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Onychomadesis and hand, foot and mouth disease – is there a connection?

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Onychomadesis is the spontaneous separation of the nail plate from the matrix, a kind of proximal onycholysis, and is a common phenomenon due to arrest of nail formation for a certain period. Short-term slowing down of nail formation leads to Beau's lines, while long-term stop of nail growth will cause onychomadesis and even nail shedding.

Hand, foot and mouth disease (HFMD) is a relatively common viral infection often seen as small epidemics in autumn or spring. It is characterised by oval blisters around the nails, on palms and soles with the long axis of the vesicles running along the dermatoglyphs, and by aphthoid small ulcerations of the oral mucosa. Small children are mostly infected, but probably many parents are non-symptomatic carriers as the condition usually runs a very mild course.

A relationship between HFMD and onychomadesis has been proposed already ten years ago [1,2], but only recently Finnish and Spanish authors observed a sufficient number of children developing onychomadesis approximately six weeks after they had suffered from HFMD [3-6] that makes this appear more than a chance association. An article by Guimbao and coworkers published in today's issue of Eurosurveillance describes an outbreak of onychomadesis in Saragossa (Spain) in July 2008 [7]. The authors noticed that a large proportion of the patients had had HFMD a few weeks before and initiated a retrospective cohort study that indicated a link between the two diseases. They conclude that onychomadesis may be a late complication of HFMD.

From these authors' and the previous ones' observation there is no doubt that there is a temporal link between HFMD and onychomadesis.

The question is now: Is the virus, more specifically the enterovirus causing HFMD, really the cause of onychomadesis? While the number of onchomadesis cases in these young patients suggests it, could it have been caused rather by the inflammation so close to the nail matrix? Or could it have been due – of course much less likely – to intensive hygienic measures taken after HFMD broke out in the nurseries? It is well known that maceration favours *Candida* infections and allergic contact dermatitis, which can also cause onychomadesis [8]. The timing of viral determination from stools and pharynx samples taken one to three weeks after the diagnosis of onychomadesis and thus between seven and nine weeks after the disease, appears to be very late considering that HFMD is a self-limited condition healing spontaneously within a week. In order to solve the problem, more viruses that could potentially be associated with the two conditions will need to be analysed, with viral analyses of nail specimens (e.g. swabs from under the proximal nail fold) performed in the early course of the disease.

However, onychomadesis *per se* is certainly not infectious; instead, it may be the consequence of an infectious disease often localised very close to the nail. Another explanation would be that HFMD has a more severe impact on the general condition of the small children so that it causes a nail growth arrest for a period sufficiently long to result in onychomadesis.

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Quantifying benefits and risks of vaccinating Australian children aged six months to four years with trivalent inactivated seasonal influenza vaccine in 2010

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Australian and New Zealand health authorities identified seasonal trivalent inactivated influenza vaccines manufactured by CSL Biotherapies as the probable cause of increased febrile convulsions in children under five within 24 hours of vaccination and recommended against their use in this age group. We quantified the benefit-risk profile of the CSL vaccines using the number needed to vaccinate and suggest they might have caused two to three hospital admissions due to febrile convulsions for every hospital admission due to influenza prevented.

Introduction

The recognition of an unexpectedly high number of febrile convulsions (not defined precisely initially) in children aged less than five years within 24 hours of receipt of trivalent inactivated influenza vaccine (TIV) in Australia in April 2010, led to the initial suspension of the childhood vaccination campaign for seasonal influenza in our country [1]. This was followed by more general discussion about the safety of influenza vaccines in children [2].

In 2010, trivalent vaccines from three manufacturers, CSL Biotherapies, Solvay Pharmaceuticals and Sanofi-Pasteur, had been licensed for use in Australian children. All vaccines contained the strains recommended by the World Health Organization (WHO) [3]. The influenza A(H1N1) virus vaccine component of these vaccines was the 2009 pandemic strain.

The increase in febrile convulsions was first recognised in the state of Western Australia [4]. This was possible because at the beginning of 2008 Western Australia had implemented a vaccine programme aimed at immunising children aged from six months to four years against influenza [5]. This programme acknowledged (i) the importance of children in the spread of influenza, (ii) the high hospitalisation rate due to laboratory-confirmed influenza in this age group and (iii) three childhood deaths associated with influenza in the state in 2007 [5]. Influenza vaccine coverage of 20%–30% had been achieved in this age group for 2008 and 2009 and also in 2010, prior to the suspension of the programme.

Given this background and following concern about the possible risk of febrile convulsions associated with influenza vaccination, the childhood influenza vaccination programme was suspended by the health authorities in Western Australia on 22 April 2010. For the whole of Australia, the precise number of febrile convulsions associated with the administration of TIV was not clear at the time. However, as a precautionary measure, the Australian Department of Health and Ageing recommended against using any formulation of 2010 TIV in young children on 23 April 2010 [1].

At the same time, the Ministry of Health in New Zealand recommended specifically against the use of Fluvax or Fluvax Junior (both manufactured by CSL Biotherapies) in children from six months to four years, but recommended the continued use of other influenza vaccines licensed for children in this age group, specifically Influvac (Solvay Pharmaceuticals) and Vaxigrip (Sanofi-Pasteur) [6], two vaccines that were also licensed in Australia. Recommendations for other age groups remained unchanged. Three months later, on 30 July 2010, the Australian Department of Health and Ageing published revised recommendations indicating it was safe to use either Influvac or Vaxigrip in all children aged from six months to four years but recommended against the use of Fluvax or Fluvax junior in children aged under five years [7].

A timeline of recommendations from health authorities in Australia and New Zealand is shown in Table 1.

Decisions regarding the suspension of an immunisation programme are important because they may have consequences for individuals and a long-term impact on vaccination programmes overall. It is therefore important that these decisions are based on objective assessments of the benefit and risk of all administered vaccines. We present an approach for quantifying the benefit-risk profile for vaccines from

two manufacturers, CSL Biotherapies and Solvay Pharmaceuticals, in 2010. We briefly compare with data collected in Western Australia on the frequency of febrile convulsions following administration of vaccines from Sanofi-Pasteur and CSL Biotherapies in 2008 and 2009.

Methods

We compared the benefit-risk profile of vaccination using data for the two vaccines (CSL Biotherapies and Solvay Pharmaceuticals) that had been administered in sufficient numbers in 2010 for meaningful comparisons to be made. To compare benefit and risk, we used hospitalisation data from 2009, obtained from the Department of Health in Western Australia, and adverse event data from 2010, sourced from a detailed investigation of adverse events in Western Australia (unpublished data).

We assessed benefit by estimating the number of children that would have required vaccination to prevent one hospital admission due to laboratory-confirmed influenza. We chose hospitalisation due to influenza of any type or subtype during the 2009 influenza A(H1N1) pandemic because viral testing for children hospitalised with febrile illnesses was intensive and relatively few children hospitalised due to influenza in 2009 would have remained undiagnosed.

We assessed risk using hospital admissions for febrile convulsions, which were defined by a systematic review of cases with reference to the criteria of the Brighton Collaboration for febrile convulsions following immunisation [8]. Receipt of at least one dose of influenza vaccine in 2010 was verified from the Australian Childhood Immunisation Register [9] and direct questioning of parents or guardians.

