ASCERTAINMENT OF MENINGOCOCCAL DISEASE IN EUROPE

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Meningococcal disease surveillance in most countries is based upon a combination of statutory notification systems and laboratory reporting, both of which are recognised to underestimate the true burden of disease. The incidence of meningococcal disease varies throughout Europe, and although there are many reasons for this, it is important to quantify the degree of under-ascertainment in order to validate international comparisons. Here, we review the literature on the ascertainment of meningococcal disease in Europe and the available methods for estimating the degree of under-reporting. We found that the sensitivity of surveillance varies between countries and over time, with estimates ranging from 40% to 96%. We identified five methods suitable for conducting ascertainment studies, from simple comparative studies to more complicated capture-recapture and regression analyses. Studies of ascertainment may be used to identify weaknesses and biases in surveillance data, and facilitate the improvement of these systems. These findings are relevant to the surveillance of other infectious diseases, particularly those with lower mortality and a lower public profile than meningococcal disease, for which ascertainment may be worse.

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Introduction

The incidence of meningococcal disease varies across Europe from less than 1 case per 100 000 population, up to 6 per 100 000 [1]. The overall case fatality ratio in Europe is around 8%, but there is considerable variation between individual countries, from 4% to 20% [1]. The extent to which differential ascertainment contributes to the variation in morbidity and mortality is not clear.

The priority for public health disease surveillance is not to identify every case of an infectious disease, but to monitor trends and changes in disease epidemiology in a timely manner. A surveillance system will be adequate so long as reporting is unbiased and the level of under-ascertainment is known and judged to be acceptable. For the surveillance of meningococcal disease, most European countries rely upon laboratory reporting systems, clinician notification systems, or a combination of the two. These systems are likely to underestimate the true number of cases of disease [2,3]. Laboratory confirmation of meningococcal disease is very useful for management of cases and contacts and offers a highly specific diagnosis, but it is not always possible to obtain an isolate, especially if antibiotics are administered early. The use of polymerase chain reaction (PCR) assays, which require only a clinical sample and not a live isolate, appears to improve laboratory ascertainment [4]. Clinician notifications are likely to be less specific (but may be more sensitive) than laboratory reporting, but under-reporting also seems to be a problem [5], even when such notifications are mandatory.

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Assessing the degree of under-ascertainment is important for four major reasons: first, to ensure that surveillance is unbiased and representative, second, to allow the true burden of disease to be estimated (which may be useful for priority setting and economic evaluations of interventions), third, to facilitate improvements in the surveillance systems and fourth, to enable international comparisons. Here, we explore different methods for assessing the quality of surveillance and degree of under-reporting and review work that has been performed in Europe (published and unpublished) specific to meningococcal disease.

The aim of this article is to synthesise current knowledge on ascertainment of meningococcal disease in Europe and to review methods for quantifying the degree of under-ascertainment in surveillance systems.

Literature review - Methods

A literature search was performed in PubMed to identify papers on the ascertainment of meningococcal disease published between 1970 and 2005. The following search terms were used: 'meningococcal and ascertainment'; 'meningococcal and under-reporting'; 'meningococcal and reporting'; 'meningococcal and capture-recapture'. The abstracts of retrieved papers were read and used to assess their relevance.

A subgroup of the European Union Invasive Bacterial Infections Surveillance Network (EU-IBIS, www.euibis.org) was convened at the 7th European Monitoring Group for Meningococci (EMGM) meeting in Lanzarote in September 2003 to discuss the problem of under-ascertainment. Members of the subgroup were later contacted and asked if they were aware of any unpublished reports on the ascertainment of meningococcal disease in their country.

Questionnaires on surveillance systems completed by EU-IBIS participants in 1999 were reviewed to identify the main sources of surveillance data in Europe. These included:

- Notifications by clinicians (usually mandatory)
- Laboratory reports (from reference laboratories and/ or local laboratories, usually voluntary)
- Official death registrations

In addition, several countries have used hospital discharge data for further analysis of meningococcal disease epidemiology, but this data source is unlikely to be timely and so is not used for routine surveillance.

