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Lyme borreliosis in Europe

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Despite improvements in prevention, diagnosis and treatment, Lyme borreliosis (LB) is still the most common arthropod-borne disease in temperate regions of the northern hemisphere, with risk of infection associated with occupation (e.g. forestry work) and certain outdoor recreational activities (e.g. mushroom collecting). In Europe, LB is caused by infection with one or more pathogenic European genospecies of the spirochaete *Borrelia burgdorferi* sensu lato, mainly transmitted by the tick *Ixodes ricinus*. Recent surveys show that the overall prevalence of LB may be stabilising, but its geographical distribution is increasing. In addition, much remains to be discovered about the factors affecting genospecific prevalence, transmission and virulence, although avoidance of tick bite still appears to be the most efficient preventive measure. Uniform, European-wide surveillance programmes (particularly on a local scale) and standardisation of diagnostic tests and treatments are still urgently needed, especially in the light of climate change scenarios and land-use and socio-economic changes. Improved epidemiological knowledge will also aid development of more accurate risk prediction models for LB. Studies on the effects of biodiversity loss and ecosystem changes on LB emergence may identify new paradigms for the prevention and control of LB and other tick-borne diseases.

Introduction

Lyme disease (or Lyme borreliosis, LB) is a multisystemic inflammatory disorder caused by an immune response to the pathogenic genomic species of *Borrelia burgdorferi* sensu lato (sl), which are transmitted by the hard ticks of the *Ixodes ricinus* species complex [1,2]. Despite substantial efforts to improve surveillance and control of LB in recent decades, it is still the most prevalent arthropod-borne disease in the temperate regions of the northern hemisphere [1], with approximately 65,500 patients annually in Europe (including notified cases and qualified estimates per country from 1987 to 2006, although the years covered vary) [3]. In the last few decades, the incidence of LB has been increasing in some countries and areas of Europe, but not in others. However, the effect of improvements in diagnosis and reporting of the disease on such statistics is unknown (see [3] for a review). Less controversial is the fact that the geographical distribution of LB is still expanding, especially towards higher altitudes and latitudes ([3] and references therein). Moreover, LB is likely to become an increasingly relevant health risk in the near future due to complex interactions between diverse environmental and socio-economic factors, which will affect various aspects of disease ecology and epidemiology, as outlined below.

The importance of LB has led to a surge in research effort, on all aspects of LB biology, ecology and epidemiology. The purpose of this review is to summarise the most recent findings (especially those of the last five years) and indicate where there is still controversy and lack of knowledge.

Transmission, epidemiology and clinical symptoms

Ecology and disease transmission

The ecology of LB is based on interactions between the pathogenic agent (*B. burgdorferi* sl), the vector (*Ixodes* ticks) and vertebrate reservoir hosts.

The *B. burgdorferi* sl complex currently comprises at least 18 genospecies [2]. In Europe, several of these are pathogenic to humans: *B. afzelii, B. garinii, B. burgdorferi* sensu stricto (ss), *B. bavariensis* (previously *B. garinii* OspA serotype 4) and *B. spielmanii*, while the pathogenicity of others such as *B. lusitaniae, B. valaisiana*, and *B. bissetii* is still uncertain [4]. In ticks, *B. afzelii and B. garinii* are the most common European circulating genospecies, followed by *B. burgdorferi* ss and *B. valaisiana* [5], whereas *B. lusitaniae* has a more focal distribution, especially in the Mediterranean basin [6]. Several genospecies may also be present simultaneously in a vector [5]. Although all pathogenic genospecies may cause erythema migrans (a red rash or patch on the skin), different genospecies are also associated with other clinical manifestations of the disease: *B. burgdorferi* ss is most often associated with arthritis and neuroborreliosis, *B. garinii* with neuroborreliosis, and *B. afzelii* with the chronic skin condition acrodermatitis chronica atrophicans [7].

The distribution and prevalence of various genospecies is known to vary on a local and regional scale, both temporally and spatially [5,8] with a higher biodiversity of genospecies between 4 °W and 20 °E, where there is a higher prevalence of ticks infected with *Borrelia* [8]. In addition, there is an uneven geographical distribution of LB manifestations across Europe: in Norway, for example, 71% of LB cases have neuroborreliosis, while in Germany, 85% of cases have erythema migrans [9]. *Borrelia* genospecies are also associated with particular reservoir hosts: for example, *B. afzelii* and *B. bavariensis* tend to be associated with rodents, *B. valaisiana* and most *B. garinii* serotypes with birds [4], *B. lusitaniae* with lizards and *B. spielmanii* with dormice [10]. On the basis of the sequence of housekeeping genes, it has been shown that the genetic structuring of *Borrelia* genospecies is dependent on the migration pattern of host populations [11], so that genospecies that are associated with birds are dispersed further than those associated with mammals. *Borrelia* can also be classified according to outer surface protein (Osp) sequences (there are 21 OspC major groups) and recent research suggests that these genotypes are ecologically and epidemiologically diverse [12,13]. However, despite its relevance to development of preventive measures and treatment, knowledge of the distribution and symptoms associated with each genospecies and genotype is still far from complete, and the genetics of *Borrelia* transmission and virulence are starting to be unravelled [10,14].

The bridge vectors (vectors that feed on more than one host species) that transmit *B. burgdorferi* to humans in Europe are primarily the tick *I. ricinus* and, less frequently, *I. persulcatus*. Ticks have three life stages: larva, nymph and adult, each lasting one to two years. Hard ticks seek hosts by 'questing' or climbing up grass stems or onto the edge of leaves, and extending their forelegs in response to thermal and chemical cues. They then drop or crawl onto hosts that pass or brush their forelegs. Larvae, nymphs and female adult ticks take one blood meal, lasting several days, from a vertebrate host (while adult males mate with feeding adult females). Between meals, the larvae and nymphs remain in leaf litter until moulting is complete, while adult females lay a batch of eggs in the litter then die). *Borrelia* may be acquired by a tick from feeding on an infected host or when feeding very close to an infected tick on the same, even uninfected, host (transmission by co-feeding) or from the site where an infected tick has recently finished its blood meal, (transmission by localised extended co-feeding) [10]. Once infected, competent tick species retain the pathogen even between moults, effectively transmitting the pathogen to the next feeding stage and/or to a host.

The most recent meta-analysis of surveillance data indicates that the overall mean prevalence of *Borrelia* infection in ticks in Europe is 13.7% (range: 0–49.1) although the prevalence is higher in adults (18.6%) than in nymphs (10.1%); Central Europe (Austria, Czech Republic , Germany, Switzerland, Slovenia and Slovakia) has by far the highest rates (in nymphs, >11%; in adults, >20%) [5]. In fact, peak prevalence has recently been confirmed between 5 °E and 25 °E longitude [8].

The capacity of ticks to transmit *Borrelia* to various hosts is influenced by a series of factors, including those intrinsic to ticks (e.g. questing behaviour, diapause duration, host preference, mating strategy [15] and tick density [16]), as well as extrinsic biotic and abiotic factors (e.g. climatic conditions, vegetation type and management, and host behaviour, abundance, susceptibility, tick burden and reservoir competence [17-20]). It has been shown that ticks infected with *Borrelia* may actually have an increased host-finding capability [21]. The tick–host interaction is particularly important for *Borrelia* infection dynamics, since the feeding tick secretes salivary vasoactive mediators and immunomodulators that facilitate the transmission of the pathogen from the tick to the host and vice versa [22]. Transmission efficiency can also vary in relation to *Borrelia* genospecies and duration of host infectivity [23,24].

Tick nymphs are mainly responsible for transmitting *Borrelia* to humans and quest most actively from spring to autumn in microenvironments with more than 85% relative humidity, such as in deciduous or mixed woodland with high ecotonal indices [17,25], as well as in suburban and urban environments [26] and roadsides [27]. For humans, exposure risk in a known tick-infested site can be as high as one infected tick per person per hour of exposure, or 0.25 infected ticks per 100 metres walking distance [21]. Transmission does not usually occur within the first 24 hours of the blood meal [28], so immediate removal of ticks is a highly recommended preventive measure (see below).

In Europe, confirmed competent reservoir hosts (i.e. tick hosts that can be infected with *Borrelia* and transmit this agent to uninfected ticks) include many common species of small and medium-sized rodent (mice, rats, squirrels, hares and rabbits), as well as several bird species (especially passerines), reptiles and insectivores [10,29]. Conversely, many large wild and domesticated vertebrates (e.g. deer and sheep) are considered non-competent reservoirs (i.e. ticks feeding on them do not acquire Borrelia; however, ticks may transmit *Borrelia* to each other when feeding very close together on these non-competent hosts). Host specificity is the result of the resistance or sensitivity of *Borrelia* genospecies to the serum complement of various host species, which leads to the survival or death of the pathogen, respectively [30]. Importantly, non-competent reservoir hosts, such as deer, may also serve as crucial maintenance hosts for feeding ticks of all stages [10]. The presence and density of these hosts is associated with the density of ticks, but their effect on tick-borne infection dynamics is complex [31]. The presence of non-competent reservoir hosts can decrease the transmission potential of Borrelia, reducing the prevalence in the vector and subsequent

disease risk to humans (a dilution effect [32,33]). Ogden and Tsao [34] have shown that any host that feeds enough ticks to reduce the overall infection prevalence in nymphs, by diverting them away from competent host species, would be likely to increase the tick population density by improving the chances of successful tick feeding. However, the overall effects of changes in biodiversity on LB emergence have yet to be thoroughly investigated [35].

Epidemiology

Although LB is not a particularly new emerging disease, an accurate description of LB epidemiology in Europe is still not possible because few countries have made this disease mandatorily notifiable [3,9,36]. Unfortunately, there appears to be no plan to continuously monitor LB at the European level [37]; instead this is recommended only 'Where the epidemiological situation in a Member State so warrants …', although such situations are not defined [38]. Therefore, surveillance statistics in Europe are based on non-standardised case criteria and uncoordinated systems of data collection [39,40]. Moreover, these data are inaccurate because patients with erythema migrans and other clinically diagnosed cases may be under-reported, the geographical distribution of referrals for testing is unknown, the criteria for serological diagnoses are not standardised, seropositivity due to past infection may be included, and data from remote regions may be lacking [41,42]. In addition, patients may be infected by one or two (rarely three) pathogenic *B. burgdorferi* genospecies and heterogeneity in symptoms caused by these various agents complicates surveillance [43].

A summary of the currently available epidemiological data is available in [3]. Epidemiological studies indicate the mean annual number of LB notified cases (including qualified estimates) in Europe is more than 65,400 (incidence rates per country range from less than one per 100,000 population to about 350 per 100,000 population). In Europe, LB occurs between 35 °N and 60 °N, and generally below 1,300 metres above sea level. However, there is strong heterogeneity in spatial distribution: the level of antibodies to *B. burgdorferi* sl is highest in residents of northern and central countries and lowest in those in the southern countries. In addition, at a local level, there is a focal pattern of distribution related to suitable tick habitat, including some hotspots where more than 100 cases per 100,000 population per year are recorded (e.g. parts of Slovenia, Germany and Austria, the Baltic coastline of southern Sweden, and some Estonian and Finnish islands).