Quantifying benefit

To quantify benefit, we calculated the number of children that would need to be vaccinated to prevent one hospital admission due to influenza, that is, the number needed to vaccinate (NNV). The NNV is calculated as the reciprocal of the absolute risk reduction. The absolute risk reduction is calculated as the product of the absolute risk in the unexposed (in this

Table 1

Timeline of decisions communicated by health authorities in Australia and New Zealand following recognition of febrile convulsions in children under five years occurring within 24 hours of receipt of trivalent inactivated vaccine, 2010

Date (2010)	Decision
22 April	The Health Department of Western Australia suspends its influenza vaccination programme for children under five years of age because of concern about an unexpected number of febrile convulsions in children within 24 hours of receipt of the seasonal vaccine.
23 April	The Australian Department of Health and Ageing suspends the influenza vaccination programme at national level for children under five years of age.
27 April	The New Zealand Ministry of Health writes to general practitioners, recommending them not to use influenza vaccines manufactured by CSL Biotherapies (Fluvax and Fluvax Junior), but to continue using licensed vaccines from other manufacturers for children under five years of age.
1 June	The Australian Department of Health and Ageing recommends influenza vaccination can be resumed for children at risk of a severe outcome of influenza. It suggests the CSL vaccines are most likely responsible for the unexpected number of febrile convulsions. Influenza vaccines, including CSL products, can be administered on a case by case basis.
8 July	The New Zealand Ministry of Health reiterates its previous advice to general practitioners regarding the use of influenza vaccines for children under five years of age.
30 July	The Australian Department of Health and Ageing recommends that vaccination of healthy children under five years of age can resume, but not with CSL vaccines. The report states that 'continued close monitoring of side effects with this year's seasonal flu vaccine in children under five years of age has shown that the higher than usual occurrence of fever and febrile convulsions appears to be confined to the vaccine Fluvax, manufactured by CSL.'

Table 2

The number needed to vaccinate to prevent one hospital admission for laboratory-confirmed influenza, all subtypes, and the risk of hospital admission for febrile convulsion following receipt of trivalent inactivated influenza vaccine[a] by year and vaccine manufacturer

Year	Manufacturer	NNV to prevent one hospital admission for influenza (2009)	Risk of hospital admission for febrile convulsion[b]	Number of hospital admissions for febrile convulsions following vaccination of NNV	Risk of hospital admission for febrile convulsion (upper limit 95% CI)	Number of hospital admissions for febrile convulsions (upper limit 95% CI)
2010	CSL	1,852	0.0013	2.4	0.0017	3.1
	Solvay	1,852	0	0	0.0003	0.6
2009	CSL/Sanofi	1,852	0	0	Not quantified	Not quantified
2008	CSL/Sanofi	1,852	0.00001	0	Not quantified	Not quantified

[a] For 2010, the influenza A(H1N1) virus vaccine component was the 2009 pandemic strain as recommended by the World Health Organization.
[b] Calculated as risk of febrile convulsion following receipt of TIV x risk of hospitalisation following febrile convulsion.
CI: confidence interval; NNV: number needed to vaccinate.

case the unvaccinated) and the relative risk reduction. Vaccine effectiveness (VE) is the standard expression of the relative risk reduction for vaccine preventable diseases [10]. Hence, the NNV to prevent one hospitalisation = 1/(hospitalisation rate in the unvaccinated x VE). We therefore needed to estimate two parameters: the hospitalisation rate in the unvaccinated and the VE.

To estimate the hospitalisation rate in the unvaccinated, we ascertained the vaccine status of children admitted to hospital for influenza in 2009, thus allowing us to calculate the number of these children who were not vaccinated. We then estimated vaccine coverage for influenza vaccine in 2009 for children aged between six months and four years from vaccine usage reported by immunisation providers state-wide. This allowed us to estimate the size of the unvaccinated population in this age group = (1- the proportion vaccinated) x (the population in that age group). The number of unvaccinated children admitted to hospital divided by the estimated number of unvaccinated children in the population gave the hospitalisation rate in the unvaccinated.

The VE for prevention of influenza infection in children aged between 2 and 16 years has been estimated in a systematic review as 59% (95% confidence interval (CI): 41 to 71) [11]. This estimate is supported by findings from a study of children aged 0 to 4 years in Western Australia in 2008, in which the VE was 68% (95% CI: 26 to 86) [5]. The study found no significant difference in VE by age group (less than two years compared with two to four years) for children with an influenza-like illness proven to be caused by influenza [5]. We assumed the VE for TIV in 2010, the year for which we calculated the benefit-risk profile, would have been similar to previous estimates of VE when vaccine and circulating strains matched. This VE estimate should be appropriate for the TIV for 2010, as vaccine manufacturing processes were the same in 2010 as for previous years. We therefore used a VE of 60% for all children aged six months to four years in this analysis.

Quantifying risk

To quantify risk, we calculated the number of hospitalisations that could be attributed to adverse events following vaccination of the NNV to prevent one hospital admission. We used vaccine-specific rates of febrile convulsions determined during the detailed investigation into suspected adverse outcomes in 2010 in Western Australia (unpublished). We compared these with vaccine-specific rates of febrile convulsions in 2008 and 2009, determined by passive surveillance in both years but augmented by active questioning of parents/guardians of children admitted to hospital in 2009. We quantified the risk of admission to hospital for a febrile convulsion following receipt of TIV as the product of the NNV, the absolute risk of a febrile convulsion and the risk of hospital admission following a febrile convulsion.

Results

Quantifying benefit: the NNV to prevent one hospitalisation due to influenza

The number of children living in Western Australia aged between six months and four years in 2009 was approximately 130,000 of whom 30.3% were estimated to have received at least one dose of TIV in that year. The number of unvaccinated children was therefore 90,610.

In that year, 432 cases of influenza were notified in children in this age range, of whom 383 (89%) were infected with 2009 pandemic influenza A(H1N1) and 49 (11%) were infected with seasonal influenza strains or influenza A not subtyped. One hundred and twenty children were hospitalised for any type of influenza, of whom 74 were unvaccinated. Vaccine status was unknown for a further 13 children. We allocated the children with unknown vaccine status to one of the two known groups in the same proportion as those whose status was known, giving an estimated total of 82 unvaccinated children admitted to hospital. The hospitalisation rate in unvaccinated children aged six months to four years was therefore 90 per 100,000.

To prevent one hospitalisation due to any strain of circulating influenza in 2009 would have required the vaccination of 1,852 children (1/[90/1000,00 x 0.6]), the NNV.

Quantifying risk: hospital admission for febrile convulsions following receipt of TIV

Prior to cessation of the immunisation programme in April 2010, more than 10,000 doses of Fluvax or Fluvax Junior and more than 3,300 doses of Influvac had been administered to children aged six months to four years in Western Australia in 2010 [4]. Detailed follow up investigation of adverse events following immunisation identified 56 children with febrile convulsions that occurred within 24 hours of receipt of TIV between 8 March and 25 April 2010, of whom 19 (34%) required overnight hospital admission. All 55 cases with information on vaccine formulation had received Fluvax or Fluvax Junior. The estimated risk of a febrile convulsion following receipt of Fluvax or Fluvax Junior was 0.39%, compared to 0% for Influvac (unpublished data).

Applying these estimates of risk to the NNV to prevent one hospitalisation due to influenza indicates that vaccination with Fluvax or Fluvax Junior would have been likely to have caused seven febrile convulsions (1,852 x 0.0039), with two to three of these children requiring hospitalisation (34% of seven children). Based on the data available, Influvac would have caused no febrile convulsions and no hospital admissions.

