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Cluster of two cases of botulism due to *Clostridium baratii* type F in France, November 2014

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The first two cases in France of botulism due to *Clostridium baratii* type F were identified in November 2014, in the same family. Both cases required prolonged respiratory assistance. One of the cases had extremely high toxin serum levels and remained paralysed for two weeks. Investigations strongly supported the hypothesis of a common exposure during a family meal with high level contamination of the source. However, all analyses of leftover food remained negative.

On 12 November 2014, two cases of botulism were notified to the regional health agency (ARS) in France. The cases were two women in the same family. They were hospitalised in intensive care where they received respiratory assistance and could therefore not be interviewed. Epidemiological and microbiological investigations were conducted by the regional office of the French Institute of Public Health Surveillance (InVS) and the national reference centre (NRC) for botulism in order to confirm the outbreak and to determine the source of exposure.

Case descriptions

Case 1 was a woman in her 60s with symptom onset on 10 November 2014 around 8 pm (20 h after the family meal) including hypercapnia, gradually descending flaccid paralysis, complete respiratory muscular paralysis and bilateral non-reactive mydriasis. She was immediately admitted to intensive care requiring mechanical ventilation. Case 1 remained completely paralysed (limbs, ocular and respiratory muscles) for two weeks. She needed respiratory assistance for 46 days. On 6 January 2015, she was discharged from hospital with a persisting flaccid paraparesis of lower limbs.

Case 2 was a woman in her late 20s with symptom onset on 11 November 2014 around 8 pm (44 h after the meal), gradually developing diplopia, ptosis, dysphonia, dysphagia and respiratory distress. She was admitted to intensive care on 12 November with flaccid paraparesis and respiratory paralysis. She needed respiratory assistance for 11 days. On 1 December she had fully recovered and was discharged from hospital.

No predisposing factors for intestinal and wound botulism such as antibiotic treatment or gastrointestinal illness during the preceding weeks or a skin lesion were identified for either case.

On 13 November, and before identification of the type of neurotoxin, both cases received intravenous botulinum antitoxin type ABE, which was inadequate for treatment of botulinum neurotoxin type F (BoNT/F) [1].

Epidemiological investigation

Both women had participated in a meal together with six other family members on 9 November 2014. Telephone interviews with family members were conducted to identify epidemiological links between the cases. The two patients also had had lunch together on 6 November in a cafeteria but eaten different meals. They live in different towns and had not met on any other occasion during the two weeks before symptom onset.

The only common exposure consistent with the usual incubation period of botulism (12–36 h [2]) was the family meal at the home of a family member. The food list included industrially processed food (potato chips, drinks, pre-packaged grated carrots and raw beets, country pâté and cheese) except for two artisanal fruit tarts, raw tomatoes, roast beef and pork and home-made mayonnaise. Beef and pork roasts were cooked by Case 1 without additional ingredients. The two cases had shared the same bottle of alcopop (a flavoured alcoholic beverage with an alcohol concentration of

5%), the only common exposure not shared with any other person. One person drank another bottle of the same type. The patients had no other common consumption. No food classically at risk of botulism such as home-made cured meat products or canned food was identified.

Laboratory investigation

The NRC confirmed the diagnosis of botulism on 17 November with an extremely high BoNT/F serum level for Case 1 (ca 400 mouse lethal doses (MLD)/mL) and a lower level for Case 2 (1–2 MLD/mL). BoNT/F was identified in a stool sample of Case 1 (160 MLD/g), whereas no toxin was detected at the limit of detection (20 MLD/g) for Case 2. *Clostridium baratii* was isolated from stool samples of both patients.

Several food leftovers (pâté, roast beef, mayonnaise and apple tart) were analysed by the NRC. Two empty and one full alcopop bottles were tested. All food and drink samples tested negative for toxin (mouse bioassay) and for the presence of neurotoxigenic *Clostridium* (PCR and culture).

Discussion

Investigations confirmed two cases of botulism type F due to *C. baratii*. The very high BoNT/F level in the serum of Case 1 suggests a high level of toxin contamination of the source, yet the analyses of the food items remained negative. However, the family meal was the only plausible common exposure. Repeated interviews of the family and of Case 2, after recovery, were not conclusive. As the only item exclusively consumed by the cases, the shared alcopop bottle was highly suspected. However, all microbiological analyses were negative. Furthermore, the acidity of the drink (pH = 3.5) was not compatible with *C. botulinum* growth and toxin production [3].

Not all food items eaten during the meal of 9 November could be tested, but the ones consumed by the two patients, with the exception of potato chips and roast pork that were fully consumed, were all tested and were negative.

Other possible routes of *C. baratii* infection include skin lesions or intestinal colonisation [1,2,4]. Neither skin lesions nor intestinal disorders nor predisposing gastrointestinal factors were identified in either case, making those routes of infection improbable.

Active case search has been carried out by interviewing family members and through the mandatory botulism notification system. No other case was identified locally or elsewhere in France.

Botulism type F is extremely unusual in France (no case reported up to now) and across the world. The few documented cases of botulism type F were mostly reported in the United States (US) [1,4-11]. Between 1981 and 2002, 13 cases of adult botulism type F were notified to the US surveillance system. All cases were sporadic; no clustering was described [4].

Characteristic early symptoms of foodborne botulism type A, B and E are blurred vision, dysphagia, dysphonia, marked fatigue and vertigo. Neurological symptoms are always descending the body [2]. Botulism type F, due to *C. botulinum* or *C. baratii*, commonly causes severe illness with tetraplegia and respiratory distress [4,6-10,12] often preceding the neurological symptoms. The presentation of Case 1 with rapidly progressing severe respiratory distress as first symptom was consistent with the case series described in the US, where mean duration of respiratory support was reported to be 24 days (10–84 days) and duration of neuromuscular impairment eight days [4].