Literature review - Results

Nine studies were found in the review of published literature, which were judged to be relevant and reported on more than 50 cases. Five of these were conducted in the United Kingdom (UK) [2,3,5,8], and one each in Belgium [9], France [10], Spain [11] and Sweden [12]. Additional studies were retrieved for England and Wales that used information from the enhanced surveillance system [13,14], but it was judged that the main findings relevant to this study have been reported by Davison et al [6].

A total of four unpublished reports were received from; England (C Trotter, Health Protection Agency), the Netherlands (S de Greeff et al, National Institute for Public Health and the Environment (RIVM)), France (2 reports, A Perrocheau et al, Institut de Veille Sanitaire) and Austria (S Heuberger et al, National Reference Centre for Meningococci). In addition, a capture-recapture study in Denmark had also been reported in a PhD thesis [15]. A further paper from Germany was identified as being prepared for publication

(Schrauder A, personal communication), but results were not available for inclusion in this review.

The results from published and unpublished studies on the ascertainment of meningococcal disease are summarised in table 1. The percentage of cases ascertained in the various surveillance systems varies from 96% in Denmark (1994, notifications) at best to 40% in England (1982-95, notifications) at worst. The most recent estimates from England suggest that under-reporting for both laboratory reports (C Trotter, unpublished data) and notifications [5] is high. Registration of deaths was more complete, with a capture-recapture analysis estimating that 85% of deaths are reported. In the Netherlands, a capture-recapture analysis estimated that 59% of cases were notified and 70% of cases were referred to a laboratory. In France, ascertainment appeared to improve between 1996 and 2000, particularly for notifications (62% to 75%). In Denmark and Austria, two of the smaller countries, ascertainment is very good. In both these countries there is a low annual total of cases (fewer than 300 cases per year).

Review of methods for measuring under-ascertainment

1. Comparison of data sources

Where more than one data source on meningococcal disease exists, a good starting point is a simple comparison of the data sources. For example laboratory reports were compared to hospital episode statistics in England and Wales by Davison et al [14].

Suitable questions to consider may include:

- What is the difference in the total number of cases?
- What is the difference in the total number of deaths / case fatality ratio?
- Are the age/ sex distributions similar?
- Are the regional distributions similar?
- Are the temporal patterns similar?

This may help to identify biases with one or other of the systems and suggest areas to investigate further, although it will not by itself allow ascertainment to be quantified.

2. Capture – recapture methods

Capture-recapture methods were originally designed by ecologists to estimate the number of animals in a closed population. These methods have been applied to epidemiological data to estimate the 'true' number of cases of a disease from two or more sources. The simple capture-recapture problem, where two data sources are used to identify the number of cases missed by both data sources is illustrated in Table 2.