The upper limit of the 95% CI for Influvac estimated a febrile convulsion risk of 0.08% (unpublished data). If the real risk were this high, Influvac may have caused one to two febrile convulsions, and zero or one hospital admission, in preventing one hospitalisation due to laboratory-confirmed influenza. The corresponding risk of febrile convulsions for the Fluvax products (that

is, estimating risk as the upper limit of the 95% CI= 0.51%, unpublished data) would have seen nine febrile convulsions attributed to these vaccines, causing three hospital admissions for febrile convulsions for each hospital admission for influenza that was prevented.

Using routine passive surveillance in 2008 and 2009, plus direct enquiry to parents or guardians of children admitted to hospital with laboratory-confirmed influenza in 2009, we estimated the risk of a febrile convulsion following receipt of any seasonal TIV to have been 0.003% in 2008 and zero in 2009. In those two years, these vaccines would have caused no hospital admissions due to febrile convulsions for each hospital admission due to influenza that was prevented (Table 2).

Discussion and conclusion

We have demonstrated a method that can be used to quantify the benefit and risk of vaccinating children aged six months to four years against influenza. In 2009, with relatively high levels of hospital admission, it would have been necessary to have vaccinated about 1,850 West Australian children with a vaccine that was 60% effective to have prevented one hospital admission due to laboratory-confirmed influenza.

If the hospitalisation rate for influenza in 2010 was the same as that in 2009, we estimated that vaccination with Fluvax or Fluvax Junior in 2010 may have caused two to three hospital admissions due to febrile convulsions for every hospital admission due to influenza prevented. Although the influenza season is not yet over in Western Australia, current data indicate that influenza virus circulation has been considerably lower in 2010 than in 2009 [12] and fewer children will have been hospitalised for influenza in 2010 than were hospitalised in 2009. This implies that the NNV to prevent one hospital admission in 2010 would be higher than in 2009.

We did not see this same risk profile with another TIV licensed for this age group in 2010, or with the vaccines manufactured by CSL Biotherapies in 2008 or 2009, despite similarly high vaccine coverage in these two years in Western Australia. Our results therefore indicate there is no excess risk over benefit with a childhood influenza vaccination programme in general. The problem identified in 2010 was related to a vaccine produced by a single manufacturer. Investigations published to date have failed to find a cause for the problem [13].

A comprehensive approach to this analysis would involve assessment of other outcomes due to laboratory-confirmed influenza and a detailed sensitivity analysis. Moreover, we have chosen to quantify the NNV using all children aged six months to four years. The benefit-risk profile would be improved if only children who were at increased risk of hospitalisation following influenza infection were targeted for vaccination.

However, we have shown that a good past benefit-risk profile for a vaccine may not guarantee a favourable profile in future years. This highlights once again the importance of continued and comprehensive safety monitoring of influenza vaccines post-marketing.

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Hepatitis A outbreak in an Orthodox Jewish community in London, July 2010

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A cluster of hepatitis A cases in the Orthodox Jewish community in London, United Kingdom in July 2010 has triggered extensive contact tracing and vaccination. Two primary cases imported from a common source in Israel and three secondary cases have resulted in immunisation of over 900 contacts to date. Rapid response by local public health, primary care services and a dedicated community health team, and active hepatitis A vaccination rather than immunoglobulin treatment were used to avert a larger outbreak.

Background

The over 20,000-strong Orthodox Jewish (OJ) community in London, United Kingdom, is the largest in Europe. A number of infectious disease outbreaks have occurred in this community in the last fifteen years, including hepatitis A [unpublished data], shigellosis [unpublished data], and measles [1]. Outbreaks of hepatitis A have also been described in other OJ communities in Canada [2] and the United States [3]. Vaccine uptake in the community is traditionally low, although this is not due to ideological reluctance [1]. Factors that facilitate rapid spread of infection in this community are: large families with a high proportion of young children, considerable household overcrowding, large numbers of children in schools, close interaction within the community and close and frequent contact with members of other OJ communities [3].

Situation and management

In July 2010, acute symptomatic hepatitis A infection was reported in two members of the OJ community in London, a person in their 50s (Case 1) and a person in their late 60s (Case 2). Both cases had travelled to Israel in mid-June and independently attended the same event in Jerusalem. They also stayed in the same hotel in southern Israel, but had no direct contact and did not travel together. Case 1 had onset of symptoms in mid-July and Case 2 had onset of symptoms in late July, suggesting that they had a common exposure in Israel. Molecular sequencing was done in the UK and showed 99.8% homology between the viruses isolated from the two cases. Phylogenetic analysis of these sequences is currently ongoing.

In the UK, post-exposure prophylaxis immunisation against hepatitis A is recommended for household and sexual contacts of a confirmed case, within 14 days of symptom onset in the case. Those aged over 50 years or with chronic liver disease or chronic hepatitis B or C are also offered human normal immunoglobulin (HNIG) [4].

A total of 69 family contacts were identified in six different English health regions and in Switzerland. They included a large number of children in the families as well as many contacts who did not reside in one of the two cases' households but had either stayed with a case or had eaten food prepared by them during the infectious period. Immunisation took place within 14 days after exposure in a variety of primary and secondary care settings, depending on availability of vaccine and the location of the case. Israeli public health services were notified of the travel-related cases but did not report any outbreaks or increase in reported cases of hepatitis A epidemiologically linked to Jerusalem or southern Israel.

In addition to immunisation of contacts, local general practitioners (GPs) who provide primary care to this community were alerted and encouraged to proactively offer immunisation to members of the OJ community. A tailored leaflet was produced and disseminated, promoting hand washing with soap and water to ensure hand washing would not be limited to ritual hand washing with water only. The leaflet also encouraged hepatitis A vaccination for travelling members of the community.

Because contacts had been identified in many English health regions, a national enhanced surveillance questionnaire was developed to ensure timely reporting of linked cases outside London.

A third case of hepatitis A (Case 3) was confirmed within two weeks of the first cases in a man in his late 20s who had attended the event in Jerusalem but not stayed in the hotel in southern Israel. He is the son of Case 2 and had been in continuous contact with Case 2 during the infectious period. Case 3 and his family were not mentioned as contacts of case 2 and as such had not been vaccinated. Although the incubation period of Case 3 includes the event in Jerusalem (47 days from attendance to onset of symptoms), we think it more likely that he was a secondary case.

Eleven contacts of Case 3 were immunised, including his five children aged between two and eight years who had also been exposed to Case 2. The risk of subclinical infection in these younger contacts [5] and the potential for ongoing transmission to the wider OJ community was assessed. It was agreed that all children and staff attending the same school/nursery as Case 3's children (over 300 persons) would be immunised directly at the school by community nurses.

Twelve days after Case 3 was confirmed one his children became symptomatic and was confirmed to have hepatitis A (Case 4). This case generated 24 new close contacts who were immediately vaccinated, and a further 469 children who attended a one-day activity camp with the case were invited for vaccination.

By late august, eight days after Case 4 was confirmed, a fifth clinically suspected case was reported in a 19 year-old relative of Case 2 who had been immunised as a close contact with Case 2 outside of the 14-day period. Sixty students at the yeshiva (a religious education institution for adults) where Case 5 studies and resides were invited for vaccination. The epidemiological curve and a summary of the contact vaccinations are presented in the Figure.

