confirmations from National Health Service (NHS) and private microbiology laboratories in England. Since 01 July 2014, all suspected, probable and confirmed IMD cases associated with universities in England were flagged by the Health Protection Teams in PHE Centres using HPZone, a national, web-based case management tool in which all meningococcal cases reported to PHE are captured. HPZone case data includes full personal identifiers (name, date of birth, and address with postcode). University-associated cases identified from HPZone were matched using these personal identifiers with laboratory-confirmed cases in the national surveillance dataset for 2014/15; those recorded as probable or possible IMD cases on HPZone (i.e., without laboratory confirmation) were excluded from further analysis.

University students were defined as those attending an English university or college registered with the University and Colleges Admission Service (UCAS); otherwise, they were classified as non-students. Because the year of study for university students is rarely recorded on HPZone and to control for age when estimating relative risk, IMD rates were compared between students and non-students born between 1 September 1995 and 31 August 1996 and diagnosed between September 2014 and June 2015 (the academic year for most universities). This cohort was due to leave school in summer 2014 and is referred to as 2014 school-leavers throughout. Those attending university in this cohort were assumed to be full-time, new university entrants in their first year, England-domiciled undergraduates unless the HPZone records specified otherwise. A similar analysis was then conducted for cases born between 1 September 1994 and 31 August 1995; university students in this cohort would have left school in summer 2013 and would, therefore, include both first (e.g. those taking a gap year and starting university a year later) and second year students. This cohort is referred to as the 2013 school-leavers.

In the 2014/15 academic year, there were 562,345 English-domiciled first year students (including full time, part time, undergraduate and postgraduate) attending English universities (Higher Education Statistics Agency (HESA) Student Record 2013/14-2014/15) including 157,290 first year, full-time undergraduates aged 18 years on entry (2014 school leavers) and 87,180 aged 19 years (2013 school-leavers); only ~500 UK students (<1%) enter university below 18 years of age (HESA Student Record 2013/14-2014/15).

The student denominator for 2014 school leavers (n=157,290) was then subtracted from the English population estimate for 18 year-olds in mid-2014 (N=655,753) to determine the non-university population in this age group (N=498,463) [6].

Of the 2013 school leavers, 153,150 entered university in the 2013/14 academic year and 87,180 in 2014/15, giving a total of 240,330 students. This was then subtracted from the English population estimate for 19 year-olds in mid-2014 (N=659,877) to determine the denominator for their non-university student peers (N=419,547) [6]. Incidence rate ratios (IRR) and 95% confidence intervals (CI) were calculated for overall and capsular group-specific IMD in students compared with non-university student peers using Stata v.13.0 (Statcorp, TX).

The potential numbers of cases that might have been averted in 2014/15 by introducing a MenACWY vaccination programme were calculated for each immunisation strategy. The mid-2014 English population denominator for 13 year olds (N=592,716) was used for the adolescent programme calculations [7]. Vaccine coverage estimates for each potential strategy were applied to cases observed in the relevant academic year. Vaccine coverage for the school-based adolescent programme in year 9 (13-14 year-olds) was assumed to be 75%, which is a conservative estimate [8], whereas we assumed only 35% of school-leavers aged 17-18 year-olds would be vaccinated, mainly during the months of August and September [9]. Coverage achievable in new university entrants was assumed to be 50% based on coverage seen in practices attached to universities [10]. The number needed to vaccinate (NNV) to prevent a single case was then estimated over a five-year period assuming the 2014/15 age-specific incidences and a sustained but conservative 90% protection from vaccine.

**RESULTS**

During the 2014/15 epidemiological year, there were 724 confirmed IMD cases across all age groups, including 418 group B (58%), 176 group W (24%) and 93 group Y (13%). A total of 112 cases were diagnosed in those born between 01/09/1991 and 31/08/2001. Groups B, W and Y accounted for 53% (n=59), 28% (n=31) and 14% (n=16) of all cases, respectively, in this 10-year age cohort. The highest number of cases occurred in the age group that left school in summer 2014 (Table 1).

**University-associated IMD cases in England in 2014/15**

During the 2014/15 academic year (from September to June inclusive), there were 73 laboratory-confirmed IMD cases linked to a university/college on HPZone; 19 were reclassified because the institution was not UCAS-registered and five were reclassified because the case was confirmed as not studying at the university (staff or visitor).

Of the remaining 49 IMD cases among students attending UCAS-registered institutions in England, the median age was 19.9 years (range, 18.2 to 28.8 years) and 26 (53%) were female. Group B IMD was responsible for 20 cases (41%) followed by group W (n=17, 35%), group Y (n=7, 14%) and group C (n=2, 4%). Of the remaining three cases, two PCR-confirmed cases were not grouped, and one isolate was ungroupable. Four cases died (2 group B, 1 group Y and 1 group C) giving a case fatality ratio of 8.2% (4/49 cases).