BoNT/F is usually detected in serum and gastric liquid but irregularly found in stool samples. *C. botulinum* F and *C. baratii* F are usually isolated from stools [6,7,9,12-14]. Here, BoNT/F was detected in serum and in stool samples. The bacteria were isolated from stools.

Food items most often associated with botulism type F are canned tuna or home-made meat preparations (dried, canned or fresh) such as liver pâté, dried meat or raw-dried game [5,7,15,16]. However, for most cases documented in the literature, the source of contamination is not reported [1,4,13,14]. For the present cluster, the food items consumed at the suspected meal were not ones typically incriminated for botulism. Indeed, most food items eaten by the cases were industrial products. It is thus important to widen the scope of the investigation into food items but also other possible sources of contamination. Continuous mandatory notification of botulism cases will help identify other toxin F cases and direct future investigations.

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Conflicts of interest

None declared.

Authors' contributions

Christine Castor: Study conduct, collecting and validating data, wrote the first draft of the paper and reviewed the manuscript critically. Christelle Mazuet: Microbiological analysis, literature review and reviewed the manuscript critically. Mélanie Saint-Leger: Clinical management of patients and reviewed the manuscript critically. Sabine Vygen: Wrote the first draft of the paper, collecting data and reviewed the manuscript critically. Juliette Coutureau: Literature review and reviewed the manuscript critically. Marion Durand: Clinical management of patients and reviewed the

manuscript critically. Michel-Robert Popoff: Microbiological analysis, literature review and reviewed the manuscript critically. Nathalie Jourdan Da Silva: Study conduct, wrote the first draft of the paper and reviewed the manuscript critically.

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Surveillance of infant pertussis in Sweden 1998–2012; severity of disease in relation to the national vaccination programme

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In Sweden, pertussis was excluded from the national vaccination programme in 1979 until acellular vaccination was introduced in a highly endemic setting in 1996. The general incidence dropped 10-fold within a decade, less in infants. Infant pertussis reached 40–45 cases per 100,000 in 2008 to 2012; few of these cases were older than five months. We present an observational 15-year study on the severity of infant pertussis based on 1,443 laboratory-confirmed cases prospectively identified from 1998 to 2012 in the national mandatory reporting system and followed up by telephone contact. Analyses were made in relation to age at onset of symptoms and vaccination history. Pertussis decreased in non-vaccinated infants (2003 to 2012, $p<0.001$), indicating herd immunity, both in those too young to be vaccinated and those older than three months. The hospitalisation rates also decreased (last five-year period vs the previous five-year periods, $p<0.001$), but 70% of all cases in under three month-old infants and 99% of cases with apnoea due to pertussis were admitted to hospital in 1998 to 2012. Median duration of hospitalisation was seven days for unvaccinated vs four days for vaccinated infants aged 3–5 months. Nine unvaccinated infants died during the study period.

Introduction

An increase in pertussis incidence, with large outbreaks, has been observed in recent years in many high-income countries despite high vaccination coverage rates. These epidemiological changes are mainly seen in adolescents, adults and infants too young to be vaccinated, with the most severe morbidity in the latter group. In response to a high rate of pertussis in infants, several countries have considered or adopted additional strategies for improved pertussis control in this age group, with the main focus on preventing severe disease and death in the youngest infants.

In this age group, the options are to induce immunity in the infant by optimising the vaccination schedule and adherence, to prevent transmission of *Bordetella pertussis* to the infant from close contacts and/or others in the community, and to reduce the effect by post-exposure chemoprophylaxis after transmission has occurred, or a combination of these primary and secondary prevention strategies. Whatever strategy is chosen, there is a need to monitor the effect in the target group over time.

In Sweden, the national vaccination programme (NVP) has included infant vaccination against pertussis at 3, 5 and 12 months of age since 1996. From 2007, an early school booster vaccination has been added, and already in 1982, post-exposure chemoprophylaxis was recommended to infants exposed to pertussis. The epidemiology of pertussis is monitored through regular surveillance and a prospective long-term enhanced pertussis surveillance project [1].

In this study of infant pertussis, markers of severity were related to age at onset of disease and to individual vaccination history as well as to the scheduled ages of the NVP. We present age-specific complication and hospitalisation rates in vaccinated and unvaccinated infants, with information on duration of hospital stay, and also the relation between early or delayed onset of antibiotic treatment and duration of cough in infants.

Methods

This observational study of pertussis in infants encompasses information obtained in two ways: within the regular Swedish surveillance of communicable diseases and from a long-term enhanced pertussis surveillance study.

Regular surveillance

In Sweden, pertussis is one of ca 60 notifiable diseases, and one of ca 40 diseases with mandatory contact tracing. Both clinicians and laboratories report any suspected or confirmed case by notifications both to the Public Health Agency of Sweden and to the County

Medical Officer in Communicable Disease Prevention and Control. The notifications are immediately available at both national and regional level through a web-based registry (SmiNet) based on disease and personal identifiers [2]. There is little or no information in the reports on vaccination status or clinical details including case contacts, but age-specific incidence rates can be calculated from age at reporting date (as a surrogate for age at onset of disease).

A suspected case in Sweden is defined by clinical signs compatible with pertussis plus an epidemiological link, whereas a confirmed case is a case with a positive culture, PCR or serology (seroconversion or significant increase in IgG against pertussis toxin) [3]. Notably, PCR has been increasingly used in the past decade, with culture-confirmed pertussis becoming rare.