LB risk is specifically linked to tick abundance and exposure. Therefore, although higher risk is no longer considered to be correlated with residency in rural areas, higher LB risk is associated with occupation (e.g. forestry work and farming) and especially with certain leisure activities (e.g. hunting, mushroom collecting and berry picking) and age (with two groups mainly affected: children aged 5–14 years and adults aged 50–64 years).

Since infection is correlated with tick abundance and exposure (and, therefore, tick activity), diagnosis of acute LB peaks in June and July in many northern and central countries of Europe, while a second smaller peak may occur in southern countries in late summer or early autumn; however, both erythema migrans and chronic forms of the disease can be diagnosed throughout the year [3]. Although the number of LB cases seems to be increasing in some areas, such trends are extremely heterogeneous and/or remain to be confirmed [3].

Clinical symptoms

The clinical presentation of LB ranges from acute to chronic illness, with wide variation attributed to the different *Borrelia* genospecies and/or genotypes implicated in the infection (as described above and in [44]), although the exact mechanisms maintaining chronic symptoms have yet to be confirmed. Diagnosis is primarily clinical and takes into account the risk of tick bite. Clinical case definitions for use in Europe – although not official European Union case definitions – are available in [45].

Briefly, several days or weeks after a tick bite, if *Borrelia* infection occurs, in 60–80% of cases this will be characterised by erythema migrans (the rash or patch on the skin about 10 cm across that may expand peripherally as a palpable band, and may or may not be itchy) [46], although early infection may be completely asymptomatic. Other early symptoms include influenza-like symptoms, fever, fatigue, headaches and muscle or joint pain. Several weeks or months after infection through a tick bite (with or without a previous history of erythema migrans), neuroborreliosis (noted in 10–20% of symptomatic patients) in the form of meningoradiculitis, meningitis or meningoencephalitis [47], Lyme arthritis or Borrelia lymphocytoma may occur [45]. Less frequently, multiple erythemata, or carditis are diagnosed [45,48]. Months or even years after *Borrelia* infection, acrodermatitis chronica atrophicans, lymphocytoma, chronic arthritis (fairly rare in Europe), encephalomyelitis or chronic neuroborreliosis (very rare in Europe) may be observed [45].

Microbial or serological confirmation of *Borrelia* infection is needed for all manifestations of the disease except for typical early skin lesions [49]. The diagnosis of some chronic forms of LB is currently controversial [50], and it has also been suggested that the overdiagnosis and overtreatment of LB may be an important problem [51].

Diagnostic methods

Direct detection of *B. burgdorferi* sl

Although the diagnosis of LB is primarily based on the most obvious clinical sign, erythema migrans, diagnosis of other forms of LB require confirmation by

means of a diagnostic test [52]. A wide range of methods have been developed for the direct detection of *B. burgdorferi* sl in clinical tissue specimens, including microscopic examination, detection of *B. burgdorferi*-specific proteins or nucleic acids, and cultivation. Although culture is the most commonly used method of direct detection, success rate depends on sample type. While mean recovery rates of *Borrelia* from skin biopsies of patients with erythema migrans and acrodermatitis chronica atrophicans are up to 70% [43], those for cerebrospinal fluid (CSF) are much lower. Future diagnostic methods may include PCR-based molecular techniques that can rapidly confirm clinical diagnosis of LB, and identify *Borrelia* genospecies in tissue specimens or cultured isolates [53]. However, even molecular methods have not yet been standardised since protocols and gene targets vary between laboratories and more clinical validations are needed [53]. Importantly, a negative PCR result does not necessarily indicate the absence of *Borrelia* [54]; therefore, the use of a PCR-based assay to confirm diagnosis of LB in the absence of serological evidence of *Borrelia* infection is not currently recommended.

Indirect diagnosis of *B. burgdorferi* sl

The complexity of the antigenic composition of *B. burgdorferi* sl and the temporal appearance of antibodies to different antigens at successive time intervals after *Borrelia* infection means the development of a serological test with high sensitivity and specificity is a challenge. The most commonly used serological methods for the detection of antibodies to *B. burgdorferi* sl include indirect immunofluorescent antibody assay (IFA) and an enzyme-linked immunosorbent assay (ELISA) [54]. Nevertheless, specific antibodies are often not detectable in the early stage of infection with the use of currently available test methods.

In more than 50% of cases, diagnosis of LB can be made on the basis of an expanding erythema (confirmed after a one-week follow-up). In the absence of erythema migrans at least one other clinical manifestation must be noted and confirmed using serological diagnosis of *Borrelia* in blood or CSF. According to the most recent German Society for Hygiene and Microbiology (Deutsche Gesellschaft für Hygiene und Mikrobiologie, DGHM) guidelines [43], serological diagnosis for patients in Europe should follow a two-step procedure: (i) ELISA and if reactive, followed by (ii) an immunoblot, if possible using recombinant antigens (p100, p58, p41i, VlsE, OspC, DbpA), including those expressed primarily in vivo (VlsE and DbpA), instead of whole-cell lysate antigen blots. OspC and VlsE are the most sensitive antigens for IgM antibody detection [54]. European standardisation of these diagnostic tests and new markers for detecting active infections are urgently required [55].

Treatment

Surprisingly, our review found that there is no European consensus on treatment and that economic considerations and national guidelines on avoidance of drug resistance also impact the current treatment of choice (no comparative costs are available). Treatment of the vast majority of LB cases is based on antibiotics, with drug type, dose, route (oral or intravenous) and duration varying with stage of the disease, as well as with symptoms. Treatment regimes and recommendations are summarised from the regularly updated European Union Concerted Action on Lyme Borreliosis (EUCALB) website [1] and [49], where doses can also be found. See also [49,51,56] for recent reviews on evaluation of treatments.

In general, in almost all LB cases, the disease is resolved with short courses of antibiotics [51,57], although longer courses are recommended for relapses or more serious and/or chronic forms. Some authors advocate that all symptomatic LB cases should be treated in order to avoid progression to later stages of the disease, and suggest that the earlier treatment begins, the less likely it is that more severe forms will follow [58]. However, overtreatment is considered a problem by others [51], although thus far, drug resistance has been noted only in vitro [59]. On the other hand, few data are available on the risk of long-term effects of non-treatment in asymptomatic LB patients [60]. Several studies have now shown that a few so-called chronic or 'post-LB' forms of the disease do not respond to antibiotics, although the reason for this is subject to some debate [50,51,61].

The main risks involved in treatment appear to be inappropriate patient management following inaccurate diagnosis. As mentioned above, both over- and under-diagnosis of LB is suspected.

Prevention

It has been suggested that individual or community measures to reduce the probability of tick bites and LB infection could be extremely effective preventive methods [62-64]. For example, in order to decrease the risk of tick bites and *Borrelia* transmission, people living in or visiting tick-infested areas are advised to avoid tick habitats, to wear long, light-coloured trousers (tucking them into socks) and to use insect repellent that contains permethrin (on clothes) or N,N-Diethyl-meta-toluamide (DEET) (on clothes or directly on skin). After visiting or working in such areas, a shower is recommended and a thorough check for ticks should be done, including careful inspection of the neck, armpits and groin. Tick bites can also be avoided by carefully inspecting and removing ticks from pets [65]. Any attached ticks should be removed immediately with tweezers if available, by seizing and pulling steadily on the mouthparts, without twisting [66] and the attachment site disinfected. Since ticks do not have a high probability of transmitting *Borrelia* until 12–24 hours after beginning to feed, immediate removal of ticks is one of the most effective ways of avoiding *Borrelia* infection. The site should be monitored for 30 days after the bite for signs of erythema migrans (there are

many websites that clearly illustrate these procedures, e.g. [67]).

There is currently no vaccine available on the European market. Thus far, the development of a vaccine for humans against *B. burgdorferi* sl infection has concentrated on the highly immunogenic outer surface proteins of this pathogen. Although an OspA-based vaccine was developed and licensed in 1998, it was withdrawn from the market in 2002 for economic reasons, as well as doubts as to its long-term efficacy (it was also not recommended for children under the age of 15 years or for people with arthritis). The future of vaccines of this type is uncertain; vaccine research continues, with the aim of generating protection against all pathogenic genospecies of *B. burgdorferi* sl [68]. New approaches include transmission-blocking vaccines, which act on proteins produced by ticks that appear to improve the transmission of the *Borrelia* spirochaetes from vector to host [69]. Factors critical to an effective and accepted vaccine will probably include the following: a detailed knowledge of the host–parasite cycle on a local, regional and European scale and of the distribution and prevalence of *Borrelia* genospecies; a better understanding of the symptoms associated with infection with each genospecies; and standardised serological confirmation of all suspected LB cases, including genospecies identification. Further studies on the role of surface lipoproteins of *B. burgdorferi* sl are also urgently needed [70]. In addition, enhancement of the epidemiological surveillance of LB, both of the disease itself and the abiotic and biotic factors that affect it, would improve risk assessment and aid prevention immeasureably [71].

Current geographical distribution of LB

LB occurs across Europe, with a distribution closely matching that of the vector *I. ricinus*. This tick species can be infected with *Borrelia* throughout its wide latitudinal range, from northern Turkey and the Atlas Mountains of Tunisia to northern Sweden [8,72,73]. Infected tick density also decreases with increasing altitude, although the ticks are now found at up to 1,300 metres [74,75]. Consequently, the incidence of LB decreases from the endemic areas of central Europe to the southern and northern limits [3,8]. However, studies on a local scale often reveal a higher incidence than previously recorded at a regional scale [16], so that monitoring LB locally may be important for treating and preventing the disease.

Factors triggering changes in LB incidence

The changes in capacity of *I. ricinus* to transmit *B. burgdorferi* sl in Europe could be due to changes in elements of the transmission process [40,76], such as: transmission coefficient (due to genetic changes in pathogen, vector and/or host [10]); survival rates of ticks (as a result of favourable abiotic changes [72]); increased tick abundance (resulting from increased availability of reservoir hosts and/or habitat [77]); increased exposure of humans to tick bites (due to an increase in outdoor activities [76]). Theoretical studies indicate that complex interactions between these factors will probably yield wide spatio-temporal fluctuations in the relative abundance of different *Borrelia* genospecies and LB incidence [23].