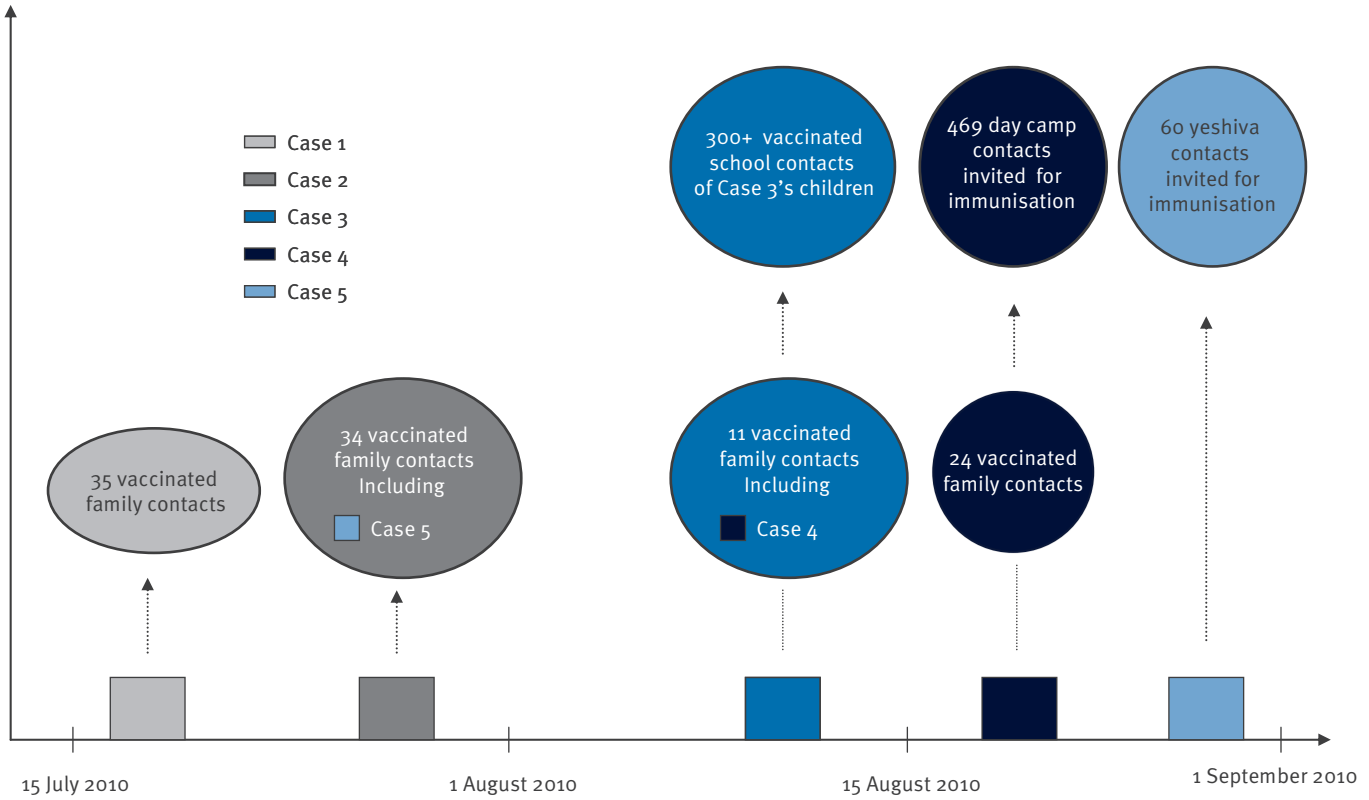
The deadline for vaccination of contacts with continuous exposure is based on a 14-day window from the date of onset of symptoms in the case; for contacts exposed after the case's onset of symptoms it is 14 days post exposure. All contacts identified and all services responsible for delivering vaccination were advised about these deadlines for vaccination.

Conclusion

Five cases of hepatitis A, two travel-related and three secondary cases, have been reported to the North East and Central London Health Protection Unit between late July and late August 2010. Through active contact tracing we identified a total of over 900 contacts of these cases. 104 family contacts and over 300 school contacts were vaccinated. About 500 contacts attending a day camp and 60 contacts from a religious education institution were invited for vaccination. Uptake in these two groups is unknown as vaccination has taken place in a variety of settings (GPs, walk-in centres and an emergency department) that do not notify us of vaccination. We think that uptake has been high judged

Figure

Epidemiological curve with a summary of contact vaccination, hepatitis A outbreak, London, July 2010 (n=5)



by the level of enquiries the health protection unit has received.

Given the progression of previous outbreaks of hepatitis A in this and other OJ communities there is a case for community-wide immunisation. However the current consensus of the incident team is that it would be disproportionate at this stage in response to five confirmed cases, four of whom are linked to the extended family of the index case (Case 2) who acquired the infection during travel to Israel. In addition, monovalent hepatitis A vaccine has been used in this incident in preference or addition to HNIG. This combined approach should prevent onward transmission more effectively than HNIG alone [6]. It should also provide longer-term protection to recipients in the event that they are exposed to subsequent cases. This, combined with rapid contact tracing, a low threshold for offering immunisation and good cooperation between local public health and clinical services may have helped contain the spread of infection to date. No further cases have been reported at the time of publication of this report. However, the situation remains under review; if a case is reported that matches the molecular sequence profile of Cases 1-5 and does not have a travel history or clear epidemiological link to a known case, this will trigger a recommendation for a community immunisation programme targeting all children aged 1–11 years. Cases can be expected until late October 2010.

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Community outbreak of group B meningococcal disease in southwest France – December 2008 to September 2009

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Between December 2008 and September 2009, 11 cases of invasive meningococcal disease (IMD) group B were reported in a 20 km diameter area in the Département Landes, France. Two of them presented with *purpura fulminans* and one of them died. The strain responsible for this community outbreak was of the clonal complex ST-269.The incidence rate for IMD group B was 3 per 100,000 inhabitants in Landes from week 40 in 2008 to week 40 in 2009; it was the highest in France during that period. The number of cases observed was significantly higher than expected, especially in young adults (standardised incidence ratio: 23.5, p<0.001). A nightclub located in the 20 km diameter area was a possible place of transmission and a prophylaxis recommended for the staff members helped in decreasing the transmission. However, several cases notified later suggested that the bacteria circulated during several months through healthy carriers in the community. This situation prompted increased surveillance of IMD in Landes and medical practitioners were asked to remain vigilant because of the possible emergence of new cases within the following months.

Introduction

Invasive meningococcal disease (IMD) is a severe infection that can create concerns in the population. The disease is notifiable in France [1] and following each notification, control measures are implemented by the concerned health district office in order to prevent secondary cases. Outbreaks are rare and when they occur, the French Institute for Public Health (InVS) may intervene to carry out an epidemiological investigation.

In December 2008, one case of IMD group B was reported to a health district office in the Département Landes (population 375,000), Aquitaine region. One month later, four more cases of IMD group B were reported to the same health district office within one week. This number was unusually high; the total number of cases notified to this department had been seven in 2007 and four in 2006. Furthermore, all five cases were living within a limited area of the Département.

An epidemiological investigation was therefore initiated in January 2009 by the local InVS team in collaboration with the health district department of Landes. The aims were to describe characteristics of the cases and their potential epidemiological links, to identify the source of infection and to suggest control and preventive measures.