TABLE 1

Summary of results on ascertainment of meningococcal disease in Europe

Country	Data source	Method	Degree of ascertainment	Reference
England, 5 regions, 1998	Enhanced surveillance	Comparison	• 66% of cases notified • 76% deaths registered	Davison et al [6]
England (Manchester), 1985	Case finding (review), laboratory reports, notifications	Retrospective review	• 63% of cases notified • 57% cases referred for laboratory testing	Davies [3]
England, 1999	Laboratory reports, hospital episode statistics	Capture-recapture	• 53% of cases laboratory reported • 83% of deaths identified in death registrations	Trotter et al, unpublished
England (Gloucestershire), 1982-95	Active case finding, laboratory reports, notifications	Retrospective case ascertainment	• 40% of cases notified • 76% of cases laboratory confirmed	Wylie et al [2]
England (Nottingham), 1980-89	Notifications, hospital case notes	Retrospective case ascertainment	• 68% of cases notified	Fortnum and Mason [5]
England, 1969-1973 (meningococcal meningitis only)	Notifications, hospital case notes	Retrospective case ascertainment	• 50% of cases notified	Goldacre et al [7]
England & Wales, 1999-2003	Enhanced surveillance; laboratory confirmed and clinically diagnosed ('probable') cases	Regression methods	• 31% to 68% (variable by age group) of estimated serogroup C cases were laboratory confirmed • 20% of probable cases estimated to be due to serogroup C	Granerod et al [8]
France, 1989-90	Notifications, laboratory reports	Capture-recapture	• 51% of cases notified • 53% laboratory reported	Hubert et al [10]
France, 1996	Notifications, laboratory reports, hospital microbiology surveillance (EPIBAC)	Capture-recapture	• 62% of cases notified • 72% laboratory reported • 50% reported in EPIBAC	Perrocheau et al, unpublished
France, 2000	Notifications, laboratory reports, hospital microbiology surveillance (EPIBAC)	Capture-recapture	• 75% of cases notified • 76% laboratory reported • 58% reported in EPIBAC	Perrocheau et al, unpublished
Belgium, 1984	Notifications, laboratory reports	Retrospective review	• 62% of confirmed cases notified • 70% of confirmed cases laboratory reported	De Wals et al [9]
Denmark, 1994	Notifications, hospital discharge diagnoses	Capture-recapture	• 96% of cases notified • 89% of cases identified from discharge diagnoses	Samuelsson, PhD thesis [15]
Spain (Barcelona), 1993-94	Notifications ('obligatory reporting'), confirmed cases	Capture-recapture	• 79% of cases notified	Panella-Noguera et al [11]
Netherlands, 1993-98	Notifications, laboratory reports, hospital admissions	Capture-recapture	• 59% of cases notified • 70% submitted to national reference lab • 80% recorded in hospital admissions	De Greeff et al, unpublished
Austria, 2002	Reference centre data (official notifications), hospital admissions	Capture-recapture	• 87% of hospital cases notified	Berghold et al, unpublished
Sweden, 1998-2002	Notifications, laboratory reports	Capture-recapture	• 91% of cases notified • 85% of cases laboratory reported	Jansson et al [12]

Table 2

The capture-recapture method (from Tilling [16])

		'Source 1'		
		+	-	
'Source 2'	+	*a*	*b*	*a* + *b*
	-	*c*	*x*	*c* + *x*
		a + *c*	*b* + *x*	*N* = *a* + *b* + *c* + *x*

where *x* is the number of cases not identified in either data source

$$\frac{a}{N} = \left(\frac{a+c}{N}\right) \times \left(\frac{a+b}{N}\right)$$

$$a(a+b+c+\hat{x}) = (a+c)(a+b) \qquad [\text{because: } N = a+b+c+x]$$

$$\text{Giving: } \hat{x} = \frac{bc}{a}$$

This method has been employed to estimate the 'true' number of cases (or deaths) due to meningococcal disease in France [10], Spain [11], England (C Trotter, unpublished), Denmark [15], Sweden [12] and the Netherlands (S de Greeff, unpublished).

To conduct an analysis like this, cases must be matched between data sources. The datasets must therefore contain adequate personal identifiers (ideally unique identifiers such as a health registration number/ national ID number). If recording errors or incomplete reports are common, then significant bias may be introduced to the study [17]. It is also important that all the cases must be 'true' cases, i.e., that the surveillance systems and case definitions are highly specific, otherwise the use of capture-recapture will overestimate the burden of disease.