Global climate change inducing higher minimum temperatures (night-time and winter) and earlier springs are likely to affect many aspects of tick phenology [78], such as their local distribution, density and survival rates. For example, as a result of climate change, ticks have already spread into higher latitudes and altitudes in many European countries [72,75,78], while tick abundance is mainly affected by host abundance and habitat structure [25,79]. Regional studies with reliable long-term surveillance data show that an increase in tick abundance has also resulted in an increased incidence of LB, and that this increase is correlated with climatic factors [77]. However, climate change may not contribute to an overall increase in LB, since there may be an extended and more intense LB transmission season in some areas, while the risk of LB could decrease, at least temporarily, in locations with repeated droughts or severe floods, as shown in [80].

Instead, climate-related changes in land use and socio-economic influences on human behaviour are more likely to have a strong impact on the distribution and abundance of ticks and *Borrelia* infection risk (as noted for tick-borne encephalitis; [81]), especially in highly disturbed ecosystems, such as managed forests, peri-agricultural and urban and peri-urban sites [79]. A concomitant increase in the density of wild and domestic vertebrates, paralleled with expansion of suitable habitats for competent reservoir hosts, is expected to increase tick density, *B. burgdorferi* circulation and hence LB incidence [22,35,40,78,82]. The specific and combined contributions of all environmental and socio-economic factors to the observed pattern and predicted future impact of several tick-borne diseases in Europe were assessed within the Framework 6 Integrated Project Emerging Diseases in a changing European eNvironment (EDEN) [83].

Assessing the risk of infection

The complex multi-strain multi-host interactions associated with *B. burgdorferi* sl infection make it difficult to determine the risk of infection to humans [29,84,85]. While risk assessment may be based on well-planned surveillance of tick and *Borrelia* genospecies distribution and abundance [86,87] and/or serological surveillance of *Borrelia* infection in humans [88-90], it has been also been suggested that high-risk biotopes should be identified [91]. Spatial models have been developed to identify high-risk areas based on environmental and climatic features [92]. A model based on the long-term trends of habitat suitability for *I. ricinus* in Europe shows that the distribution of such habitats has remained relatively stable, although parts of Europe show increasing (Ireland, and parts of the United Kingdom, France, Spain, Portugal and Italy) or

a decreasing (Balkans, countries in the central parts of Europe and southern Scandinavia) suitability [80]. On a smaller spatio-temporal scale, the risk of exposure to Borrelia-infected ticks in the Italian Alps was predicted with a model based on bootstrap aggregation of tree-based classifiers within a geographic information system (GIS) [93]. The resulting map of the probability of encountering a questing *I. ricinus* nymph infected with *B. burgdorferi* sl has provided an important risk assessment tool for local human health authorities and policymakers.

Although the above methods can be used for risk and human exposure assessments, they cannot be used for addressing these as dynamic processes during a growing or declining epidemic. A detailed Ro (basic reproduction number) map would be an easy-to-interpret overview of LB risk following the introduction of *B. burgdorferi* sl into an area and could be suitable for following an LB epidemic (Ro being a measure of the risk of establishment of a disease in a certain area or population, defined as the expected number of new infections induced by a typical infectious individual during the full infectious period in a susceptible population [94]). For tick-borne pathogens, Ro can now be estimated using a next-generation matrix method [95], based on accurate biological conditions. However, Rosà and Pugliese [96] found that the effect of host densities on the Ro of tick-borne infections depends strongly on the regulation of tick populations. Since there is currently very little information on which factors affect natural tick populations, more complete, long-term field data are still needed before accurate Ro maps can be produced.

Conclusion

In Europe, the annual number LB cases is increasing in some areas, and tick vectors are expanding their range, to higher altitudes and latitudes, suggesting that LB will remain an important health concern in the coming decades, especially in light of economic, land use and climate change predictions. In addition, the effect of the resulting biodiversity loss and ecosystem changes on LB emergence should be an important focus of investigation, especially to identify new paradigms for the prevention and control of LB and other tick-borne diseases. It emerges from our review that standardised diagnoses are crucial to treating and combatting LB in Europe, as are European-wide reporting systems and datasets concerning all aspects of the molecular ecology and epidemiology of LB [10]. Preventive measures aimed at minimising tick-bite risk are promoted as one of the best ways to avoid *Borrelia* infection. Many authors agree that a concerted effort to improve surveillance is essential for monitoring this disease [9,36,49,55] and we consider that more complete eco-epidemiological knowledge is also needed to develop accurate risk prediction models.

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The *Chlamydia* surveillance system in Sweden delivers relevant and accurate data: results from the system evaluation, 1997-2008

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This study evaluates the ability of the *Chlamydia* surveillance system to provide relevant information to inform prevention and control activities in Sweden. The system was evaluated, according to the Guidelines for Evaluating Public Health Surveillance Systems from the United States Centers for Disease Prevention and Control, using surveillance data from 1997 to 2008. We interviewed staff from the Swedish Institute for Communicable Disease Control, the National Board of Health and Welfare and one county medical officer (CMO). We conducted a survey among laboratories, CMOs and a sample of clinics. Satisfaction with the system was good for 86% of CMOs, all laboratories, and 99% of clinics. The interviewed stakeholders considered the system to deliver relevant and accurate information that is useful for health policy decision making. However, the objectives for *Chlamydia* surveillance should be clearly defined in order to adapt the system requirements, simplify data collection and improve timeliness.

Introduction

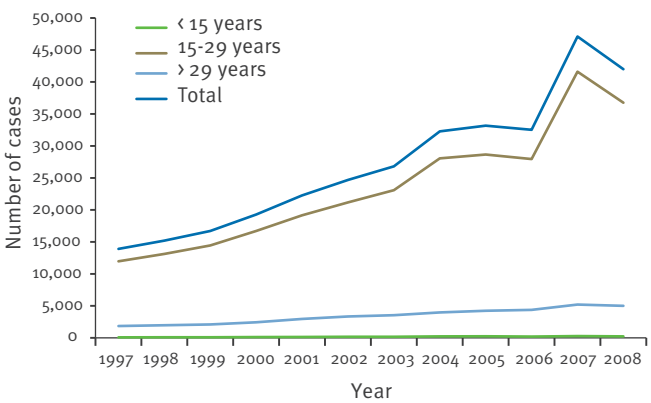
Chlamydia *trachomatis* (Ct) is the most common bacterial sexually transmitted infection (STI) in Europe [1]. According to the latest report from the European Centre for Disease Prevention and Control (ECDC), 335,329 cases were notified in 2008 by 23 Member States of the European Union (EU), the European Economic Area and the European Free Trade Association (EEA/EFTA), with an incidence rate of 150 cases per 100,000. The incidence was even higher in the age group of 15–24 year-olds where it reached a rate of 976 cases per 100,000. Underreporting is common and the real incidence in Europe is supposed to be much higher [1].

In Sweden, the absolute number as well as the incidence of Ct cases have been rising since 1997 (Figure 1), with a sharp increase in 2007 when diagnostic tests became available that detected the new Ct variant that had previously been missed with some of the standard tests [2]. The most affected group have been teenagers and young adults between 15 and 29 years of age, particularly women. This age group was responsible for most of the increase in incidence observed over the years, with little change over time in the other age groups. The Ct control strategy in Sweden includes free testing and treatment, active partner tracing and opportunistic screening, mainly of young women (when *Chlamydia* testing is offered during a visit to a gynaecologist or a youth health or STI clinic for other reasons (e.g. contraception counselling).

With the number of Ct cases steadily increasing, a reliable and functioning surveillance system is paramount to follow trends, inform public health action and monitor prevention and control interventions. Although the electronic surveillance system used in Sweden for all notifiable diseases (SmiNet) has been evaluated concerning the sensitivity and timeliness for four selected diseases in the past [3,4], the Ct surveillance system has never been formally evaluated in Sweden. This study aimed to determine whether the current Ct surveillance system delivers relevant, accurate and timely information to those who need it in order to enable adequate prevention and control measures.

Figure 1

Chlamydia trachomatis infections notified per year and age group, Sweden 1997-2008*



Methods

Chlamydia surveillance in Sweden

In Sweden, notification of Ct infection cases started on a voluntary basis for laboratories in 1982. Mandatory notification for clinicians was introduced in 1988 and for laboratories in 2004. Initially the reporting of cases was aggregated but case-based reporting was introduced in 1997 for clinical notifications and in 2005 for laboratory notifications. According to the case definition for Ct adopted in Sweden [5], all laboratory-confirmed cases have to be reported to the national surveillance system SmiNet. Confirmation of the diagnosis is made by the 29 laboratories that test for Ct.

The Ct surveillance system is comprehensive, including the entire Swedish population, and has two components: case-based reporting and aggregated reporting of the number of tests performed annually.

Case-based reporting is made through an electronic surveillance system (SmiNet) which was introduced in 1997 and upgraded and changed to web-based reporting in 2004 (SmiNet-2) [6]. Clinics and laboratories are required to report individual cases through SmiNet-2 using a web-based interface. Individual cases are reported anonymously using a modified code based on the unique personal identification number that all residents in Sweden have. The modified code itself is not unique, because reporting of STIs must by law be anonymous. Therefore laboratory and clinical notifications cannot be linked in the system. For the national surveillance, only clinical notifications are taken into account, since one case may have more than one laboratory report.

Aggregated reporting is a parallel voluntary surveillance system for laboratories to report the number of tests performed for Ct and the number of positives by sex and age group. This is reported electronically via SmiNet or on paper once a year. Although it is voluntary, all laboratories performing ***Chlamydia*** testing in Sweden report the data.

Data flow

Figure 2 shows the data flow between the different components of the Ct surveillance system, from the reporting sources to the data recipients. The data are collected at clinics and laboratories and entered in SmiNet through a web-based interface. The CMOs can access the data on cases reported in their own county, and SMI can access all the data. A summary of the data obtained from surveillance is published weekly on the SMI website, biannually in Epi-Aktuellt (SMI's official publication) and annually at SMI´s Annual Epidemiological Report. This information is then used by SMI, CMOs and the National Board of Health and Welfare (SoS) to monitor trends and guide public health action concerning Ct.

Evaluation of performance attributes

We followed the Guidelines for Evaluating Public Health Surveillance Systems from the United States Centers for Disease Prevention and Control (CDC) for the evaluation [7]. We aimed to evaluate the following system performance attributes: usefulness, simplicity, data quality, flexibility, acceptability, representativeness, timeliness and stability.