Methods

Cases were reported to the health district department by hospital practitioners through the French surveillance system of IMD. Since 2006, the case definition of IMD in France has been the following [1]:

- Either a patient laboratory-confirmed by at least one of the following methods:
  - detection of *Neisseria meningitidis* by culture and/or detection of *N. meningitidis* nucleic acid by PCR from any sterile site;
  - detection of Gram-negative diplococci in cerebrospinal fluid (CSF);
  - SF findings compatible with bacterial meningitis together with detection of *N. meningitidis* antigens in blood, urine or CSF;
- Or a patient with clinical presentation suggestive of IMD (CSF findings compatible with bacterial menin-

gitis together with a petechial rash and /or *purpura fulminans* (haemorrhagic septic shock).

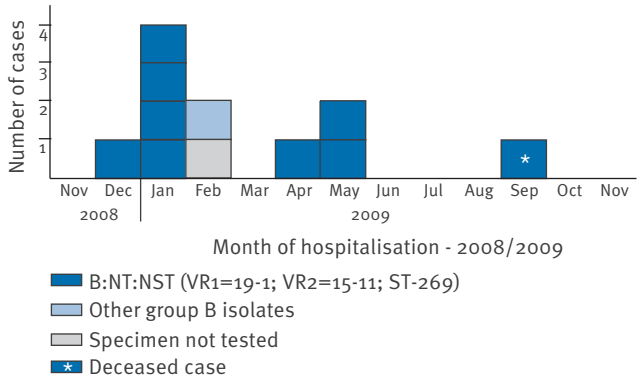
All cases of IMD group B notified from December 2008 onwards who were living, working or going to school in the Département Landes were interviewed by the health district department or by epidemiologists of the local InVS team. Information on sociodemographic characteristics, medical history were collected, as well as on activities within the 10 days before symptoms onset (work or school place, travel, meetings, celebrations and any other occasion involving close contacts).

Specimens from each case were sent to the national reference centre for meningococci (CNR) for complete typing that consists of phenotyping (serogroup:sero type:serosubtype) and genotyping using multilocus sequence typing (MLST) [2] as well as typing of *porA*.

The study area was defined as the smallest area covering all cases occurred. Incidence of IMD by age group was estimated in this area and in the Département Landes and compared with the incidence in the rest of France. The number of expected cases in Landes was estimated by age group using incidence rates of IMD group B in the rest of France (indirect standardisation). Standardised incidence ratios (SIR, ratio of observed to expected cases) was calculated for each group.

FIGURE 1

Cases of invasive meningococcal disease group B by month of notification, December 2008-September 2009, Landes, France (N=11)



Source : French Institute for Public Health, 2009.

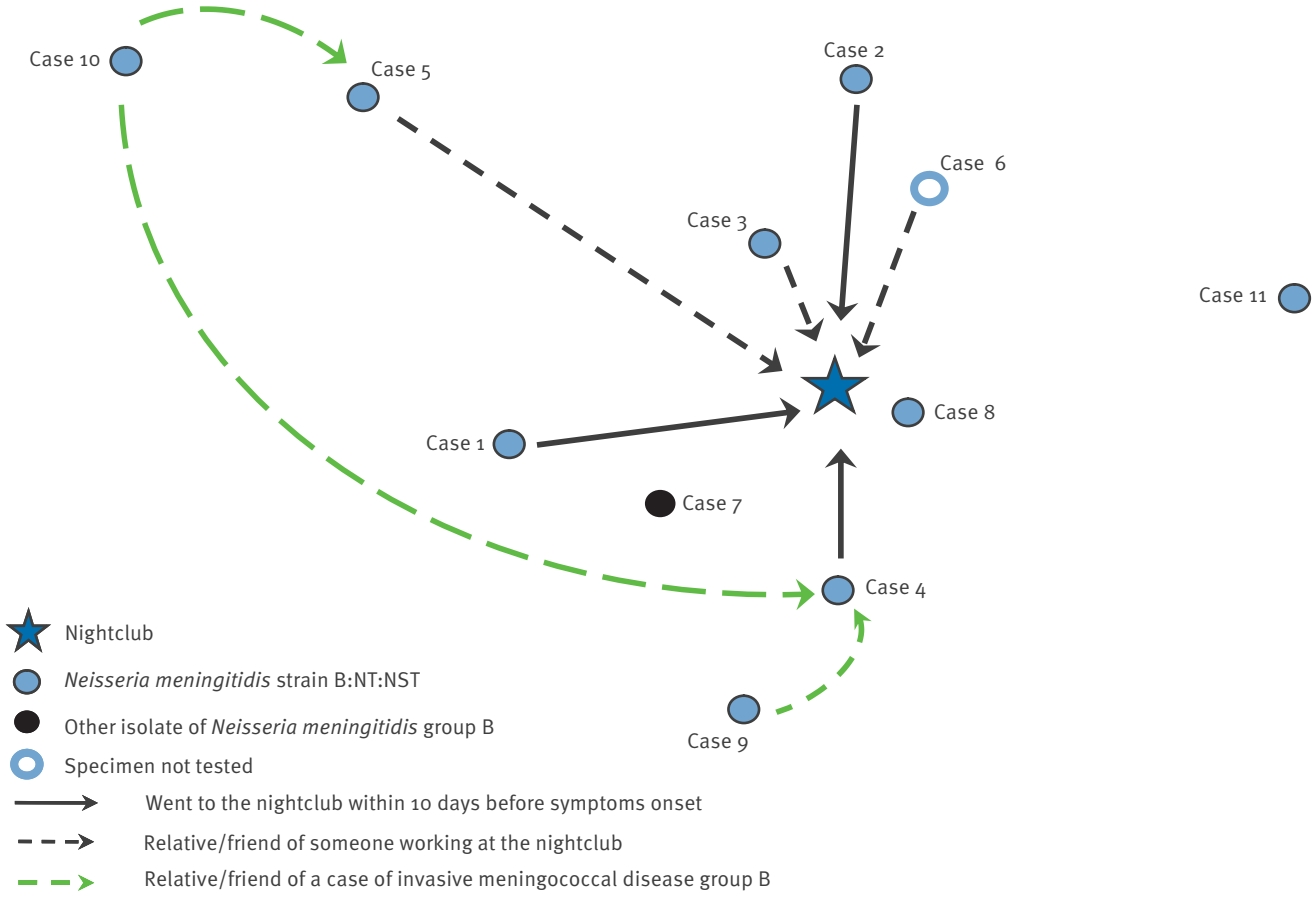
Results

Outbreak description

A total of 11 cases of IMD group B were notified in Landes between December 2008 and September 2009 (Figure 1). The cases were localised in an area of 20 km

FIGURE 2

Relations between cases of invasive meningococcal disease group B, Landes, France, December 2008-September 2009 (N=11)



Cases numbered in order of appearence.

diameter (population 125,000) near the city of Dax, in the south west of the Département Landes.

The age range of the cases was between seven months and 47 years (median age: 18 years), six cases were male. Two cases presented with *purpura fulminans* and one of them (a four-year-old child) died the day after hospitalisation. The nine other cases fully recovered a few days after their admission to hospital.

Eight of the 11 cases lived in the Dax area permanently, two during week-ends and holidays only, and one only during the week. No case of IMD was reported in the rest of the Département or in the neighbouring Département (Pyrénées-Atlantiques) between December 2008 and September 2009.