Enhanced surveillance

The enhanced surveillance of pertussis in Sweden was established in October 1997 and is still ongoing. Every case of laboratory-reported pertussis in children born in 1996 or later is identified in SmiNet for detailed follow-up, with the exception until 2003 of cases in one area where a local surveillance project was in place [4]. The present analysis includes all infant cases identified from start of the project through 2012. The number of live births in Sweden ranged from 90,502 in 1997 to 113,177 in 2012.

All identified infant reports were matched against the population registry for parental contact details and to check that there was no death notification. A research nurse performed structured telephone interviews with the parents of each case, using a standardised questionnaire. The clinical questions included type and duration of cough, presence of apnoea and other complications, number and length of hospital admissions, and timing of antibiotic treatment if given. The nurse also contacted the child healthcare centre (CHC) of every infant to obtain documented vaccination dates, products and batch numbers. Families of deceased infants were not contacted, but their CHC provided vaccination status, and information on gestational age was obtained from the medical birth register. Infants were also excluded from detailed follow-up if an interview was impossible due to language problems or if the family could not be found.

The individual vaccination history allowed for calculation of age-specific incidence rates in vaccinated and non-vaccinated children. Because of the clinical information, these calculations were based on age at onset of symptoms, which is important when analysing age-specific severity of disease in infants.

Clinical data were analysed according to several cough definitions, including 14 days of coughing corresponding to the current case definitions for surveillance for the European Union (EU) [5] and from the World Health Organization (WHO) [6] and 21 days of paroxysmal cough according to a previous WHO definition established for use in efficacy trials.

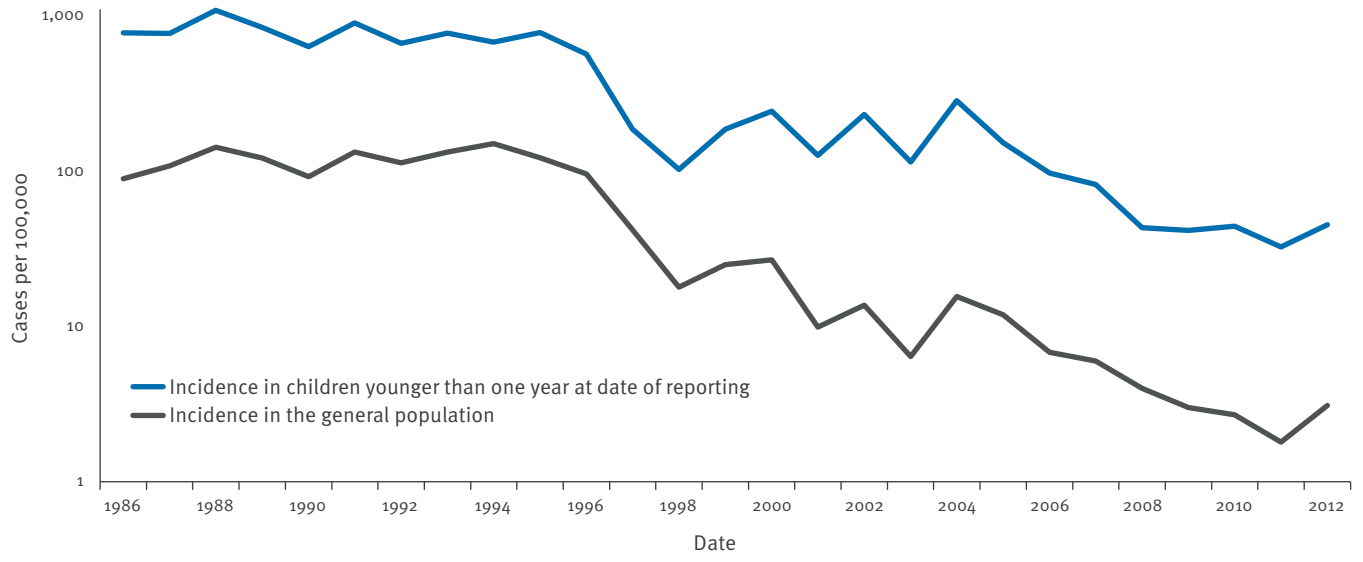
Statistics

Population data used when calculating the incidences were obtained from Statistics Sweden (www.scb.se).

A test for time trend of the incidence was calculated using a quasi-Poisson regression model, used due to overdispersion. Interquartile range (IQR) was used to describe variability in duration of hospital stay. Fisher's exact test was used for comparison of proportions.

Figure 1

Pertussis incidence according to regular notifications of laboratory-confirmed pertussis, Sweden, 1986–2012



Results

Regular surveillance

Figure 1 illustrates the incidence of laboratory-confirmed pertussis in the whole Swedish population and in infants, before and after introduction of the acellular vaccination in 1996. During the first decade of vaccination there was a marked initial drop in disease incidence followed by a more stable period albeit with remaining epidemic cycles. During the last five-year period of the study there was again an initial drop followed by a more stable period, this time without substantial variation in incidence from year to year. Throughout the 15 years 1998 to 2012, the incidence in the general population decreased more or less continuously from ca 90 per 100,000 before 1996 to less than 10 per 100,000 in 2006 and onwards. The incidence in infants also decreased, but more slowly and more stepwise, from over 500 per 100,000 in 1996 to less than 50 per 100,000 during the last five of the 15 studied years.

Enhanced surveillance

From October 1997 through 2012, there were 1,803 laboratory-reported cases of pertussis in infants in Sweden. The families of nine deceased infants were not contacted for ethical reasons, 315 infant cases between 1997 and 2002 occurred in the area not included in the enhanced surveillance at the time and were therefore non-eligible, and 36 families were excluded due to lack of contact details or language problems. Vaccination history and information on cough and antibiotic treatment was collected for all remaining 1,443 cases, including date of onset of coughing. Data on complications or hospitalisation were available for 1,426 of the 1,443 of the cases.