In addition, there are two critical assumptions that underpin this method: (1) the data sources are independent and (2) all individuals have an equal probability of 'capture'. These assumptions are unlikely to be valid when considering epidemiological data. For example, the probability of capture may vary by age or disease severity. This problem may be overcome by stratifying by e.g. age or severity, but this may limit the power of the study. It is very unlikely that the data sources used for surveillance are entirely independent. If positive dependency exists, the global estimate will be underestimated and the exhaustivity of each source overestimated. Log linear methods may be used to model dependence between more than two sources, which may help to overcome these problems of heterogeneity of capture and of dependency between sources. Three (or more) data sources may not always be available as part of the routine surveillance system, but it is possible to conduct punctual surveys in randomly selected hospitals or laboratories. These modelling methods can detect heterogeneity between or within sources, and although the interpretation of these effects may sometimes be difficult (and results may have to be stratified), it does improve the reliability of the estimates.

For a full review of these methods, their uses and limitations see Hook and Regal, 1995 [18] and Tilling, 2001 [16]. Capture-recapture may be useful for meningococcal disease, but the results should be interpreted according to the conditions and assumptions of the method to draw valid estimates.

3. Retrospective review

The degree of ascertainment has also been estimated through retrospective reviews. Individuals identified from clinical case notes as having meningococcal disease were matched with the available data sources (e.g. laboratory reports, notifications) to see whether they were recorded in the official statistics. The completeness of the official records can then be estimated. This type of study was conducted in Manchester (England) in 1985 [3] and Nottingham (England) in 1980-1989 [5], both of which identified substantial under-notification of cases (only 50-67% of cases were notified). This type of analysis may not be possible in all situations. The case notes must contain sufficient information for a reasonably sensitive and specific diagnosis to be made. In addition, reviewing case notes can be very time consuming and requires a skilled individual.

4. Prospective follow-up

The rationale of this method is similar to the method above, except that cases are recruited to the study prospectively rather than retrospectively. For example Wylie et al [2] established an enhanced surveillance system to ascertain all suspected and confirmed cases of meningococcal disease identified by local clinicians. The cases were followed up retrospectively to identify whether they were officially notified and/ or laboratory confirmed. The advantage of a prospective approach is that standardised clinical and laboratory investigations can be carried out, rather than having to rely on possibly incomplete historical case notes. The disadvantage of this approach is that clinicians may alter their reporting practices if they are aware that a study is being conducted, so that ascertainment may be overestimated. However, this may encourage good reporting practises that are maintained beyond the duration of the study.

5. Regression methods

It is clear that even where very good surveillance systems are in place, it is not possible to obtain laboratory confirmation in all 'true' cases of disease. Diagnoses based on clinical evidence alone are useful but are likely to be less specific than those based on laboratory reporting, and 'false positives', i.e., cases attributable to other organisms, may be reported. The underlying aetiology of clinically defined syndromes can be examined using regression methods, which have previously been used to investigate the burden of disease attributable to rotavirus [19] and respiratory syncytial virus (RSV) [20], among others.

The temporal variability in infectious diseases is exploited by comparing the trends in laboratory reports (which are highly specific) with the trends in a clinically defined syndrome. Laboratory reports of meningococcal disease have a distinct temporal pattern and if a clinical diagnosis of meningococcal disease is specific, then there should be a high correlation between the seasonal patterns in clinical diagnoses and the seasonal patterns in laboratory reports, even if the total number of reports differ. This is also a useful way to investigate alternative aetiologies of the clinical syndrome; for example, clinical 'cases' of meningococcal disease may be due to viral infection.

The formula for calculating the expected number of 'syndrome' cases Yj in 4-week period j is: $Yj = C + \Sigma\, \alpha i\, Lij$

Where Lij is the number of laboratory reports of type i in a 4 week period j and αi is the regression co-efficient for type i used to estimate the number of 'syndrome' cases associated with each report of type i (e.g. confirmed meningococcal disease and possible alternative diagnoses such as enterovirus, *Streptococcus pneumoniae*, *Haemophilus influenzae* [6]). C is a constant representing the background number of 'syndrome' cases in each 4 week period associated with other infectious or non-infectious causes of clinically suspected meningococcal disease where the temporal trend is not strong enough to be individually significant. The values of αi and C can be estimated by least squares regression. Data may be taken from a variety of sources, or from the same source, provided that the data is representative and unbiased. Appropriate data may include, laboratory reports, hospital statistics, notifications and death registrations. Clearly, to estimate Lij, the reports must be specific to a particular pathogen, although the sensitivity and specificity of different types of reports may vary (for example, laboratory reports are highly specific, but notifications based on clinical diagnoses may be less specific).