Relations between cases

Epidemiological investigations could not identify a common link among the first eight cases. However, three of them went to the same nightclub on different nights within 10 days before symptoms onset and three others had relatives or friends working at the nightclub (Figure 2). The ninth and tenth case (onset in May 2009) were friend or family of respectively one and two previous cases. No link with other cases was found for the last case that occurred in September 2009. No other common place or more confined community (school, social group, etc.) was identified.

Incidence rates

The incidence rate for group B IMD was 3 per 100,000 inhabitants in the Département Landes and 8.9 in the affected area of Dax, whereas the incidence in the same time period at national level was 0.6 per 100,000 (Table). The incidence in Landes was the highest observed in any French Département in the period under investigation. For all age groups, the observed number of cases was 4.5 times higher than the expected number of cases (p<0.001).

The age distribution of the cases in Landes differed from that observed for the whole of France in that four (36%) of the Landes cases were between 20 and 24 years of age, whereas at the national level this age group only represented 10% in 2008. The incidence rate was therefore particularly high in this age group (25.1/100,000) and the number of cases observed was 23.5 times higher than expected (p<0.001). A similar but less pronounced trend was observed in the group of 15-19-year-olds with the number of observed cases nearly seven times higher than the number of expected cases (p=0.08) (Table).

Laboratory investigation

All 11 cases were laboratory-confirmed as infected with *N. meningitidis* serogroup B and further analyses were performed by the CNR on 10 specimens (testing was technically not possible for one specimen). The strains were not typable and not serosubtypable (B:NT:NST). PorA sequencing revealed identical variable regions (VR) among most of the tested isolates (VR1=19-1; VR2=15-11) (9 of 10 strains tested) and MLST analysis clustered these isolates in the clonal complex (CC) ST-269. All the tested isolates were susceptible to the antibiotics that are currently used in treatment and prophylaxis (rifampicin, cefotaxime, penicillin G, ciprofloxacin).

Control measures

In order to prevent further spread of the disease and according to the national recommendations and policy [1], individual control measures were implemented for each case by the local health department, including post-exposure chemoprophylaxis for all close contacts of cases.

Furthermore, prophylaxis with rifampicin was recommended for the nightclub staff (10 people) at the end of February 2009, after the occurrence of several cases who had a direct or indirect link with this venue. All general practitioners and acute care hospital practitioners were sent an email describing the outbreak. They were alerted to be vigilant and notification was encouraged. Information on early symptoms of IMD

Table

Cases of invasive meningococcal disease group B and incidence rates by age group for the Département Landes (52 weeks: from week 40 in 2008 to week 40 in 2009) and the rest of France (year 2008)

	Incidence rate in the Département Landes			Incidence rate in the rest of France[a]			Estimation of the risk excess in the Département Landes			
Age groups (years)	Number of cases	(%)	Incidence per 100,000	Number of cases	(%)	Incidence per 100,000	Number of cases	SIR[b]	p[c]	Confidence interval
<5	3	27	15.5	189	46	4.8	0.94	3.2	0.14	0.6 - 9.2
5-14	1	9	2.4	43	10	0.5	0.23	4.3	0.41	0.1 - 24.2
15-19	2	18	10.0	63	15	1.5	0.30	6.7	0.08	0.7 - 24.1
20-24	4	36	25.1	42	10	1.0	0.17	23.5	<0.001	6.3 - 60.2
≥25	1	9	0.4	77	19	0.2	0.48	2.1	0.75	0.0 - 11.6
Total	11	100	3.0	414	100	0.6	2.41	4.6	<0.001	2.3 - 8.2

[a] excluding Landes.

[b] Standardised incidence ratio : ratio of observed to expected cases.

[c] p-value number of observed cases ≠ number of expected cases.

Source : French Institute for Public Health, 2009.

was communicated to the general population through the local press.

Discussion and conclusion

Between December 2008 and September 2009, an outbreak of group B IMD occurred in the French Département of Landes. It was caused by one clone of *N. meningitidis* belonging to the CC ST-269. The cases were concentrated in a limited geographical area, with an unusually high incidence rate compared with the preceding years: since the year 2000, the mean annual incidence rate of group B IMD has been 1.4 per 100,000 inhabitants in Landes (data from the French surveillance system of IMD [3])

The investigation suggested that the nightclub was one place of transmission of the disease and, as no cases were notified for the two months following the implementation of the recommendation (Case 8 occurred at the end of April), that the prophylaxis recommended for the staff members of the nightclub in February helped to stop the transmission.

The appearance of new cases that were not related to the nightclub but to previous cases, suggested that bacteria had circulated during several months through healthy carriers. Indeed, it was shown that at any time, approximately 10% of the general population were carrying *N. meningitidis* in the nasopharynx and that the carriage rate was 30% in teenagers and young adults [4]. Moreover, the time intervals between the occurrence of cases who knew each other were not consistent with a direct transmission.

In this outbreak, the age group of 15-24-year-olds seems to have been particularly affected. Teenagers and young adults have been shown previously to be at higher risk during IMD outbreaks [5-7]. This could be due to lifestyle since an active social life can increase the risk of infection when bacteria circulate in the population. Moreover, as nightclubs are mainly frequented by teenagers and young adults, high incidence among this group may also be a consequence of the nightclub as a possible place of transmission.

However, a shift in the age distribution of meningococcal disease towards higher age groups (≥ 20 years-old) can be observed during outbreaks and epidemics following the introduction of new clone [8].

Since 2007 there has been an increase of CC ST-269 isolates in France: 10% of the strains responsible for IMD analysed by the CNR in 2009 belonged to this CC (5% in the last ten years). These isolates may differ in virulence, as has been observed for the common CCs ST-32 and ST 41/44 [9], and seem to be highly transmissible.

Since no universal vaccine against serogroup B exists, the relevance of implementing a mass chemoprophylaxis was widely discussed by local authorities and national experts on IMD infections. This strategy had been implemented twice before in France to control IMD group B outbreaks confined to small areas [10,11]. However, it was finally not recommended in the Landes department because of the dynamics of the outbreak: indeed, cases were spread over time and space and were part of an open population. Such a recommendation would have had a limited effect because of a high risk that individuals not targeted by the prophylaxis would rapidly reintroduce the bacteria in the treated population [12]. In a larger epidemic of group B IMD that recently occurred in another French Département, a massive preventive intervention could be launched because an unlicensed outer membrane vesicle vaccine was available against the strain responsible for the outbreak [5].

General and acute care hospital practitioners were asked to remain vigilant in case new cases should emerge in the following months. No new case was reported until the end of 2009, but the increased surveillance implemented during this outbreak showed that the bacteria are still present in the Département Landes in 2010. Indeed, two cases of group B meningococcal disease infected with *N. meningitidis* CC ST-269 were reported in January and August 2010; one died a few days after hospitalisation. Both were living in the Dax area.

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Onychomadesis outbreak linked to hand, foot, and mouth disease, Spain, July 2008

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In July 2008 an onychomadesis outbreak in a nursery setting was reported in Saragossa (Spain). Some of the cases had previously suffered from hand, foot and mouth disease (HFMD). In order to study the outbreak and to determine the relation between the two diseases, two epidemiological studies were conducted: a descriptive study focused on cases and a retrospective cohort study. Samples from stool, pharynx and nails were obtained from cases for microbiological analysis. During the study period, 27 children fulfilled the case definition. The average age was 1.8 years. A case shed on average four nails (minimum one maximum twelve). Twenty-four of the 27 cases had previously presented with HFMD which started an average of 40 days before the onset of onychomadesis (relative risk: 14). Unidentified non-polio enterovirus (n=10), coxsackie B1 (n=4) and coxsackie B2 virus (n=3) were isolated in 28 specimens obtained from 14 cases. The analysis showed a strong association between HMFD and onychomadesis. Microbiological results have not been conclusive; consequently more studies are necessary to determine the causal agent of infectious onychomadesis.