Most cases in students were in 2014 and 2013 school-leavers (Table 1). Two other university-associated cases were younger than the defined 2014 school-leavers (having presumably completed school earlier than their expected leave date of summer 2015), and 25 were from older cohorts – including two group B cases in those born before 01/09/1991; (these two cases are not included in table 1).

IMD cases in university students peaked in October and November, the start of the first academic term, with a smaller second peak in March (spring term), although cases continued to be diagnosed throughout the academic year in the fresher group (Figure 1).

**Relative risk of IMD among 2013 and 2014 school-leavers**

In the 2014/15 epidemiological year, amongst the 33 IMD cases in 2014 school-leavers, five cases were diagnosed in July and August before the university term began, 22 occurred in students attending UCAS-registered universities and six were in non-students. Among 2013 school-leavers, three cases were diagnosed in July and August, 13 cases were in university students (including a group B case in a French resident who was excluded from further analysis) and five occurred in non-students.

In the 2014/15 academic year, therefore, for 2014 school-leavers, 22 IMD cases occurred among 157,290 university students (14.0/ 100,000) and 6 cases occurred in 498,463 (1.2/100,000) non-students. The relative risk of IMD was higher among students compared to non-students for all capsular groups (RR 11.6; 95% CI 4.7-28.7), for groups A/C/W/Y (RR 14.8; 95% CI, 4.3-51.5; incidence 8.9/100,000 vs 0.6/100,000), and group B alone (RR, 7.4; 95% CI, 1.9-28.6; incidence 4.5/100,000 vs. 0.60/100,000).

In 2013 school-leavers, 12 cases occurred among 240,330 (5.0/100,000) students compared to five cases in 419,547 (1.2/100,000) non-students. The relative risk of IMD was higher among students compared to non-students in the same age cohort for all capsular groups (RR 4.2 (95% CI 1.5-11.9), for groups A/C/W/Y (RR 8.7; 95% CI, 1.0-74.7; incidence 2.1/100,000 vs 0.2/100,000), and for group B alone (RR 3.1; 95% CI, 0.9-10.4; incidence 2.9/100,000 vs 1.0/100,000).

**IMD cases potentially preventable by MenACWY vaccination**

*School-based adolescent immunisation programme*

A routine year 9 school-based MenACWY vaccination programme (children aged 13-14 years) had potential to prevent all 20 ACWY cases in the 2014 school-leavers. This included three cases that occurred in July and August, 14 cases that occurred in students throughout the university term, and three cases in school leavers who did not go onto university. Over a five year period, however, such a programme would also prevent cases in school years 10 to 13 which, based on 2014/15 incidence, included 16 potentially preventable cases. The NNV, assuming 75% vaccine coverage and 90% efficacy, was 18,000 (Table 2).

*GP-based school-leaver immunisation programme*

If MenACWY vaccine had been offered to 2014 school-leavers during the summer of 2014, the programme would probably have been delivered too late to prevent the cases during July and August 2014. Such a programme could have prevented 17 ACWY cases during the 2014/15 academic year (14 cases in students and three cases in school leavers who did not go onto university). Over a five-year period, this programme would also have prevented cases in older cohorts, regardless of university attendance, which would be an additional 13 cases based on 2014/15 incidence. Assuming 35% vaccine coverage and 90% efficacy, the NNV was estimated to be 24,000 (Table 2).

*Freshers targeted programme*

A programme to vaccinate university freshers once they arrived at university in September and October 2014, would have failed to prevent cases early in the academic term. Of the 14 ACWY student cases among 2014 school-leavers, three had onset in September or October, leaving only 11 cases that were potentially preventable. This programme could prevent cases in other first year students - not just those who left school in summer 2014 - and provide on-going protection to those vaccinated throughout their university career. Assuming a similar future incidence to that seen in 2014/15, vaccination of first year students could also have prevented 11 ACWY cases reported in other student cohorts (both older and younger). Assuming 50% vaccine coverage amongst all England-domiciled first year students (including full time, part time, undergraduate and postgraduate) in English universities, would give an approximate NNV of 28,000 (Table 2). A programme offering vaccination only to freshers under 20 years of age (n=244,995 in 2014/15) would have the potential to prevent at least 18 cases that occurred in students under 20 (school leavers in 2013, 2014 and 2015), which would reduce the NNV to around 15,000.

**DISCUSSION**

In August 2015, as an emergency public health response to the continuing increase in group W IMD cases nationally, a MenACWY conjugate vaccine directly replaced the existing MenC vaccine programmes for adolescents and freshers. A catch-up programme was also launched for 13-18 year olds phased over a 24-month period, starting with 17-18 year-olds (school leavers) [4]. As general practices are unable to identify adolescents who are about to start university, the new MenACWY programme required practices to invite (via a call-recall system) those of school leaver age (identified by their dates of birth) using their electronic practice registers, irrespective of whether they were planning to attend university.