Overall, 840 infants were unvaccinated and 603 had received at least one vaccine dose against pertussis by the time of disease onset. Among the unvaccinated cases, 698 were younger than the scheduled age of three months for the first pertussis vaccine dose. Approximately one quarter of infants aged 3–5 months (104/395, 26%) had not received their first scheduled dose and approximately one third of infants aged 5–12 months (121/348, 35%) had received only one but not both of the recommended doses at three and five months of age.

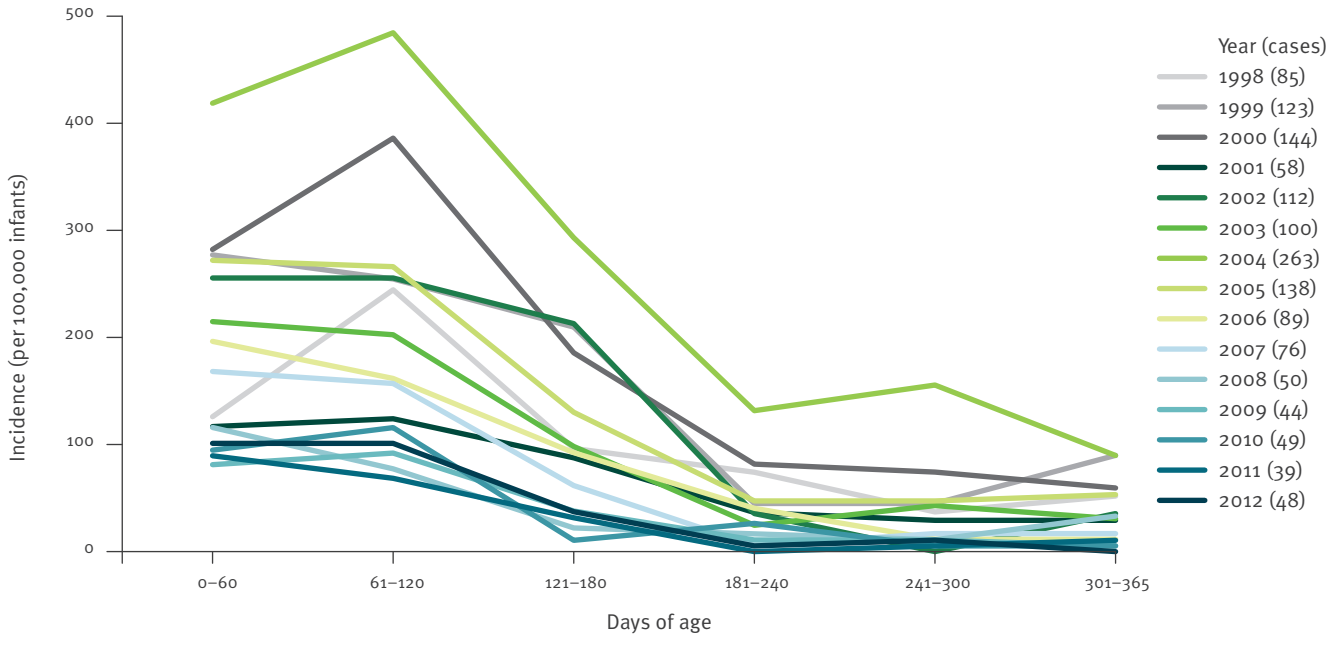
The difference between the date of first symptoms and the date of laboratory reporting (which also is the date of the laboratory analysis) ranged from –12 to 93 days, with a median of 12 days. The negative value means that some laboratory samples were drawn in asymptomatic infants in the context of contact investigation.

Time trend for incidence in infancy

There was a high incidence of pertussis with onset of symptoms during the first four or five months of life, followed by a steep decline in infants six months and older. The incidence of pertussis was 150, 208 and 193 per 100,000 person years for the first, second and third month of infancy, respectively, but with a successive decrease over the years after vaccination was introduced. This time trend is illustrated in Figure 2.

Figure 2

Age-specific number of laboratory-confirmed pertussis cases per 100,000 infants, Sweden, 1998–2012 (n = 1,418 infants in enhanced surveillance project)



Incidence rates are provided by infant age in months, with age calculated at date of onset of disease.

Reported pertussis in non-vaccinated infants decreased in the period 2003 to 2012 when comparing to the previous five-year period ($p < 0.001$ for infants ≤90 days: odds ratio (OR) = 0.36; 95% confidence interval (CI): 0.29–0.44; $p < 0.001$ for infants >90 days: OR = 0.33; 95% CI: 0.18–0.58). This was seen both in infants younger than three months, too young to be vaccinated, and in those who were unvaccinated although they were between three and 12 months-old.

Deaths

There were nine infant deaths during the first 11 years of the surveillance period. All were unvaccinated and all were healthy before falling ill with pertussis. Eight infants died at the age of 1–4 month and one at six months of age. Five were full term whereas four were born before gestational week 37. The child who died aged six months was extremely preterm with a birth weight of 630 g.

An estimate of the case fatality rate can be made from age at laboratory report of pertussis in relation to the total number of laboratory-confirmed pertussis cases in children younger than six months at date of laboratory report. On this basis, the case fatality rate in this age group was 0.65% (9/1,375).

Duration of cough

All but 36 infants had a cough of at least two weeks (1,407/1,443; 98%). Among the 36 infants, coughing lasted for a range of zero to 13 days, and the cough was of paroxysmal type in 15 cases. Six of the 36 infants were hospitalised.