Introduction

Onychomadesis is an acute, painless, non-inflammatory disease that affects the nail matrix [1,2]. Patients present a wide clinical profile from transverse ridging of the nail plate (Beau's lines) up to complete nail shedding. Apart from serious generalised diseases, trauma or exposure to specific drugs, most cases have been considered idiopathic. Isolated onychomadesis cases following hand, foot and mouth disease (HFMD) have been described in the United States [1] and in France [3]. More recently, HFMD-related onychomadesis cases have been observed in Spain – Valencia [4] and Valladolid [8] – and also in Finland [10]. HFMD is a disease caused by enteroviruses (genus *Enterovirus,* family *Picornaviridae*). Complications from HFMD are rare, but pneumonia, meningitis or encephalitis may occur. HFMD is characterised by a low grade fever, a vesicular eruption of the hands, feet and ulcerations on the tongue, soft palate, buccal mucosa or gums. These symptoms usually resolve spontaneously after six days. It is assumed that virus replication damages the nail matrix and results in temporary nail dystrophy [3].

In July 2008, a paediatrician reported an onychomadesis outbreak to the Epidemiological Surveillance Unit of Saragossa, Spain. The cases were children who attended two nurseries in Ricla and Calatorao, two adjacent villages situated in Aragon (north-east Spain). Some cases had suffered from HFMD a few weeks before. A descriptive study was carried out, and a retrospective cohort study was performed aiming to investigate the relation between onychomadesis and HFMD.

Methods

Study design

Two studies were performed. A descriptive study focused on cases to describe the basic person-place-time variables of the outbreak, and a retrospective cohort study to assess the onychomadesis risk after HFMD. The cohort members were the children who attended the two nurseries during follow-up period from 1 May 2008 (two month before disease onset of the first case of onychomadesis) to 15 July 2008 (a week after disease onset of the last case). The follow-up period was chosen to correspond to the average time by which HFMD precedes onychomadesis [4,8,10].

Data source

The nurseries' records provided the target population. An *ad hoc* epidemiological questionnaire was designed collecting the following variables:

- General information: sex, date of birth, previous illness or underlying condition (yes/no/which one), nursery attended.
- During the follow-up period: lunches in the nursery, HFMD diagnosis (yes/no), symptoms (type, onset date, duration), onychomadesis diagnosis (yes/no, onset date, number of nails shed or injured), contact to other cases, medication, nail trauma. In the questionnaire, travel history with date and place of travel was collected, mainly to areas with recent HFMD outbreaks.

- Following onychomadesis symptoms: isolation at home, complications (admission to hospital).

The data were obtained from the children's families through telephone interview. Informed consent was requested from the families. Medical information was validated in paediatric records from the local medical office.

Case definitions

A case of onychomadesis was defined as a cohort member who during the follow-up period presented changes on the nail plates followed by complete nail shedding [1,2]. An HFMD case was defined as a cohort member who, at least for three days, presented a macular-vesicular rash involving oropharynx area and limbs and/or buttocks (classical herpangina) [1,5,6].

Microbiological analysis

Stool, pharynx exudates and nail specimens were obtained from onychomadesis cases. The specimens were sent to the microbiological reference laboratory at the Miguel Servet Hospital in Saragossa to be analysed for viruses. Enteroviruses were isolated on MRC-5 human embryonic lung fibroblasts or a human rhabdomyosarcoma (RD) cell line, and the presence of non-polio enteroviruses was confirmed using indirect inmunofluorescence [9]. The isolates were serotyped at the National Microbiological Centre in Majadahonda by PCR of the 5'-non-coding region. If this PCR was positive, a specific region of the VP1 capsid protein gene was amplified and sequenced [9]. If the first PCR was negative, the isolate was considered as an unidentified non-polio enterovirus.

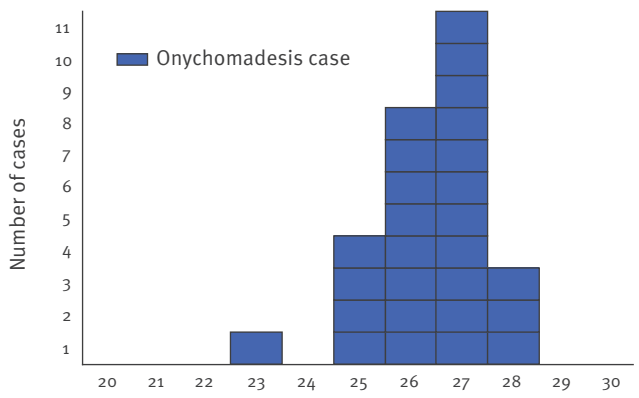
Statistical analysis

Student's t-test and the ANOVA test were applied to compare quantitative variables, and the chi-square test was used for qualitative variables; p-values less than 0.05 were considered statistically significant.

The risk of developing onychomadesis and attack rates were calculated for the different variables or risk factors. The relative risk (RR) was calculated as the ratio of the two attack rates (with versus without prior risk factor such as HFMD); confidence intervals (CI) at 95% were estimated. A stratified analysis was performed to detect a possible age-HFMD interaction, and the risk of onychomadesis was estimated for the children with prior HFMD and those without in each age group.

Figure

Epidemic curve, onychomadesis outbreak, Saragossa, Spain, July 2008 (n=27)



Results

Descriptive study

Ricla nursery had 54 children and a staff of four child carers and one cleaner. The staff of Calatorao nursery comprised three child carers for 48 children. The nurseries did not have meal service, but some children ate food they had brought from home. Interview responses were not available for 14 of the 102 children, leaving a total study population of 88 children.

None of the staff members developed onychomadesis or HFMD during the follow-up period. However, 27 children showed clinical symptoms that fulfilled the case definition for onychomadesis, 15 children in Ricla (attack rate: 35%) and 12 children in Calatorao (attack rate: 26%). Of those 27, 14 were girls, and the age average was 21 months (standard deviation 6 months), ranging from 11 to 40 months. The average number of shed nails per case was four, with a minimum of one and a maximum of twelve. Three children had an underlying condition: coeliac disease, bronchitis (undergoing cortisone treatment) and hereditary spherocytosis (undergoing folic acid treatment)..

The date of onset of the first case was on 7 June 2008 (23rd epidemiological week) and of the last case on 7 July 2008 (28th epidemiological week). The epidemic curve reaches a peak of 11 cases in the 27th epidemiological week (Figure).

Of the 88 children who participated in the study, 32 had a record of HFMD, and 24 of them developed onychomadesis. HFMD in those 24 cases had started an average of 40 days before onset of onychomadesis and the changes on the nail plates, followed by complete nail shedding, appeared after an asymptomatic period. Spontaneous resolution of HFMD symptoms occurred on average within eight days.