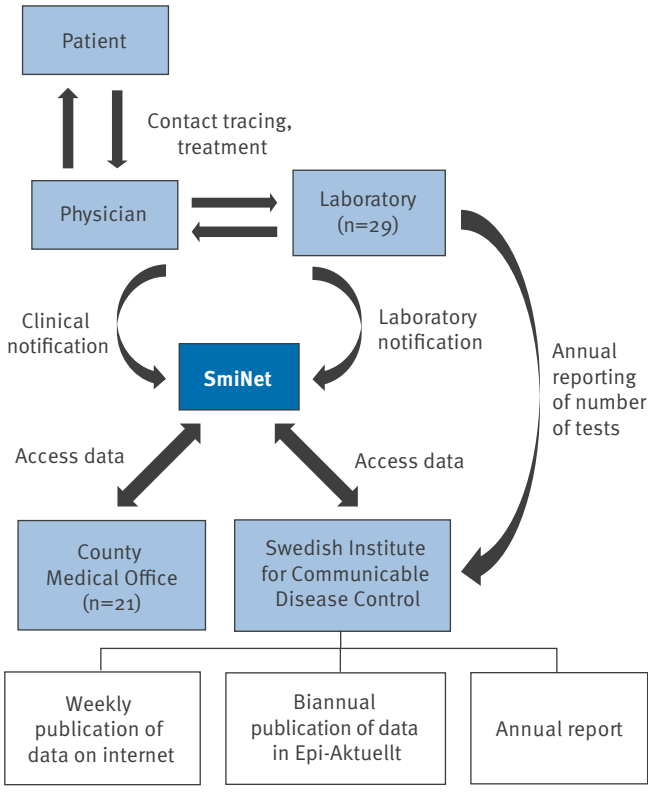
Usefulness, flexibility and acceptability were evaluated through semi-structured interviews conducted with key staff involved in Ct surveillance and control at the Swedish Institute for Communicable Disease Control (SMI) and the SoS as well as with the county medical officer from Västerbotten county. The CMO from Västerbotten county was chosen because of his expertise and research experience in Ct infections.

Data quality and timeliness were evaluated analysing the surveillance data for the period from 1997 to 2008 for clinical notifications and for the period from 2005 to 2008 for laboratory notifications.

We calculated the proportion of completeness for all variables, the proportion of invalid values and the median number of days with interquartile range (IQR) between the date of laboratory diagnosis and the date of notification. In order to assess timeliness we also calculated the percentage of notifications received within 24 hours, 7 days and 30 days of diagnosis (arbitrarily selected time spans) for the period from 2005 to 2008. We restricted the analysis to this period because the requirements were changed in 2004 to reporting within 24 hours of diagnosis.

Figure 2

Chlamydia surveillance data flow in Sweden



We considered that the most probable factor that could affect the system's representativeness in Sweden would be differences in access to healthcare between the different counties. The number of youth health clinics differs per county and some counties offer the possibility to request a free test through the Internet or even by mobile phone message. This can give different degrees of access to Ct testing in the different counties, and thus affect the representativeness of the Ct surveillance system. We calculated the number of youth clinics available per 10,000 population aged between 16 and 23 years in each county to get a rough estimate of access to Ct testing. The number of youth clinics per county was obtained from the official site for youth health clinics (www.umo.se). The population aged between 16 and 23 years per county was obtained from Statistics Sweden (www.scb.se) using the data for the year 2008. We chose this indicator because the majority of infections occur in the age group of 16–23 year-olds in Sweden and most of these infections are diagnosed and treated in youth clinics. We also examined differences between the sexes in the number of people screened per year for Ct infection to explore how this could affect the representativeness of the surveillance system.

Additionally, simplicity, data quality, acceptability, representativeness and stability were evaluated through self-administered questionnaires sent to all county medical offices (CMOs, n=21), all laboratories testing for Ct (n=29) and a sample of clinics participating in Ct surveillance (n=300). The questionnaires were sent by post and a reminder was sent by post or e-mail after four weeks to the CMOs and laboratories. No reminder was sent for the clinics due to logistics constraints. The sample of clinics was selected randomly among all clinics in Sweden that had reported at least 12 cases of Ct infection in 2008. We calculated that a sample of 200 clinics would be required to calculate proportions with a 95% confidence interval and a margin of error of less than 0.1. With an expected response rate of 70% based on previous surveys among healthcare workers in Sweden [8-10], we increased our sample by 30% to compensate. The final sample was 300 clinics.

Data analysis

The responses from the CMOs and laboratories were entered manually in EpiData. The questionnaires from the clinics were scanned and exported to Excel. After data cleaning and validation, data analysis was carried out using Stata 10 (StataCorp) and MS Excel. Qualitative data obtained from the interviews and from open questions in the questionnaires were reviewed and organised into specific themes. These were then reviewed in relevance to the related attribute.

Results

We interviewed two staff from SMI, five staff from SoS and one county medical officer. All 21 CMOs, 26 of 29 laboratories (90%) and 183 of 300 clinics (61%) returned the questionnaire.

Purpose of the surveillance system

The overall aim of the Ct surveillance system as part of the national surveillance system is to meet the requirements of the Swedish *Communicable Disease Act* [11] in order to protect the population against the spread of infectious diseases. However, we could not identify any documents stating the specific objectives for Ct surveillance. That was a justification to use CDC's guidelines for the evaluation of the surveillance system and not to evaluate the system against its objectives. According to the staff involved in ***Chlamydia*** surveillance the objectives were: to estimate the incidence of ***Chlamydia*** infection in Sweden, to monitor trends in notified cases by age, sex and reporting county, and to identify potential risk groups for further preventive interventions.

Usefulness

All the stakeholders interviewed agreed that the data collected through surveillance were useful for health policy decision making, stimulating research and monitoring interventions aimed at controlling and preventing Ct infection. As a direct result of the analysis and interpretation of surveillance data showing a steady increase in the number of cases in recent years, a new ***Chlamydia*** National Action Plan was launched in 2009 [12]. This plan aims at reducing prevalence of Ct infection by 2014 through increased use of condoms among teenagers and young adults (15-29 years-old), increased awareness and understanding of Ct infection in the population, increased access to testing, counselling and treatment and improvement in sexual education in schools [12]. In addition, there is a KAP (Knowledge, Attitudes and Practices) study underway among youths in Sweden (UngKAB, Socialstyrelsen) to improve understanding of underlying factors influencing the increase in the number of cases and to identify opportunities for prevention and control.

Simplicity

Data collection

The data collected for surveillance has a set of compulsory fields and a set of voluntary fields. For the clinical notifications, the following fields are compulsory: registration date (assigned automatically by SmiNet), diagnosis (disease), type of patient identification (ID) used, patient ID, age, sex, county of residence, type of clinic, reporting clinic and responsible physician's name. The median time needed to collect this information in the studied period was 20 minutes (range: 1–180 minutes). The information needed for the laboratory notification is obtained from the laboratory request form. The following fields are compulsory: registration date (assigned automatically by SmiNet), diagnosis (disease), laboratory, type of report, type of patient ID used, patient ID, age, responsible laboratory physician, referring clinic and county of the clinic.

Data management

Once the information is collected in the clinics, the data must be manually entered into SmiNet (or sent

in paper to the CMO). Fifty-three percent of the clinics (96 of 182) reported entering data less than once a week, while only 6% (11 of 182) did so daily. The median time to fill in the form was 5 minutes (range: 1–30 minutes).

Laboratory notifications can be done automatically by direct link of the laboratory database to SmiNet or manually entering the data into SmiNet. Fifteen of 24 laboratories reported having automatic notification. The data was entered daily in all of the laboratories with automatic reporting and in seven of the nine laboratories with manual reporting.

After the notifications are entered into SmiNet, they must be approved by the CMOs. This was done daily by 18 of the 21 CMOs. Twelve CMOs reported checking for double reporting using the laboratory number, the numeric code or the date of sampling.

Ninety-six percent of the clinics (173 of 180) and all laboratories reported dedicating less than 5 hours per week to activities related to surveillance, while 15 of 21 CMOs reported less than 10 hours.

At SMI, the notifications are reviewed weekly by an epidemiologist. Regular contact is maintained with CMOs when required.

Flexibility

SmiNet was introduced in 1997 and upgraded to SmiNet-2 in 2004. Before 2004 all the data was sent to the CMOs or SMI to be entered, but since the introduction of SmiNet-2 notifications have been entered directly by the clinics and laboratories. The notification reports in SmiNet for Ct can be easily modified if new variables need to be added or unnecessary ones eliminated. However, any changes must be approved by the CMOs, SMI and SoS.

Data quality

Perceived data quality

Fifty-seven percent of the clinics (102 of 180) reported never or only occasionally filling in all the information requested in the notification form. The main reason given for this was that the requested information was considered to be irrelevant for Ct surveillance.

Observed completeness of the data

In the period under evaluation there were 325,925 clinical notifications and 104,642 laboratory notifications. The compulsory variables were 100% complete for all the years for both types of notifications. Tables 1 and 2 show the percentages of completeness for selected non-compulsory variables in clinical and laboratory notifications for the time period under evaluation. We also examined the percentage of clinical notifications with invalid values. For most variables, it was under 1%. However, for infection date and onset date, this percentage was as high as 7%.

Acceptability

Eighteen of the 21 CMOs, all the laboratories and 168 of 169 of the clinics (99%) reported being satisfied or

Table 2

Completeness of non-compulsory variables (%) in laboratory notifications for *Chlamydia trachomatis* infection, Sweden 2005–2008

Variable	2005	2006	2007	2008
Sex	99	100	100	100
Date of receipt of sample	79	80	87	86
Date of testing	99	99	98	97
Sample material	98	94	98	98
Test number	86	96	97	97

Table 1

Completeness of non-compulsory variables (%) in clinical notifications for *Chlamydia trachomatis* infection, Sweden 1997–2008

Variable	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Date of diagnosis	4	60	85	89	89	92	93	92	95	94	93	92
Type of infection	5	77	78	90	93	97	97	96	92	91	91	90
Reason for examination	4	43	56	56	59	62	62	64	70	81	87	87
Infection date	1	9	18	20	28	27	27	32	45	38	37	29
Onset date	1	7	11	12	13	14	14	13	15	18	17	16
Country of infection	9	47	67	79	85	89	90	92	93	92	91	91
Place of infection	5	37	55	54	56	62	64	66	66	64	60	58
Place of onset	1	11	16	17	19	21	23	25	32	33	32	33
Route of transmission	8	71	92	94	94	96	98	98	96	95	95	89
Country of birth	0	0	0	0	0	0	0	0	6	23	29	34
Reporting laboratory	NA	NA	NA	NA	NA	NA	NA	1	31	60	76	77
Laboratory number	NA	NA	NA	NA	NA	NA	NA	1	18	59	77	76

NA: not available

very satisfied with the Ct surveillance system. CMOs and laboratories mentioned as the main disadvantage of the system the impossibility to use the personal identification number in the reporting, while clinics reported the lack of access to the report once is sent as the main disadvantage.

Representativeness

Perceived representativeness

On the questionnaires, 12 CMOs reported having an estimation of the degree of underreporting in their counties. They estimated it to be between 0 and 10% with a median of 4%. In the interviews, the stakeholders estimated that they had 5% underreporting based on the difference in the number of clinical and laboratory notifications.

Observed representativeness

In Sweden, there are between one and 10 youth clinics per 10,000 population aged between 16 and 23 years per county, with a median of three. There was no correlation between number of youth clinics per 10,000 16-23 year-olds and *Chlamydia* incidence in the same age group (Spearman's rank correlation test, p=0.8812).