Among 700 cases younger than three months, 599 (86%) had a paroxysmal cough of 21 days or more. In 1,281 of all 1,443 infants (89%) paroxysmal cough was observed, which lasted for 21 days or longer in 1,151 infants (79.8%).

Complications

The complication rate was 41% (287/694) in infants younger than three months and 16% (116/732) in infants aged 3–12 months (Table 1). In children younger than three months who suffered from apnoea, 99% (153/155) were hospitalised. In the age group 3–12 months, seven of eight unvaccinated children with dehydration were hospitalised compared with 12 of 21 vaccinated children ($p = 0.201$).

Hospitalisation rates in vaccinated and non-vaccinated infants

Hospital admission rates in infants aged 0–2, 3–4 and 5–12 months at onset of disease were 131, 58 and 5 per 100,000 person-years, respectively. The incidence in the youngest infants aged 0, 1 or 2 months was, respectively, 127, 152 and 114 per 100,000. The proportions of laboratory-confirmed cases that were hospitalised in the same age groups were 82, 71, and 57%. In the two older age groups 3–4 and 5–12 months, the proportions were 36 and 12%, respectively. Figure 3A compares incidence of laboratory-confirmed pertussis in these age groups with the hospital admission incidence rates per 100,000 infants. The younger the infant, the higher the proportion of cases hospitalised. In the youngest group (0–30 days) the confidence intervals overlapped, indicating that almost all cases were hospitalised. The peak of incidence and of hospitalisations was during the second month of life.

In Figure 3B we have plotted the hospital admission rates per 100,000 person-years during the three five-year periods of 1998–2002, 2003–07 and 2008–12. We found a similar age pattern over these three time periods, with slightly higher incidences during the second compared with the first period because of a large outbreak in 2004. The incidence was lower during the third five-year period.

Unvaccinated infants younger than five months were discharged after a median of seven days (IQR: 4–12 days for infants younger than three months; IQR: 3–13 days for 3–5 month-old infants), whereas the vaccinated infants aged 3–5 months had a median duration of hospital stay of four days (IQR 2–8 days). All infants five months or older were discharged after a median of 3.5 days (unvaccinated IQR: 2–14 days, vaccinated IQR: 2–5 days).

Table 1

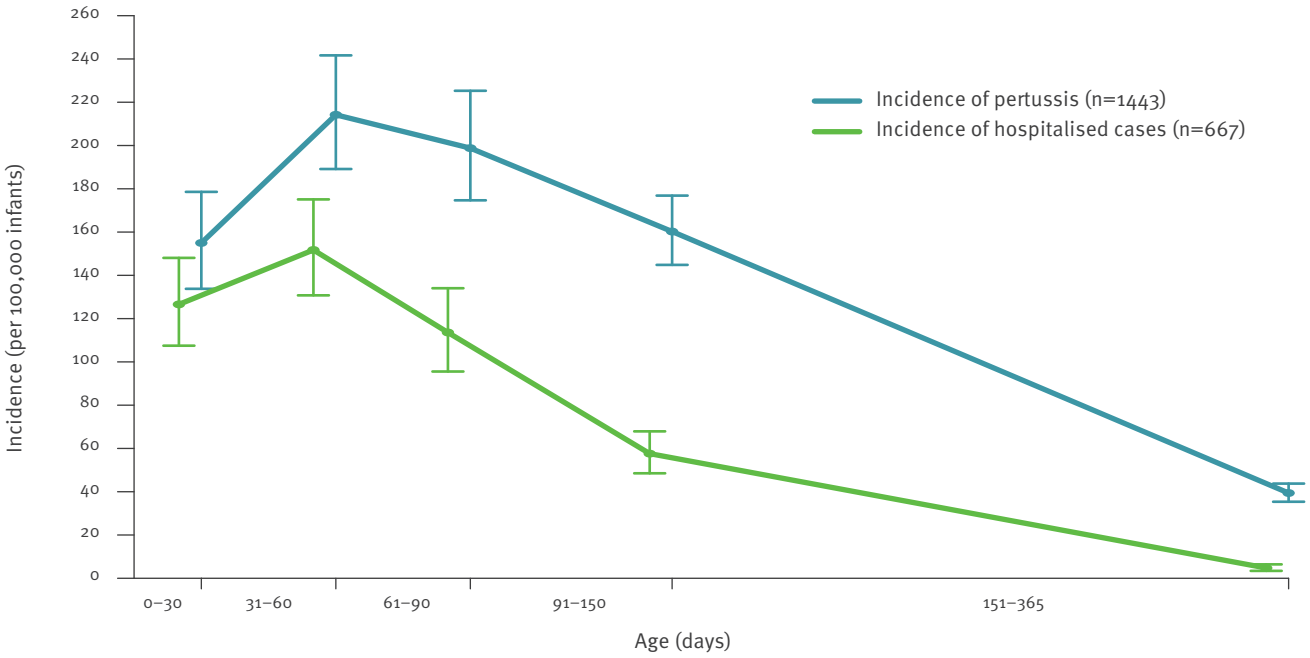
Hospitalisation rates among infants with (n = 403) and without (n = 1,023) complications due to pertussis, by age group and vaccination status (at least one dose), Sweden, 1998–2012