In 2014/15, more than half of the IMD cases in adolescents and young adults occurred in those expected to have left school in 2012, 2013 or 2014. We showed that university students were at significantly higher risk for IMD than non-students. The highest relative risk was in 2014 school leavers, who would mainly be university freshers during the 2014/15 academic year. The risk was still elevated in 2013 school leavers, because around 87,000 of this cohort were new university entrants in the 2014/15 academic year, most likely because they took a gap year before entering university.

The elevated risk of IMD in university students and, in particular, freshers living in university halls, is well-documented[11,12, 13]. Of the university-associated IMD cases in our cohort, around half were due to capsular groups preventable by MenACWY vaccination. While the relative risk of group B IMD was high in students, the incidence rate ratio for group ACWY IMD was even higher compared to non-student peers. Although the risk of IMD remains high in older students the number of cases declines with age, demonstrating that the highest risk of ACWY IMD is in freshers entering university immediately after leaving school.

Our analysis suggests that a school-based MenACWY programme at age 14 years (academic year 9) has the greatest potential to prevent cases in freshers, with the lowest NNV among the different strategies evaluated. Such a programme would be optimal because of its high vaccine coverage compared to other strategies, and because vaccination would be completed before the period of highest incidence (i.e. university entry). In comparison, a GP-based programme offering MenACWY vaccine to school leavers during the summer would achieve lower vaccine coverage, offer little protection against cases that occur during the summer months and not prevent cases in younger teenagers; it does however prevent cases in non-university students, and so not offering vaccination to school leavers may be seen as disadvantageous to non-university students which may present an equity issue.

Vaccinating new university entrants, ideally before they start university, should offer protection during the period of greatest risk and during subsequent years in university. Because many freshers need to register with a new GP or health centre away from their home address, vaccination may not take place early enough to prevent the majority of cases that occur in the autumn term. In many cases, the students may not even register with a GP practice whilst at university. As cases continue to be diagnosed throughout winter and spring, vaccination of students throughout the academic year may still be beneficial. Despite the high risk in university students, the NNV for a fresher-based programme was higher than the school-based programme, mainly because older first year students at lower risk would also be eligible. A lower NNV would be achieved by limiting eligibility only to younger freshers, for example, those under 20 years of age, or to full-time undergraduates.

Comparing direct benefits alone, the routine adolescent programme appears most attractive, but as this commenced in England in the 2015/16 academic year, it will likely take some years for these cohorts to enter their period of highest risk; therefore, a catch-up programme for older adolescents, school leavers and new university entrants was offered alongside the routine adolescent MenACWY programme. Conjugate vaccines not only offer excellent protection against invasive disease, but they are also highly effective in reducing carriage of vaccine-related capsular groups [14]. Vaccination strategies to directly protect cohorts with high meningococcal carriage rates may also provide indirect protection across the whole population over time. As the peak of carriage is around 19 years of age [15], the school leavers programme should help achieve indirect protection more quickly than vaccination strategies in younger school children, although the impact will depend on the coverage achieved. Whether a programme targeted only at freshers could provide indirect protection across the whole population is speculative, but it could help to further reduce the risk in university students through a combination of direct and indirect effects.

Enhanced national surveillance undertaken by PHE has consistently achieved very high case ascertainment [16]. We were unable, however, to accurately assign the university year in all cases and used date of birth as a proxy. Although most England-domiciled students study in England, it is also possible that we might have missed cases in students who went to study in other UK countries or abroad. Although we calculated the potential numbers of cases prevented using simplified assumptions of the effectiveness of MenACWY vaccination and the future incidence of group W IMD, we believe the relative NNVs, are useful in helping to decide the optimal strategy to control a rapidly evolving situation, although we acknowledge that equity and ethical issues around access to vaccination in a cohort may play an important role in other health systems in other countries.

Our findings support the UK decision to introduce an adolescent MenACWY vaccine programme, prioritising school-leavers with a freshers’ catch-up, in response to a national increase of group W IMD. Close monitoring will be crucial to evaluate the short-term and long-term population impact of the programme. A number of countries in Europe and elsewhere are now experiencing rapid increases in group W IMD due to the hypervirulent ST-11 clonal complex. This analysis may aid other countries in identifying the optimal MenW immunisation strategy for their population, taking into account programmatic as well as epidemiological considerations.

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**CONFLICT OF INTEREST:** None

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**CONTRIBUTIONS**

All authors contributed substantially to the conception and design of the study, acquisition of data, analysis and interpretation of data, preparation and critical revision of the manuscript, and approval of the final version of manuscript.