We also examined differences between sexes in the number of tests performed annually for Ct infection for the period for which such information was available. Between the years 2000 and 2008 almost 3 million tests were performed among women compared with just under 1 million among men. Although the number of tests increased over the years, especially among men, there were still 2.6 times more tests per year among women than among men in 2008. However, the rate of positive tests was higher among men.

Timeliness

Perceived timeliness

In the interviews, publication of the data on the SMI website once a week was considered to be timely enough. However, publication only every six months of the aggregated reporting of the number of tests was considered to be insufficient.

Observed timeliness

The median delay between the date of the laboratory test and the date of notification to SmiNet was 5 days (interquartile range (IQR): IQR 3-7 days) for laboratory notifications and 11 days (IQR 6-20 days) for clinical notifications for the whole study period (Figures 3 and 4).

Overall, 1% of all laboratory notifications during the study period were notified within 24 hours, 85% within

Figure 3

Median delay time (in days) between date of diagnosis and date of laboratory notification of *Chlamydia trachomatis* infections, Sweden 2005–2008 (n=104,642)

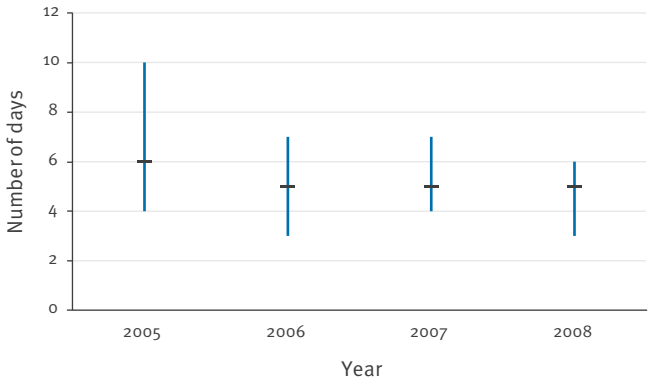
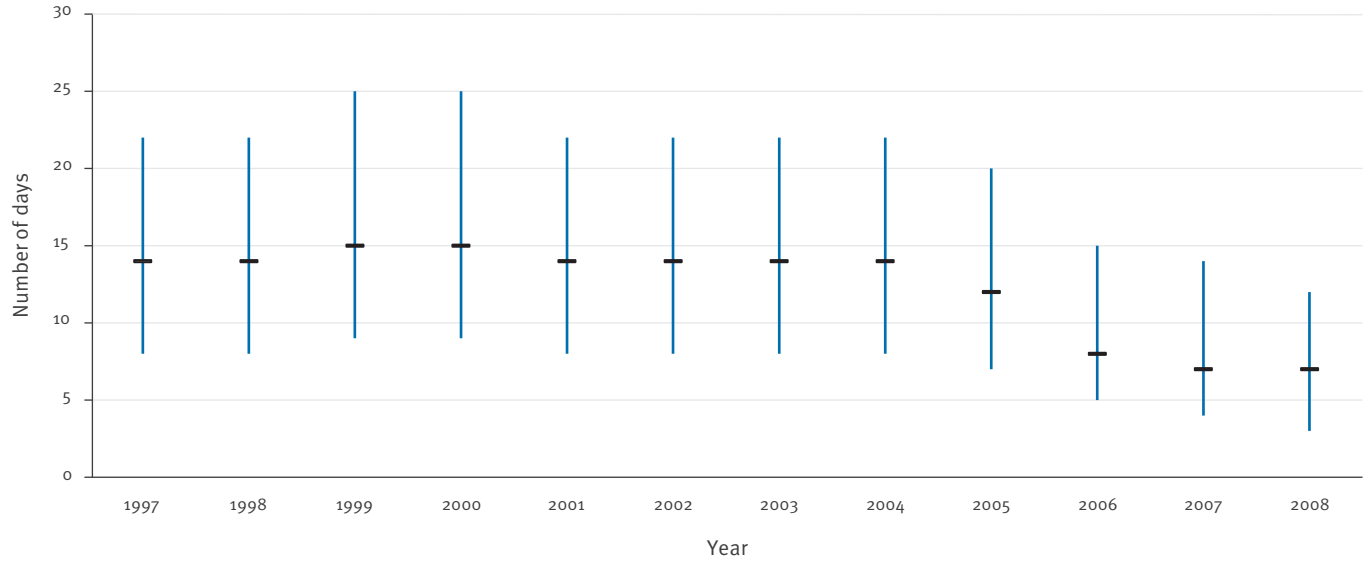


Figure 4

Median delay time (in days) between the date of diagnosis and the date of clinical notifications of *Chlamydia trachomatis* infections, Sweden 1997–2008 (n=325,925)



7 days and 99% within 30 days. For clinical notifications the figures were 9%, 45% and 91%, respectively.

Stability

Five per cent of the clinics, 10% of the laboratories and 81% of the CMOs reported having technical problems with SmiNet. The frequency of these problems was once a year or less for 97% of the clinics and 75% of the laboratories, and at least once a month for 88% of CMOs. The problems most frequently reported were system freeze and problems with login. When asked about the use of SmiNet technical support, 54% of the clinics, 58% of the laboratories and all the CMOs reported always receiving it when required.

Discussion

We aimed to evaluate the Ct surveillance system in Sweden by describing the system and measuring the usefulness, simplicity, data quality, acceptability, representativeness, timeliness and stability of the system. We could not identify any documents stating the specific objectives for the Ct surveillance system. Defining the objectives of the system would be crucial to establish whether the current system is adequate for Ct surveillance and better define the improvements necessary for the system to deliver the relevant information needed for action.

An important challenge with the surveillance system in Sweden is the anonymous notification of cases which makes automatic linkage between clinical and laboratory notifications impossible. Due to this complexity of linkage it was decided to consider only the clinical notifications with epidemiological information for case counting. The laboratory notifications, mandatory according to the *Communicable Disease Act*, are therefore not used for routine surveillance (but for could be used for the research). This means that we may miss laboratory-confirmed cases for which a clinical notification does not exist. This lack of unique personal identification number (which would allow linking clinical and laboratory notifications) was perceived as an important disadvantage of the Ct surveillance system by all stakeholders.

The simplicity of the Ct surveillance system was perceived as adequate by the respondents. System users considered the data flow as good (fast enough and technically less problematic than manual reporting) between the different levels (clinics/laboratories, CMOs and SMI). The number of compulsory variables needed to fill in a clinical or laboratory notification is low. However, the total number of variables in the clinical notification is high. The variation between clinics in the time needed to collect all the information for the clinical notification may be related to how thorough they are in their data collection, although we did not assess this aspect. For the laboratories, the introduction of automatic reporting linked to the databases has made the reporting easier and less resource-intensive. Simplicity of use and speed were the main advantages of the system perceived by CMOs, clinics and laboratories.

The information gathered through surveillance was considered to be useful by health policy decision makers. All interviewed stakeholders reported using the information gathered through surveillance to decide on public health action, such as the implementation of a new ***Chlamydia*** National Action Plan in 2009 [12]. However, there were suggestions to collect more information on the social background and sexual behaviour of cases. This would help to identify particular risk groups and to better target prevention activities but would be time- and resource-consuming. Finland has a sentinel surveillance network for STIs where detailed information concerning risk behaviour is collected through a self-administered anonymous questionnaire in 12 clinics around the country [13]. A similar approach could be explored in Sweden.

The Ct surveillance system is flexible and modifying the notification forms is possible and relatively easy to do. However, agreement between all stakeholders (SMI, SoS and CMOs) is needed before any changes can be implemented, which can result in delays. Data quality was considered to be 'good' for compulsory variables and for voluntary variables perceived as important for Ct surveillance. Variables like infection date, onset date, place of onset, place of infection and country of birth had a low completeness rate. They were considered to be 'irrelevant' and it was suggested to remove them from the notification because this information is rarely available.

The general acceptability of the Ct surveillance system is high. Most CMOs, laboratories and clinics are satisfied or very satisfied with the system.

Representativeness was very difficult to evaluate. Ct surveillance comprises all laboratory-confirmed cases in Sweden. However, there is no information on the real prevalence of the infection among the Swedish population, so it is very difficult to evaluate the number of unreported cases or the number of undiagnosed cases. The interviewed CMOs and the SMI estimated underreporting to be around 5% based on the discrepancy between the number of laboratory and clinical notifications. All stakeholders interviewed agreed that the real incidence was probably higher than reported although there are no prevalence studies for Ct in Sweden to compare it with. According to the stakeholders, the trends obtained through the surveillance system should be considered as accurate. Although there is no data on Ct prevalence in Sweden and Ct incidence is underreported (due to many asymptomatic and untested persons), general trends are considered to mirror reality quite well.

The number of tests performed among women was higher than among men in all studied years since 2000. However, the positivity rate was higher among

men. Rather than a shortcoming of the surveillance system itself, this could indicate differences in health seeking behaviour among men, or that prevention activities like opportunistic screening are more targeted at women. We believe that surveillance system is mirroring the real distribution of ***Chlamydia*** cases in the population by age group, with underrepresentation of cases among men due to the reasons mentioned above.

The timeliness of case reporting and data publication was adequate, and it improved during the period evaluated. However, only 1% of laboratory notifications and 9% of clinical notifications were notified within 24 hours of diagnosis as required by the *Communicable Diseases Act*. The weekly updates of Ct surveillance data on the SMI website was considered timely enough by all stakeholders. From a surveillance point of view, the notification period could be extended to one week to match the frequency of reporting. This could be improved by implementing automated data reporting from the laboratories, similar to what is already done with the case-based reporting. However, this would require the laboratories to invest in the development of programmes for automated data transfer, which can take time to implement.

The system stability was perceived as 'good' with few technical problems reported and efficient technical support when required.

In conclusion, the Ct surveillance system in Sweden delivers relevant and accurate data to inform public health action. However, the system could be improved further by implementing the following recommendations:

- Establish clear objectives for Ct surveillance in order to adapt the current system to the needs of stakeholders;
- Equate Ct with other notifiable diseases enabling reporting with the personal identification number to avoid case duplication and evaluation of reinfections;
- Adapt the clinical and laboratory notification forms specifically for Ct eliminating unnecessary variables in order to simplify data collection and improve data quality, acceptability and timeliness;
- Extend automatic reporting to all laboratories to increase timeliness.

***Erratum:** In the version originally published on 7 July 2011, the curves in Figure 1 were assigned to the wrong age groups. This mistake was corrected on 14 July 2011.