	Hospitalisation rates in infants < 3 months				Hospitalisation rates in infants 3–12 months				Hospitalisation rates in all infants	
	Unvaccinated		Vaccinated		Unvaccinated		Vaccinated			
	n/total	%	n/total	%	n/total	%	n/total	%	n/total	%
Apnoea	152/154	99	1/1	100	9/10	90	27/32	84	189/197	96
Breathing problems	75/76	99	1/1	100	15/19	79	16/25	64	106/121	88
Dehydration	48/53	91	0/0	0	7/8	88	12/21	57	67/82	82
Seizures	1/1	100	0/0	0	1/1	100	0/0	0	2/2	100
All complications	276/285	97	2/2	100	32/38	84	55/78	71	365/403	91
No complications	206/407	51	0/0	0	26/101	26	71/515	14	303/1,023	30

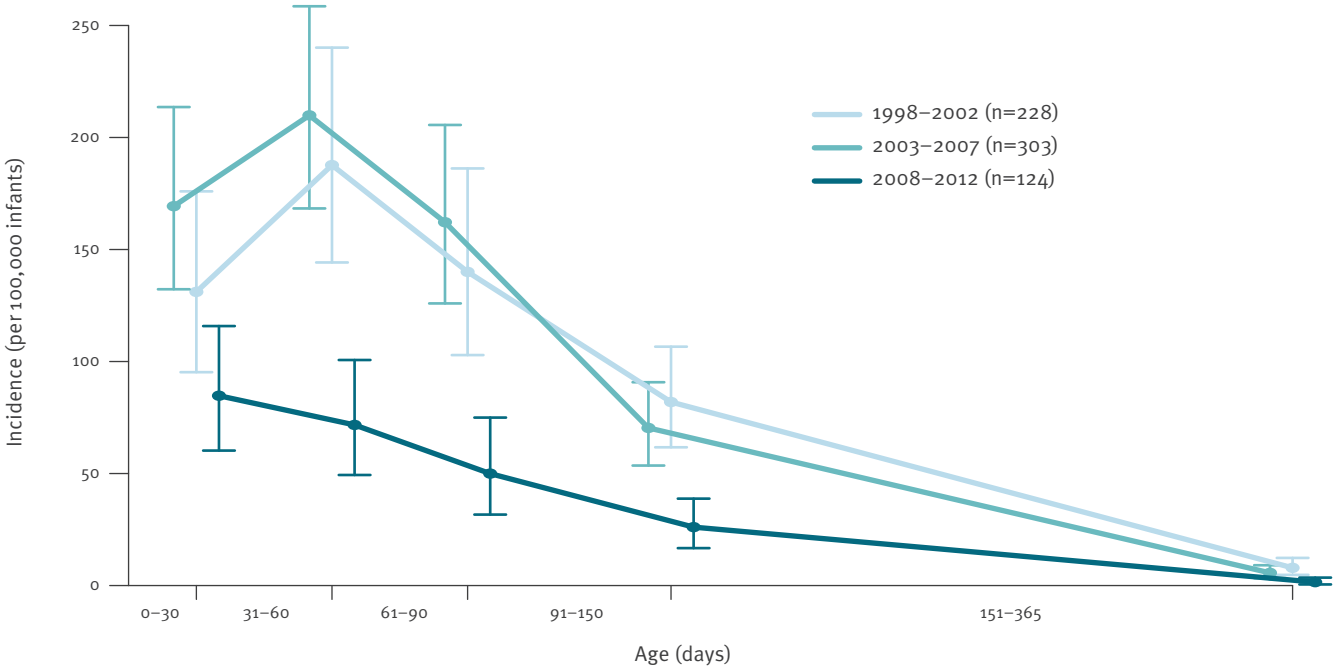
Figure 3

Laboratory-confirmed pertussis cases per 100,000 infants, 1 October 1997–31 December 2012 (n = 1,443, whereof n=667 hospitalised) and hospitalised cases per 100,000 infants, 1998–2002, 2003–07 and 2008–12, Sweden

A. Incidence of pertussis by age group



B. Incidence of hospitalisations by time period



Age is calculated at date of onset of disease and the age intervals during the infant year are chosen in relation to the vaccination schedule at age 3, 5 and 12 months (0–90, 91–150 and 151–365 days), with the 0–90-day interval further divided in months (0–30, 31–60 and 61–90 days).

Antibiotic treatment

Antibiotics were prescribed to 1,233 of 1,443 (85%) of the infants, of whom 1,109 (77%) had paroxysmal cough Figure 4. We compared the median durations of cough (in days) by Fisher's exact test. Doing this pairwise in the group aged 0–90 days and the group aged 91–365 days, an early start of the antibiotic treatment, within the first week (≤ 6 days) after onset of cough during the episode was shown to be associated, in all age groups, with a shorter duration of the coughing period compared with those who had antibiotic treatment initiated later than two weeks after onset of cough or no treatment (Table 2).

Furthermore, antibiotics were prescribed to 33 of 36 infants with cough duration of less than two weeks, and most of these (26/32) had an early start of the antibiotic treatment. This is in contrast to a late start in the vast majority (1,033/1,192) of cases with at least 14 days of cough; among those, the antimicrobial therapies were initiated during the first week in only 13% (79/619) of infants younger than three months, and in 14% (80/573) of infants aged 3–12 months.