Retrospective cohort study

The analysis (Table 1) showed a significant association between onychomadesis and prior HFMD (RR: 14; 95% CI: 4.57-42.86). The onychomadesis attack rate changed with age: It was 55% in the youngest group (under two years-old (9-23 months)), 30% in the middle group (2-3-years-old (24-32 months)) and 4% in the oldest group (3-3.5-years-old (33-42 months)). The association between onychomadesis and prior HFMD remained when analysed separately for each age group (Table 2).

No significant associations were found between onychomadesis and the rest of the studied variables during the follow-up period: sex, nursery location, lunches in the nursery, travel history and underlying condition. Previous trauma and regular medication were considered but were not reported among the children in this study and could therefore not be evaluated as a risk factor onychomadesis.

Microbiological results

We obtained 28 specimens from 14 onychomadesis cases for microbiological analysis. The time between nail shedding and sample collection was between one and three weeks. The first cases had symptom onset in week 23. Enterovirus was isolated from 17 specimens (61%) collected from 11 of the 14 cases. These isolates were identified as: coxsakievirus B2 (two cases, both with previous HFMD), coxsakievirus B1 (two cases, both with previous HFMD) and non-polio enterovirus (seven cases, one with previous HFMD). Table 3 shows aggregated data by case and specimen type.

Table 1

Risk factors for onychomadesis, outbreak in Saragossa, Spain, July 2008 (n=88 study participants)

Risk factors	Study participants	Cases	Attack rate (%)	Relative risk	95% confidence interval
Nursery location					
Ricla	43	15	34.9	1.3	0.69-2.46
Calatorao	45	12	26.7		
Sex					
Female	44	14	31.8	1.1	0.57-2.01
Male	44	13	29.5		
Lunch in the nursery					
Yes	61	20	32.8	1.2	0.56-2.41
No	25	7	28.0		
Unknown	2	0			
Recent travel					
Yes	19	6	31.6	0.66	0.31-1.38
No	42	20	47.6		
Unknown	27	1			
Underlying condition					
Yes	3	1[a]	33.3	0.86	0.16-4.42
No	65	25	38.5		
Unknown	20	1			
Age (years)					
‹2	33	18	54.5	16,25*	2.31-114.01
2-3	27	8	29.6	7,72*	1.03-57.81
›3 (reference group)	28	1	3.6	1	
Hand, foot and mouth disease					
Yes	32	24	75.0	14,0*	4.57-42.86
No	56	3	5.4		

[a] Hereditary spherocytosis.

* Statistically significant at p‹0.05

Table 2

Hand, foot and mouth disease record and onychomadesis by age group, Saragossa, Spain, July 2008 (n=88 study participants)

Age group		‹2 years				2-3 years				›3 years			
		Onychomadesis				Onychomadesis				Onychomadesis			
		Yes	No	RR	CI 95%	Yes	No	RR	CI 95%	Yes	No	RR[a]	CI 95%
HFMD	Yes	16	2	6.66	1.8-24.4*	7	4	10.18	1.4-71.5*	1	2	8.66	0,7-105.6
	No	2	13			1	15			0	25		
Total		**18**	**15**			**8**	**19**			**1**	**27**		

CI: confidence interval; HFMD: hand, foot and mouth disease; RR: relative risk.

[a] RR was calculated with 1 case in the box without cases.

* Chi-square p‹0.05.

Discussion

This study describes an onychomadesis outbreak in children. Our analysis showed a strong association between onychomadesis and previous HFMD (RR: 14). HFMD happened 40 days before onychomadesis. That association has already been pointed out by Clementz and Mancini [1], Bernier *et al.* [3], Redondo *et al.* [8] and Österback *et al.* [10]. There are few outbreaks in which it has been possible to isolate viruses from onychomadesis cases. In an HFMD outbreak in Finland in 2008, shed nails were obtained from two siblings who had HFMD eight weeks before the nail shedding; the virus in one of them was identified as coxsackievirus A6 [10].

Our estimations also confirm the results of Salazar *et al.* [2] who analysed a community outbreak of onychomadesis in Valencia (Spain) in 2008. These authors found that 121 cases (59,6%) had a record of previous HFMD, compared with only 13,6% of controls (odds ratio: 14.9). They further found that HFMD had occurred an average of 39 days before onychomadesis, similar to the outbreak in Valladolid (Spain) [8] with an average of 42 days, and the one in Finland in 2008 [10], where the children shed fingernails and/or toenails within one to two months after HFMD.

In addition, we found a significant association between age and onychomadesis, but age was not a confounder because the stratified analysis showed that there was an association between onychomadesis and previous HFMD in each age group.

Taken together, we think that onychomadesis could be a late complication of HFMD, mainly in young children. Two limitations could be considered. Firstly, 14 children did not participate in the study, but we do not think this had a relevant effect on the results since the non-responders did not visit the medical office during the study period and it is therefore not likely that they fell ill. Secondly, recall bias is described in studies based on interviews, but in our case the answers were validated in the paediatric records from the local medical office.

HFMD epidemics have primarily been associated with different enteroviruses, such as CVA16, echovirus 4 [7] or enterovirus 71. Those caused by enterovirus 71 have occurred more frequently in Southeast Asia in recent years. An outbreak in Singapore, described by Chan *et al.* [6] had thousands of cases, but onychomadesis was not reported as a complication of HFMD in that epidemic. Other enteroviruses, such as CVA6 and CVA10, and new genetic variants of these viruses, were a primary pathogens associated with HFMD during a nationwide outbreak in Finland in autumn 2008 in which onychmadesis cases following HFMD were observed [10,11].

In an outbreak of enterovirus in a nursery it is important to introduce control measures such as staff hand washing, disinfection of all materials exposed to potentially infected biological fluids, increased staff hygiene precautions in the kitchen, and use of a different basin for bathing each baby [12].

In our study, the microbiological results were not conclusive. Moreover, at least two different viruses were isolated from the onychomadesis cases: coxsackie virus B1, coxsackie virus B2 and unidentified non-polio virus enterovirus, suggesting that co-circulation of coxsackie virus B1 and B2 was likely. These two viruses are not usually associated with HFMD. The number of

Table 3

Microbiological results, onychomadesis outbreak, Saragossa, Spain, July 2008 (n=14 cases)

Case number	Total samples for case	Stool	Pharynx smear	Nail
1	2	Coxsackievirus B2	Negative	ND
2	3	Coxsackievirus B2 (2 samples)	Negative	ND
3	2	Unidentified non-polio enterovirus	Unidentified non-polio enterovirus	ND
4	2	Negative	Unidentified non-polio enterovirus	ND
5	1	ND	Unidentified non-polio enterovirus	ND
6	2	ND	Negative	Unidentified non-polio enterovirus
7	2	Unidentified non-polio enterovirus	Unidentified non-polio enterovirus	ND
8	2	Negative	Unidentified non-polio enterovirus	ND
9	1	ND	Unidentified non-polio enterovirus	ND
10	3	Coxsackievirus B1 (2 samples)	Unidentified non-polio enterovirus	ND
11	3	Coxsackievirus B1 (2 samples)	Negative	ND
12	2	Negative	Negative	ND
13	2	Negative	Negative	ND
14	1	ND	Negative	ND
Total	**28**	**13**	**14**	**1**

ND: not done.

enterovirus-positive specimens could have been higher if the samples had been collected in the acute phase or from subclinical cases that were sustaining the outbreak, but our number of 61% is similar to the proportion of positive specimens in other outbreaks such as the 66% observed in Finland [10].

In conclusion, more studies are needed to settle doubts about the aetiology of possibly infectious onychomadesis.

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