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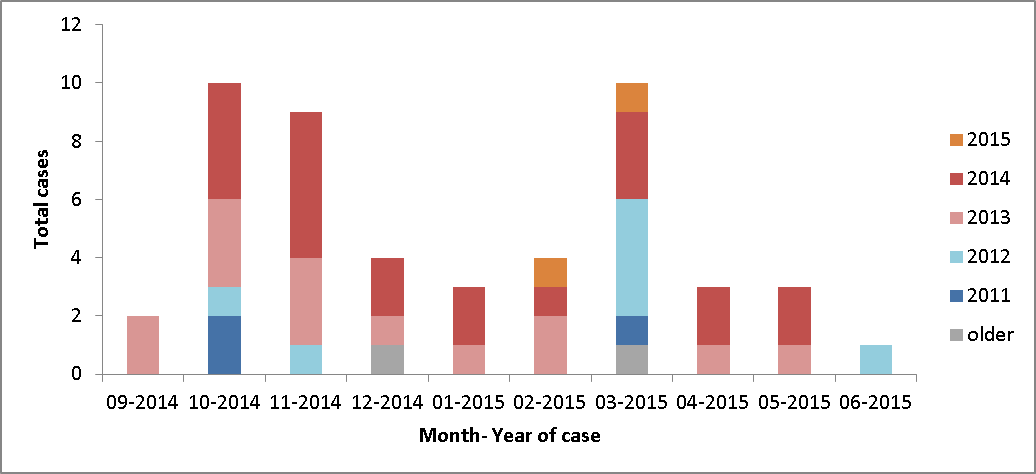
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**Figures and Tables**

**Figure 1: Confirmed cases of invasive meningococcal disease in university students (n=49) by month-year of diagnosis and school leaver year during the 2014/15 academic year (September to June).**



Note: 2015 school leavers included were due to leave school in that year but are assumed to completed school early as these were identified as university cases.

**Table 1: Laboratory confirmed IMD cases recorded in adolescents and young adults in 2014/15, by dates of birth and year expected to have left school and capsular group.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **School leaver in summer** | **Equivalent expected school**  **/ university year** | **Dates of birth** | **Number of cases**  **(cases in students)**  **2014/15** | | | |
| B | ACWY | Other | **Total** |
| **2010** | Postgraduate | 01/09/1991 - 31/08/1992 | 6 (0) | 1 (0) | 0 (0) | **6 (0)** |
| **2011** | Postgraduate | 01/09/1992 - 31/08/1993 | 4 (1) | 2 (2) | 0 (0) | **6 (3)** |
| **2012** | University year 3 | 01/09/1993 - 31/08/1994 | 4 (3) | 3 (2) | 2 (2) | **9 (7)** |
| **2013** | University year 2 | 01/09/1994 - 31/08/1995 | 14 (8)1 | 7 (5) | 0 (0) | **21 (13)** |
| **2014** | University year 1 | 01/09/1995 - 31/08/1996 | 12 (7) | 20 (14) | 1 (1) | **33 (22)** |
| **2015** | School year 13 | 01/09/1996 - 31/08/1997 | 10 (0) | 8 (2) | 0 (0) | **18 (2)** |
| **2016** | School year 12 | 01/09/1997 - 31/08/1998 | 2 (0) | 3 (0) | 0 (0) | **5 (0)** |
| **2017** | School year 11 | 01/09/1998 - 31/08/1999 | 0 (0) | 3 (0) | 0 (0) | **3 (0)** |
| **2018** | School year 10 | 01/09/1999 - 31/08/2000 | 1 (0) | 2 (0) | 0 (0) | **3 (0)** |
| **2019** | School year 9 | 01/09/2000 - 31/08/2001 | 7 (0) | 1 (0) | 0 (0) | **8 (8)** |
|  |  | **Total cases** | **59 (19)** 2 | **50 (25)** | **3 (3)** | **112 (47)** 2 |

1 Includes one group B case in a French national (excluded from further analysis)

2 Excludes an additional two group B cases in university students born before 01/09/1991

**Table 2: Annual numbers of vaccines delivered and potential cases averted by various MenACWY vaccination programmes**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Vaccine strategy | Total cases potentially preventable over five year period | Expected coverage | Population denominator | Number vaccinated annually | Cases averted over five year period | Approximate number  vaccinated to prevent  one case over a five  year period |
| Routine adolescent (year 9) school programme | 36 | 75% | 592,716 | 444,537 | 24.3 | 18,000 |
| School leavers GP programme | 30 | 35% | 655,753 | 229,514 | 9.5 | 24,000 |
| Freshers university programme | 22 | 50% | 562,345 | 281,173 | 9.9 | 28,000 |