Discussion

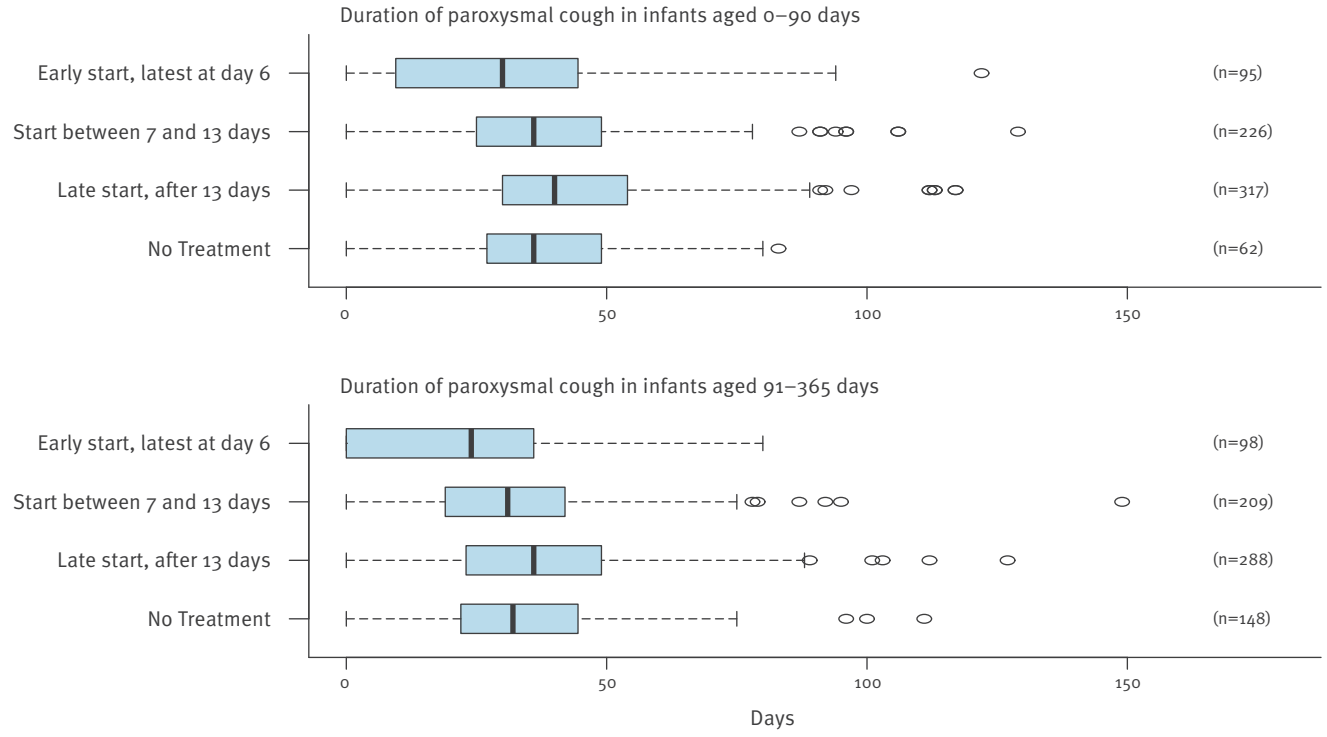
The paper describes data on severity of pertussis in Swedish infants during the first 15 years of an acellular vaccination programme, as reflected through regular and enhanced surveillance.

Regular surveillance data indicate a dramatic decrease in laboratory-confirmed pertussis in the first 10 years after the introduction of pertussis vaccination in the NVP in 1996 [7]. There was a steep initial decline in both the general populations and in infants. The incidence decreased further in the general population, while infant pertussis continued to oscillate above the level of 100 per 100.000, with a large outbreak in 2004. Because there were signs of waning immunity six or seven years after vaccination in infancy [8], a pre-school booster was introduced at the age of six years in 2007, with a catch-up at the age of 10 years. During the subsequent period 2008–12, pertussis incidence decreased further. Infant pertussis settled at a low level of ca 40–45 per 100,000, with no major oscillations, and the overall level in the population at between two and four cases per 100,000.

This stepwise achievement of pertussis control through acellular vaccination is unique for Sweden because all other countries introduced these vaccines in an already controlled situation by changing from whole-cell vaccination. Interestingly, epidemiological data from the United Kingdom (UK) after 1957, when whole-cell pertussis vaccines were introduced in a non-vaccinating and highly endemic setting [9], are compatible with the Swedish data after 1997, when acellular pertussis vaccines were introduced in a similar situation. However, it is too early to tell if the acellular vaccines also in the

Figure 4

Duration of paroxysmal cough in infants with laboratory-confirmed pertussis, in relation to antibiotic treatment and to age, Sweden, 1998–2012 (n = 1,443)



Boxes show first and fourth quartile, whiskers extend to the most extreme point.
Antibiotic treatment was with erythromycin or trimethoprim-sulfametoxazol.

longer run will result in an epidemiological situation similar to when whole cell vaccines are used.
The data from the enhanced surveillance reveal that over the 15-year study period, the age-specific incidence rates decreased also in non-vaccinated infants too young to be vaccinated and in those who were unvaccinated despite their age of 3–12 months. These results indicate indirect protection from reduced exposure. With no cocooning strategy or vaccination during late pregnancy implemented in Sweden, it seems likely that the explanation is a general decrease in the circulation of *B. pertussis*. Seroprevalence data comparing 1997 and 2007 are also supportive of this assumption [10].

There was also a significant reduction in hospitalisation rates in the period 2008 to 2012. A similar time-trend has been reported from the UK and from the Netherlands, with decreasing hospital rates noted four or five years after introduction of a pre-school booster [11,12].

The hospital admission rates in Swedish infants were generally lower than those reported from the UK or the Netherlands [11,12]. The true hospitalisation rates in Sweden may be underestimated, as the trigger point for investigation was a positive laboratory sample. Others have demonstrated that linking of datasets may detect additional infants with hospital admissions, including presentation to emergency rooms [13]. This capture–recapture analysis is yet to be done in Sweden.