This method was recently used to investigate the aetiology of probable (i.e., clinically diagnosed cases of meningococcal disease without laboratory confirmation) cases of meningococcal disease in the England & Wales Enhanced Surveillance of Meningococcal disease (ESMD) system between 1999 and 2003, by Granerod et al (in press) [8]. The contribution of other organisms (including enterovirus, influenza and *S. pneumoniae*) to probable cases was investigated in a regression model similar to that described above.

Discussion

We have reviewed published and unpublished reports to explore the ascertainment of meningococcal disease in Europe. In all cases the surveillance systems underestimated the burden of meningococcal disease, although there was quite a range in the estimated proportion of cases represented in the surveillance statistics, from around 40% to 96%. It is not clear what, if any, action was taken to improve surveillance following study results demonstrating poor ascertainment, but clearly, studies such as these could be used to facilitate improvements, such as reconciliation of clinical and laboratory confirmed cases.

There is no 'gold standard' of disease incidence, so a range of methods have been developed to quantify the level of ascertainment through standard surveillance sources. We reviewed these methods, ranging from simple comparison of two data sources to more complex statistical analysis such as capture-recapture or regression methods. We have not attempted to evaluate the different methods, as the appropriateness of each will depend on the research questions being addressed and the data available. The potential biases of these methods have been highlighted, and should always be considered. A precise description of the surveillance system is important because this allows qualitative assessment of potential problems that may affect the level of ascertainment.

In addition to measuring ascertainment, it is also important to consider the results of such studies in context, particularly for temporal analyses. Important factors may include epidemiological trends [21], changes in clinical practice, changes in reporting requirements [22] and the introduction of new laboratory methods (such as PCR [4]). For example, laboratory confirmation by culture may decrease as a result of the introduction of a policy to administer pre-admission antibiotics, or because of a reduction in the number of lumbar punctures performed. Surveillance is likely to have been enhanced in countries that have introduced serogroup C conjugate vaccines (including the UK, Spain, and the Netherlands) so that they may identify vaccine failures and estimate vaccine effectiveness. In addition, other countries who have not yet introduced the serogroup C conjugate vaccine may have improved their surveillance in order to be able to respond promptly to any increase in the incidence of C serogroup disease.

EU-IBIS continues to collect a large amount of data across Europe and analyses based on these data may be very powerful. However, a potential criticism of such analyses is that they may be biased by differential quality of reporting across countries. Some countries rely more on clinician notifications, others on laboratory reports, some countries report locally and collate at a national level, whereas others collect national statistics only. Because reporting systems vary between the participant countries of EU-IBIS, it will be important to consider some degree of 'quality control' of the combined data to ensure international data analyses are valid. On the laboratory side this has been achieved through the external quality assurance scheme, whereby all participating laboratories test a standard panel of isolates. Such harmonisation is more difficult to envisage for reporting and notification systems. Given the wide range of incidence experienced in Europe, it is likely that factors other than ascertainment will also be important in explaining these differences, particularly geographical variation in the prevalent meningococcal strains, some of which are more virulent than others [23]. International comparisons that are likely to be valid despite differences in the reporting systems include the proportion of cases due to different serogroups, or the impact of vaccination (taking into account the different vaccine schedules/strategies used in each country).

This study may also be relevant for other European surveillance networks. Indeed, given the characteristics of meningococcal disease - it is severe, has high mortality, all patients are admitted to hospital and cases generate much public concern - it is surprising that there is still considerable under-ascertainment in most European countries. The situation for other, less severe, infectious diseases may be much worse, and attempts should be made to quantify this.

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