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Surveillance of influenza in Finland during the 2009 pandemic, 10 May 2009 to 8 March 2010

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The first infection caused by pandemic influenza A(H1N1)2009 virus was confirmed in Finland on 10 May 2009. The spread of the disease and its impact were monitored using several surveillance systems, such as the national infectious disease register, notifications of clusters of influenza, influenza-like or influenza-related illnesses, as well as virological, hospital, case-based and mortality surveillance. The epidemic started in early October in the north and then spread to the south about two weeks later. Based on the data from laboratory-confirmed cases, the morbidity was highest in children. The daily number of patients hospitalised with influenza A(H1N1)2009 reached a maximum of over 400 in late November. Of the 1,580 hospitalised patients (median age 32 years), 672 (43%) had at least one chronic underlying illness, 35 (2%) were pregnant, 132 (8%) were treated in intensive care units and 74 (5%) required mechanical ventilation. The median age of patients admitted to intensive care units was 48 years and 78 (59%) of them had at least one chronic underlying disease, none were pregnant. Altogether 44 deaths related to influenza A(H1N1)2009 were recorded (median age 56 years): 40 belonged to high-risk groups on the basis of underlying chronic diseases. Combining data from different surveillance systems gave timely information about the spread of the pandemic and contributed to identifying risk groups.

Introduction

In April 2009, the first cases of pandemic influenza A(H1N1)2009 were confirmed in Mexico and in California, United States [1]. On June 11, 2009, the World Health Organization declared the first influenza pandemic of the 21 century [2]. In Finland, the first infection caused by the pandemic influenza virus was confirmed on 10 May 2009 [3]. During the early stages of the epidemic until the end of August, all suspected cases were referred to specialist care for virological confirmation and placed in isolation at home or in a hospital depending on the patient's condition. During this period, most of the cases were found among travellers returning from abroad. At the end of July 2009, operational activities related to the containment phase were stopped.

One pandemic vaccine dose per each citizen was purchased by the Finnish government for Finland and the vaccine became first available on 12 October 2009. The vaccination was carried out according to the recommended prioritisation order as soon as the vaccines had arrived in the country [4,5].

Here we report how the national surveillance systems were used and adapted to monitor the spread of pandemic influenza and its impact. Moreover, we describe novel surveillance systems that were set up during the 2009 pandemic in Finland. We also present national surveillance data and compare that to data collected in other countries.

Methods

Population-based surveillance

In Finland (population 5.3 million), the national healthcare system is organised into 20 healthcare districts (with catchment populations ranging from 68,000 to 1.4 million), which form five tertiary care districts.
All clinical microbiology laboratories report (generally electronically) all influenza A (culture, antigen, serology, PCR) positive findings to the National Infectious Disease Register (NIDR). With each notification, the following information is transmitted to NIDR: type of specimen and date of collection, patient's date of birth, sex, unique national identity code, and place of treatment. After the first case of pandemic influenza A(H1N1)2009 virus infection in Finland, findings positive for pandemic influenza A(H1N1)2009 virus were recorded in a specific data collection field. Notifications concerning the same patient were merged into a single case. To avoid delays in notification, the laboratories were requested to report their findings every workday between 8 and 9 am. In addition, the laboratories performing specific PCR-based diagnostics for 2009 pandemic influenza A(H1N1) virus reported every Monday the total number of specimens processed and the number of positive specimens during the preceding week to a web-based notification system.

Virological surveillance

A specific PCR test for pandemic influenza A(H1N1)2009 virus was set up on 30 April 2009, at the National Influenza Center of the National Institute for Health and Welfare (THL) [6]. Participants in a pre-existing sentinel network were asked to continue the surveillance and submit up to five nasopharyngeal samples per week from patients who presented with influenza-like illness (ILI) and/or acute respiratory tract infection (URTI) to THL. The sites of the network are located at garrisons (n=14) and healthcare centres at border guard posts (n=3), municipalities/counties (n=6) and private occupational health services (n=8). Specimens obtained via the sentinel network were tested by PCR for seasonal influenza A and B types, parainfluenza 1, 2 and 3, adenovirus, respiratory syncytial virus and specifically for the pandemic influenza A(H1N1)2009 virus. In addition, arrangements were made with the laboratories performing specific PCR for 2009 pandemic influenza A(H1N1)2009 virus to send positive specimens to the National Influenza Center at THL for further confirmation, virus isolation and characterisation (genetic and antigenic characterisation of viruses, oseltamivir resistance).

Case-based surveillance

The following background information was collected from individual cases of pandemic influenza A(H1N1)2009 to a web-based notification system: unique national identity code, symptoms, travelling history within two weeks before the onset of symptoms such as fever ≥38°C, cough, sore throat, diarrhoea and vomiting, underlying illnesses, pregnancy, hospitalisation, radiologically confirmed pneumonia, treatment in intensive care unit, mechanical ventilation, and death. During the early stages of the pandemic from May to June, notifications were made from all suspected cases, of whom specific PCR-based diagnostics were performed. From the beginning of July 2009, only confirmed pandemic influenza cases and from the beginning of November, only hospitalised and deceased cases were notified to this system.

Cluster identification

The doctors responsible for communicable disease control at healthcare districts were requested to ensure that local clusters of ILI cases would be identified. Later, when sustained local transmission was going on, the focus of data collection shifted to clusters of severe acute respiratory illness (SARI) and situations where schools or day care centres were closed due to illness in children or shortage of staff. Notifications were made by using the outbreak notification system, which is usually used only for suspected food- and waterborne disease outbreaks. The field in the form for additional data was used to provide information on acute respiratory illness with fever. The notifications were processed as usual in the municipality but sent for information only to the doctor responsible for communicable disease control at the healthcare district in question. When needed, THL provided consultation on diagnostic and infection control measures.

Influenza-like illness outpatients visits

When not all ILI cases were tested by laboratory diagnostics, ILI surveillance was recommended to be conducted at one to two primary healthcare centres in each healthcare district depending on the catchment population and local resources. The clinical case definitions for ILI accepted by the European commission (28/IV/2008) were available at the THL website. Also the corresponding international primary healthcare (ICPC2) and disease classification (ICD-10) codes could be used for outpatient visit calculations. The number and/or percentage of ILI visits to doctors and/or nurses were recorded. No comprehensive data was transmitted to national level, but ILI surveillance was carried out in all healthcare districts.

Hospital surveillance

From 19 November to 23 December 2009, THL collected daily the number of patients hospitalised with pandemic influenza A(H1N1)2009 by a web-based surveillance system. The healthcare districts were asked to report every working day the total number of inpatients at hospital wards and in intensive care units for whom pandemic influenza A(H1N1)2009 infection was either confirmed or suspected, and separately the number for confirmed cases.

Table 1

Prioritisation order of population groups to be vaccinated against pandemic influenza A(H1N1)2009, Finland, 12 October 2009–21 February 2010

Order	Population group	Mean starting week of vaccinations, (range)
1	Social and health care professionals, ambulance personnel, and pharmacists in customer service	43 (42–45) 2009
2	Pregnant women	44 (42–46) 2009
3	People from 6 months to 64 years of age at high risk due to their underlying illness	45 (43–48) 2009
4	Healthy children from 6 to 35 months of age	46–47 (45–49) 2009
5	Healthy children and adolescents from 3 to 24 years of age as well as army conscripts	47 (45–50) 2009
6	People aged 65 years and above who belong to high risk groups due to an underlying illness	51 (47–4) 2009-10
7	Rest of the population	2 (48–7) 2009-10

Mortality surveillance

Information on all deaths in Finland was obtained from the Population Information System. These data were linked to the cases of pandemic influenza A(H1N1)2009 notified to NIDR by using the national identity code. Influenza-related death was defined as a death, which occurred within 30 days after the date when the influenza-positive specimen had been taken. In addition, all-cause and excess mortality were assessed by age groups and compared to the previous influenza seasons by participating in the European Commission funded European Monitoring of Excess Mortality for Public Health Action (EuroMOMO) project.

Vaccinations

A total of 5.3 million vaccine doses arrived in Finland between 12 October 2009 and 15 February 2010, first approximately 150,000 doses per week and later more, up to 1.4 million doses per week. The starting weeks of vaccinations of different population groups are shown in Table 1.

Feedback of the surveillance results was given to healthcare districts and health authorities by emails and to the public and media on THL website.

Results

A total of 7,669 laboratory-confirmed pandemic influenza A(H1N1)2009 cases were identified in Finland from 10 May 2009 through 8 March 2010.

The first suspected case was reported on 5 May 2009. However, this case was not confirmed by laboratory tests. Between 19 May and 31 August (period prior to sustained domestic transmission including the containment phase), background information was reported for 203 laboratory-confirmed cases; 102 (50%) were males, and the median age was 24 years (range: 1–66 years). All healthcare districts reported at

Figure 1

Pandemic influenza A(H1N1)2009 cases per 100,000 population reported to the National Infectious Diseases Register by tertiary care districts, Finland 21 September 2009–3 January 2010 (n=7,403)

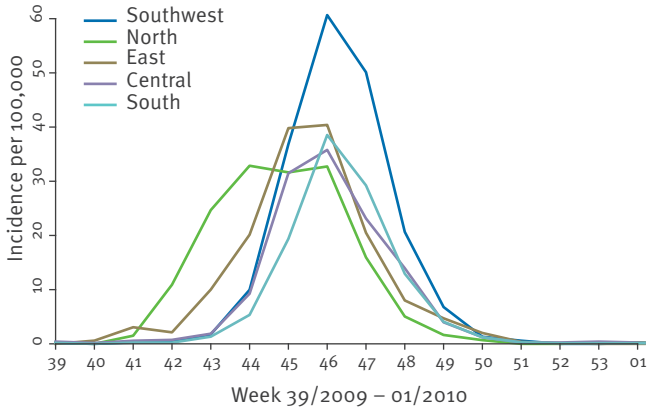
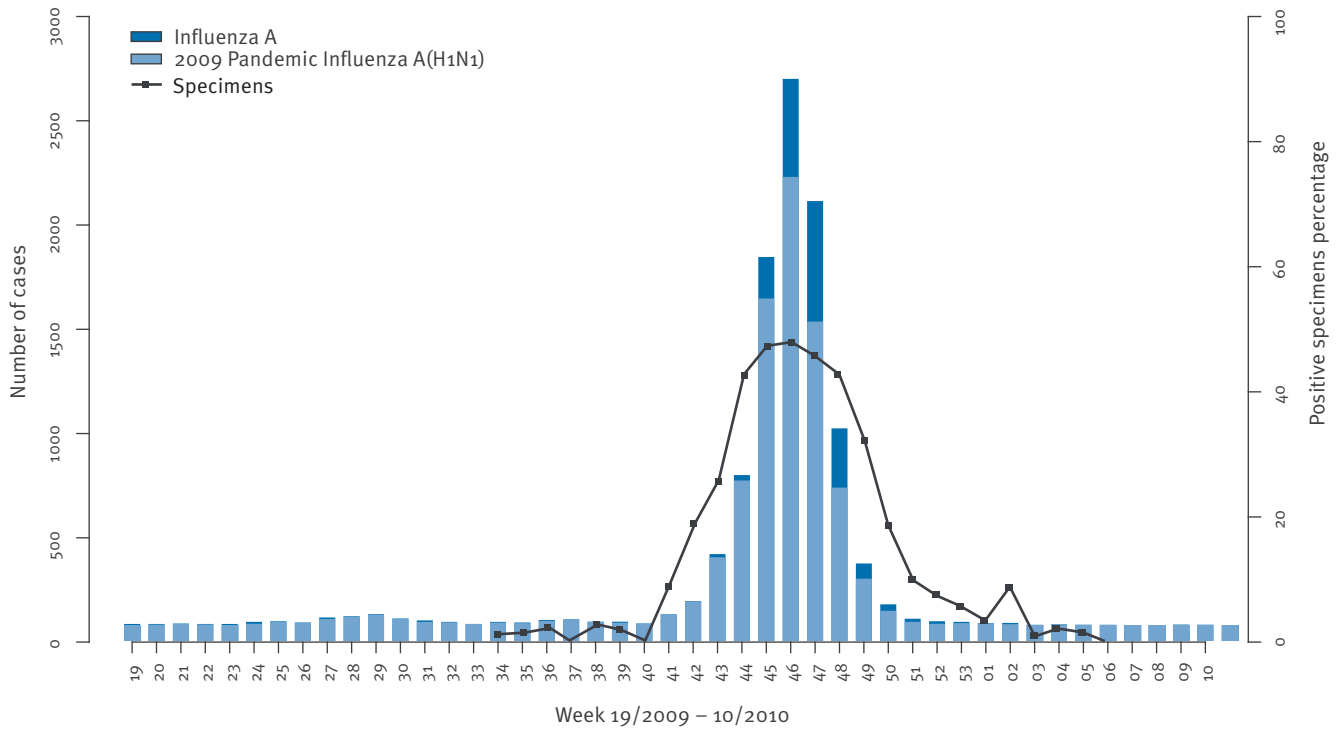


Figure 2

Influenza A and pandemic influenza A(H1N1)2009 cases reported to the National Infectious Diseases Register, and proportion of specimens positive for 2009 pandemic influenza A(H1N1)2009 virus, Finland, 4 May 2009–14 March 2010



Influenza A cases (dark blue bar, n=1,793) likely included cases caused by pandemic influenza A(H1N1)2009 virus infection (n=7,669), but they were not confirmed by a subtype-specific PCR test.

least one laboratory-confirmed case, and almost half of the cases were from the Helsinki-Uusimaa healthcare district. Three of the cases were pregnant women, and 171 (84%) of the patients had no underlying illness. About one third of the reported underlying illnesses (n=32) were mild, such as allergies. Seven cases had diabetes and six chronic pulmonary disease. The most common influenza symptoms were fever ≥38°C 167 (82%), cough 156 (77%) and sore throat 133 (66%). Of the 150 adult cases, 24 (16%) presented with diarrhoea and vomiting, while in children (≤15years of age) these symptoms were found in nearly one quarter (13/53) of cases. Seven cases had radiologically confirmed pneumonia. Out of the 203 laboratory-confirmed cases, 22 (11%) were hospitalised and three were admitted to an intensive care unit.

Among the cases with disease onset during May and June 2009, nearly 90% had travelled abroad within two weeks before the onset of symptoms. The corresponding figure for the cases reported in August was 60%. Between May and August, the most common travel destinations were the United States (n=53), Asia (n=49), United Kingdom (UK) (n=22), other European countries (n=40), Canada (n=4) and Mexico (n=4). Patients falling ill in August had mainly travelled in Europe.

The number of cases started to increase in Finland between 19 October and 8 November 2009 (weeks 43–45), and peaked first in the north (weeks 43–45) and thereafter, between 2 and 29 November in the south (weeks 45–48) (Figure 1).

A week before the numbers of cases began to rise, the proportion of positive specimens doubled (9.6–19.2%) and reached nearly 50% between 9 and 15 November (Week 46, Figure 2). At the turn of November to December, the proportion of positive specimens decreased, first in the north and thereafter in the south, and from mid-December onwards the pandemic influenza A(H1N1)2009 positivity rate of the samples was less than 10% throughout the whole country. In January 2010 there were 20 positive specimens and in February–March only two. As a whole, the proportion of specimens positive for pandemic influenza A(H1N1)2009 was 33%.

Based on the positive laboratory findings, the morbidity was highest in children (0–14 years) (Figure 3).

The geographical distribution was uneven, and the highest incidence of influenza infection was found in the northern part of Finland (Lapland) (Figure 4).

Based on the hospital surveillance, which started in mid-November (week 47), the burden of influenza patient in hospitals decreased quickly after the epidemic peak occurring at weeks 46–47. During weeks 47–48 there were daily over 400 suspected or confirmed cases in hospitals and daily over 50 patients were treated in intensive care units (approximately 13% of the intensive care beds in Finland).

In the specimens sent from sentinel sites, garrisons and healthcare centres, the pandemic influenza A(H1N1)2009 virus was the main virus type detected. In addition, sporadic influenza A(H3N2), parainfluenza, adeno and respiratory syncytial (RS) virus were also identified. The hemagglutinin (HA) and neuraminidase (NA) sequences of more than 140 virus isolates were analysed. According to NA sequence, all of them

Figure 3

Pandemic influenza A(H1N1)2009 cases reported to the National Infectious Diseases Register by age groups, Finland, 21 September 2009–3 January 2010 (n=7,403)

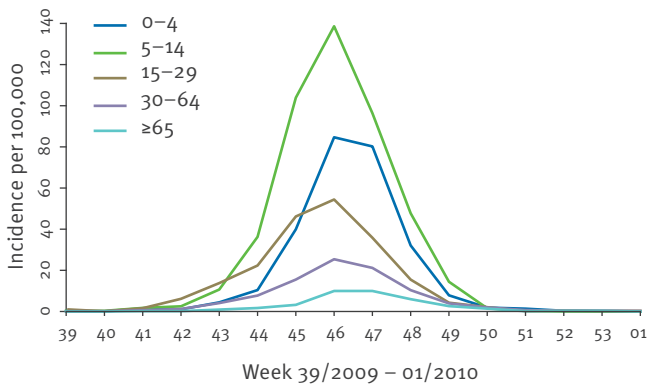
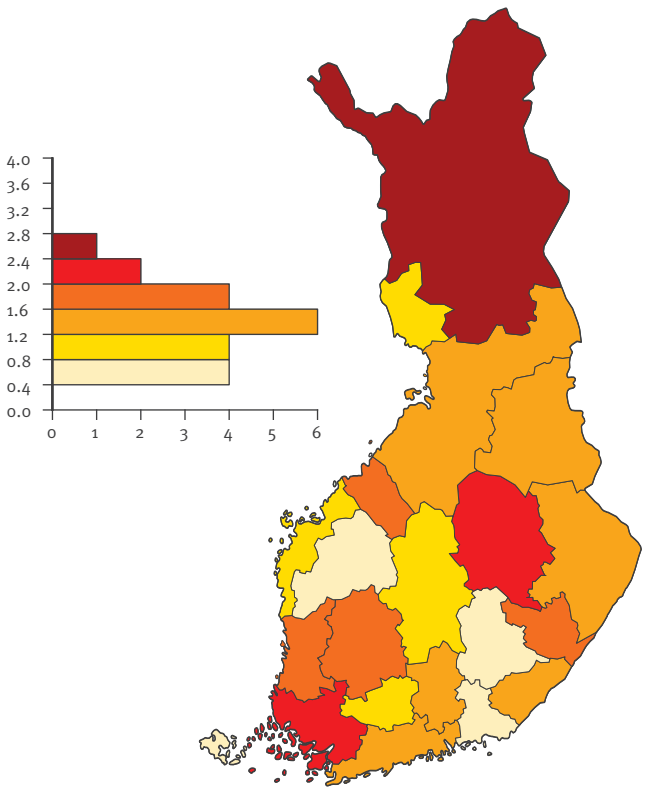


Figure 4

Influenza A cases reported to the National Infectious Diseases Register per 10,000 population by health care districts, Finland, 5 May 2009–8 March 2010 (n=9,465)



showed a genotype sensitive to oseltamivir. As compared with the influenza A/California/07/2009 prototype virus, the Finnish isolates collected between May 2009 and February 2010 showed maximally 1.4% and 1.1% variation in their HA and NA amino acid sequence, respectively. Some viruses isolated from severe cases had mutations at the residue 222 of the HA protein, but otherwise the viruses from mild and severe infection cases were genetically alike [3].

By the beginning of September 2009, a total of 38 ILI clusters were reported; most of them (n=33) from the Helsinki-Uusimaa healthcare district. Laboratory diagnostics were performed on ILI patient specimens from 13 clusters and in three clusters, several pandemic influenza A(H1N1)2009 infections were confirmed: two clusters were in garrisons [7] and one in a day care centre. At the end of September, at one school in Central Finland, one third of the students and some teachers suffered from ILI; pandemic influenza A(H1N1)2009 was identified in two students. From the end of September to the beginning of October there was an ILI cluster at one school in eastern Finland where around 20 students fell ill; pandemic influenza A(H1N1)2009 infection was confirmed for two students. Almost simultaneously in the same region the number of outpatient visits and telephone calls from the public increased in one healthcare centre where pandemic influenza A(H1N1)2009 was confirmed in three patients. At the end of October ILI clusters were reported from garrisons in northern and north-eastern Finland. At the beginning of November half a dozen ILI clusters were reported from schools in Helsinki metropolitan area, where up to half of the students fell ill and some cases were laboratory confirmed as pandemic influenza. No reports of school or day care closures were received.

Background information was reported for 2,032 of 7,669 cases (26%) of which 753 (37%) had at least one chronic underlying illness, 48 (2%) were pregnant women, 1,580 (78%) were hospitalised, 132 (6%) were admitted to intensive care (Table 2), and 74 (4%) required mechanical ventilation. Of the 48 pregnant women, six (13%) had a chronic pulmonary disease and one (2%) had diabetes. The underlying conditions included chronic pulmonary disease (310, 15%), heart disease (167, 8%), diabetes (141, 7%), receiving immunosuppressive treatment (92, 5%) or being immunocompromised (84, 4%), neurologic disease (79, 4%), obesity (37, 2%) and kidney (26, 1%), liver (11, 0.5%) or neuromuscular (10, 0.5%) diseases.

A total of 44 patients infected with pandemic influenza A(H1N1)2009 died (eight deaths per million), nine of whom were from northern Finland and 15 from the Helsinki metropolitan area, while other cases were scattered throughout the country (median age, 56 years; range 1–88). Of the 44 deceased cases, four were children (range of age, 1–17 years), 26 males and 40 (93%) belonged to risk groups based on their underlying illnesses, three did not have any underlying illness and for one the information was missing. The preliminary mortality analysis did not reveal excess overall mortality in any age group during the peak pandemic period.

3.7 million vaccine doses were delivered to the regional medical centres and hospital pharmacies. In total, 2.6 million vaccine doses were given [unpublished data THL]. The starting weeks of vaccinations of different population groups are shown in Table 1. Vaccination coverage for the entire country was approximately 50%, but varied considerably in the different age groups: it was highest in children aged 5–14 (76%) and lowest among young adults aged 20–29 (31%).

Discussion

During summer 2009 most of the pandemic influenza A(H1N1)2009 infections were detected among travellers returning from abroad. Persons who fell ill were mainly previously healthy young adults of whom few developed a severe disease. In early summer, the United States had been the most common travel destination, but later on in the summer infections were also identified among travellers who returned back to Finland from other European countries such as the UK. This is explained by the fact that both New York and London are popular travel destinations. In both cities the first wave of the pandemic influenza A(H1N1)2009 infections started before the closing of the schools for summer holidays [8,9].

In Finland the pandemic started in the north in the beginning of October, followed by spread to the south a couple of weeks later. The epidemic peak in Finland was observed somewhat later than in Norway and Sweden but earlier than in Denmark [9]. The reported ILI clusters at schools and garrisons were often the first sign of the starting epidemic at local level. By December 2009, the number of infections quickly decreased. Like in many other countries, based on the laboratory confirmed cases, the morbidity was highest in children and lowest in the elderly. Following the results of a study by Ikonen et al., the elderly population was considered partly immune: at least 10–20% of persons aged 65–79 years, ca. 60% of those aged 80–89 years and 95% of those aged ≥90 years had cross-reacting antibodies that likely originated from infections by the Spanish flu and its descendent viruses in the early 20th century [10]. Regionally, there were significant differences in morbidity which may be due to differences in the diagnostic activity. This can also be related to the fact that in some population groups and regions the vaccination campaign began too late to control the local epidemic. For example, according to Table 1 and Figure 1, the epidemic peaked in the north during the same week as the first vaccinations occurred in Finland (week 43). The epidemic peaked nationally at week 46 (Figure 2), but the start of vaccinations among the group aged 3 to 24 years occurred one week later (week 47), and the incidence

among the group of 5 to 14 year olds turned out to be the highest (Figure 3).

During the peak of the pandemic, the daily hospital burden due to suspected or confirmed pandemic influenza A(H1N1)2009 was more than 400 inpatients in the whole country. Like in other countries, hospitalised patients were younger (90% under 65 years of age) when compared to previous influenza seasons (90%, 65 years of age or older). Approximately half of the patients had at least one underlying chronic illness. The proportion of pregnant women was low (2% vs 5% in many other countries before vaccination). The most common underlying diseases were chronic pulmonary disease, heart disease and diabetes like in other countries [11-15]. The patients requiring intensive care were older, and more than half of them had some underlying illness. THL received no reports of pregnant women requiring intensive care which, beside the low proportion of pregnant women in general, may be due to the early start and good coverage of the vaccination campaign among pregnant women in Finland.

Altogether, 44 deaths related to pandemic influenza A(H1N1)2009 infections were confirmed in Finland which, in relation to population size, is more than what was found in other Nordic countries [9]. The linkage of national registers is not internationally commonly available as a tool to assess deaths in relation to specific laboratory-confirmed infections. Thus, the comparisons between countries should be made with caution. The patients who died were older than other hospitalised patients but younger than during previous influenza seasons. Almost all deceased patients had some underlying diseases and thus belonged to the influenza risk groups. One previously healthy child and two other individuals with no underlying diseases died from pandemic influenza A(H1N1)2009 infection.

When estimating influenza morbidity and mortality, the cases reported to national registries represent only a small proportion of those who were infected with the pandemic influenza A(H1N1)2009 virus [16]. Atypical clinical pictures, which are common among the elderly and those with underlying diseases are easily missed, as well as mild infections, which recover at home and do not require any medical attention. To obtain a timely picture on the emergence and spread of an influenza epidemic or pandemic, a population-based ILI follow-up system tightly linked with virological surveillance systems should be established in Finland. The final estimates on the effects of the pandemic can be made retrospectively by comparing morbidity and mortality data in the population with previous influenza seasons. Preliminary analyses from the United States and Europe suggest that there was excess mortality among children during the 2009–2010 influenza pandemic compared to previous influenza seasons [17,18].

At present the pandemic influenza A(H1N1)2009 virus has not undergone significant evolution that would hamper the efficacy of the present influenza A/California/07/2009 H1N1 vaccine. It seems that the evolution speed of the influenza A(H1N1)2009 pandemic virus is typical for influenza virus with a yearly rate of 1–1.5% of amino acid substitutions in HA and NA proteins. Some of these changes have and will be located at antigenically important sites of the virus requiring constant evaluation of the best possible vaccine candidates for the virus. In addition, no oseltamivir resistant influenza A(H1N1)2009 virus strains were found in Finland [3]. Thus, epidemiological, virological and population immune status surveillance are important tools in the fight against pandemic and epidemic influenza infections.

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Letter to the editor: Prioritisation of infectious diseases in public health: feedback on the prioritisation methodology, 15 July 2008 to 15 January 2009

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To the editor: We read with great interest the results presented by Gilsdorf and Krause (2011) [1] of a survey to experts on the methodology used by Krause et al. (2008) [2] to prioritise 85 pathogens of public health importance. Their work deals with a very relevant subject, given current pressure on health budgets: the allocation of finite disease surveillance and control resources among competing alternatives, infectious diseases in this case. The authors correctly identify the evaluation as being multi-dimensional and compensatory. Unfortunately, they appear to have overlooked findings and principles of well-established methodologies for assessing the impact of multiple effects on non-tradable goods, such as multi-criteria decision analysis (MCDA) [5]. It is within this perspective that we make our comments.

First, we noted that some of the criteria considered by the authors do not exhibit certain essential properties of evaluation criteria, particularly with regards to preferential independence. For example, it seems difficult to assess the "treatability" of a pathogen without considering simultaneously the "evidence for pathogenesis". We observed that lack of preferential independence may also exist between other criteria within the groups "Information needed" and "Health gain opportunity". When criteria are not preferentially independent, the use of linear additive models of weighted pathogen-specific scores, as in Krause et al. (2008), should not be used, as the overall impact cannot be assessed by simply adding up partial impacts. The criteria set should be redefined to make sure the essential properties hold and a simple weighted sum may be employed [4].

Second, the score's scale, -1, 0 or 1, lacks granularity and discretises continuous variables unnecessarily. Under the current model, a disease with an incidence of 20/100,000 would score "0" whereas as a disease with incidence of 20.1/100,000 would score "1". As suggested by some of the respondents to the survey, a continuous score is better suited. This issue is easily dealt with in MCDA, with the assessment of value functions, which map out and normalise different levels of impact into 0-100 scales.

The score "0" holds a double label: "average importance" and "lack of knowledge". The ambiguity of criteria labels is something to avoid in all prioritisation exercises. In this particular application, two diseases, one well known but "average" and the other suffering from lack of evidence, could score similarly. This would not help in the ranking of diseases and the subsequent distribution of resources that would probably allocate greater relevance to the unknown than to the average known. The survey respondents were rightly concerned about the need to incorporate uncertainty in their assessment against a number of criteria. To this request, the authors argued that the complexity of such addition to their model may outweigh the benefits. We would just like to add that simple approaches to handling uncertainty in decision frameworks similar to this are already available and widely used and that uncertainty about impacts should not increase the ambiguity in assessments.

Third, when allocating the weights to the criteria, the authors failed to recognise that weights are scaling constants, which aggregate partial impacts into overall impacts, and not direct measurements of importance. Indeed, a survey respondent correctly identified the limitations associated with this approach to weighting "*that the difference in importance between each criterion is always equal*". This could lead to misleading conclusions. Weights should reflect explicitly public value trade-offs of the group involved in model building and their assessment has to follow careful elicitation procedures to avoid well-known biases [4].

Fourth, a number of survey respondents raised the need for a time frame for some of the criteria. This is a very genuine concern that should be expanded to

include all the characteristics that define the context (e.g. geographical location). In our experience, prioritisation of diseases is a valid exercise that allows systematic comparisons to support strategic resource allocation. Like any other general strategy, it will fail to capture all possible presentations and heterogeneities that will surely be present depending on the risk pathways involved. Alternative methods to reactively measure the impact of such variability are required to feed into the regular strategic prioritisation of diseases. MCDA has been successfully used in these contexts and, in our view, provides a robust methodological framework for such evaluations [3].

We would like to finish our note with a comment on the composition of the expert group for prioritisation and congratulate the authors for engaging with a wide group of technical experts. If we may, we would like to suggest that the authors consider the incorporation of experts on MCDA to this group. This would follow common practice in other scientific fields such as nuclear waste management and drugs risk-benefit assessments.

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Authors' reply: Prioritisation of infectious diseases in public health: feedback on the prioritisation methodology, 15 July 2008 to 15 January 2009

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To the editors: We thank the authors of the letter in reply to our article „Prioritisation of infectious diseases in public health: feedback on the prioritisation methodology, 15 July to 15 January 2009" for contributing to the discussion, that we initiated by launching the described feedback survey on the prioritisation methodology.

The points raised are mainly addressing concerns against the original prioritisation method, described in „Prioritisation of infectious disease in public health – call for comments" by Krause et al. in 2008. As mentioned in our article in 2011, the survey was launched in order to get outside expertise for improving the prioritisation methodology, as we were preparing a new round of prioritisation. The suggestions that the survey participants raised were included in our review of the method. As the authors of the letter repeat several of the concerns addressed by the participants, it should be pointed out that they were taken into consideration in the latest prioritisation.

We are aware that some of the criteria are not exclusive and interdependent on each other. That was partly changed in the new round, but as we consider the criteria „incidence", as a very relevant criteria, we decided to score some other criteria based on their effect on the population and not the individual, taking incidence again in account. The majority of participants considered a three tiered criteria scoring as sufficient, and it is challenging enough to define three scores for each criteria and often estimation is needed for the scoring. The use of a 0-100 scale would suggest a precision, that is often not reflected in reality. As mentioned in our article, there was ambiguity in some score descriptions. In the new round we tried to give clearer guidance on how to score in this situation. We were also aware that the categorical scoring of weights was not optimal and changed that in the new round. And we have defined a five year time period for the recent prioritisation, acknowledging the need for such a time frame.

We are pleased about the attention regarding prioritisation in public health, and that many of the concerns of the authors of the letter were reflected in the reply of the survey participants. These concerns are therefore addressed in the revised prioritisation method. This method was used for the latest prioritisation round, that was finished in February 2011 and is in the review process for publication right now. As we believe that such prioritisation has to be updated regularly, we are looking forward to continue the discussion and development of the methodology also in the future.