There was a peak in pertussis during second month of life, which is in accordance with other studies from the United States and Australia [14,15]. Their hospital admission rates, however, remained high also during third month of life in contrast to the marked reduction in hospital stay observed in Swedish infants of this age. The discrepant observations may be a consequence of data sources and study methods, with our analyses related to age at onset of symptoms instead of age at hospital admission (or discharge).

It is well known that the highest complication and hospitalisation rates are found in infants too young to be vaccinated [16]. In the present study, a complication of any kind was reported in between one fourth and one third of the infants, and more frequently in unvaccinated infants. Respiratory distress, with or without apnoea, was the most frequent problem, and 97–99% of infants with breathing problems were admitted to hospital in the age group 0–3 months. These findings are in accordance with 15-year data collected prospectively in the Swiss sentinel reporting system [17].

We have previously demonstrated some protection from the first dose of a pertussis vaccine, which significantly lowers incidence and hospitalisation rates in infants of the same age [18]. The present study confirms that vaccination reduces severity beyond what is attributable to age at onset of disease.

Post-exposure chemoprophylaxis to unvaccinated infants younger than six months was recommended in Sweden already in 1982 and so was early treatment to infants six to 12 months-old. These guidelines are still being followed: 91% of infants under the age of three months, and 78% of 3–11 month-old infants received antibiotics in the present study. However, these medications started two weeks after onset of symptoms in about half of the cases. This delay relates to the delay in case ascertainment, with a median of 11 days between the first day of symptoms and the day of laboratory confirmation. Unfortunately, we do not have information on the date of first medical visit. The research nurse who performed almost all of the 1,443 interviews, had the impression that many parents had to seek medical care several times before pertussis was suspected. Reasons seem to be that the baby was healthy between attacks of paroxysmal coughing and/or that the medical personnel erroneously considered pertussis to be eliminated because of the NVP. Some parents complained that the doctors did not test for pertussis even in infants with typical pertussis, resulting in an unfortunate delay before proper diagnosis.

When treatment was initiated during first week of symptoms, the duration of paroxysmal cough was significantly shorter. These results partly contradict the general view that antibiotics usually have no effect on the course of the illness if given once the paroxysms are established [19], but are well in accordance with the opinion that antibiotics against pertussis limit the severity of disease if started in the catarrhal phase [20].

In our study, the general surveillance was able to indicate when control of pertussis was achieved by

Table 2

Comparison of duration of paroxysmal cough (p values) in relation to onset of antibiotic treatment in infants with laboratory-confirmed pertussis, Sweden, 1998–2012 (n=1,443)

Comparison	Age group	
	≤90 days	91–365 days
Early start, latest at day 6 vs Start between day 7 and 13	0.014	0.02
Early start, latest at day 6 vs Late start, after day 13	0.002	<0.001
Early start, latest at day 6 vs No treatment	0.024	<0.001
Start between day 7 and 13 vs Late start, after day 13	0.258	0.001
Start between day 7 and 13 vs No treatment	>0.999	0.746
Late start, after day 13 vs No treatment	0.129	0.107

Four treatment categories were chosen and median durations of cough were compared pairwise by Fisher's exact test: (i) no treatment, (ii) early start (≤6 days), (iii) start during second week (7–13 days) or (iv) late start (>2 weeks) after onset of cough.

comparing the decrease of laboratory-reported pertussis in infants with that in the general population. But once the incidence of infant pertussis was at a low and stable level, only the enhanced surveillance could detect signs of herd immunity in the form of a significant decrease of pertussis in unvaccinated infants and also a significant decrease in hospitalisation rates. We conclude that there are two reasons to perform age-specific surveillance of pertussis in infants: to follow-up on vaccination effects in the priority target group, and because infants mirror the circulation of *B. pertussis*. How such surveillance is organised in detail will vary between countries, but detailed vaccination data and access to hospital admission data seem crucial, as well as monitoring of infant deaths due to pertussis.

In Sweden after 2009, there had not been any infant deaths due to pertussis until spring 2014, when a healthy full-term infant was in contact with two coughing parents already at birth. Unfortunately, pertussis was not considered and the infant died at three weeks of age from intractable pulmonary hypertension. In early summer 2014, another death occurred, also in a healthy full-term infant less than one month-old. Since the decrease in the circulation of *B. pertussis* means that mothers transfer lower concentrations of IgG antibodies against pertussis to their offspring [10], the risk of severe pertussis in the youngest infants may increase although their overall risk of contracting the disease is reduced. Careful surveillance, including age-specific data, will indicate if there is a need to consider complementary strategies such as maternal vaccination or cocooning.

Meanwhile, the present strategies to control infant pertussis could be improved, for instance through earlier primary prevention by adherence to the vaccination schedule, a higher degree of secondary prevention by increased awareness of symptoms compatible with the disease, and an earlier implementation of control measures around identified cases.

Acknowledgments

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Conflict of interest

None declared.

Authors' contributions

Rose-Marie Carlsson, who is a former head of the enhanced surveillance project, drafted and wrote the manuscript, and assisted in the analyses. Kerstin von Segebaden is the research nurse who called almost all 1443 families during 15 years, entering the data in the study database. Jakob Bergström and Anna-Maria Kling have performed the statistical analyses and commented on the manuscript. Lennart Nilsson, who is the current project leader, coordinated the work including the analyses, and assisted in writing.

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Timeliness of epidemiological outbreak investigations in peer-reviewed European publications, January 2003 to August 2013

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Timely outbreak investigations are central in containing communicable disease outbreaks; despite this, no guidance currently exists on expectations of timeliness for investigations. A literature review was conducted to assess the length of epidemiological outbreak investigations in Europe in peer-reviewed publications. We determined time intervals between outbreak declaration to hypothesis generation, and hypothesis generation to availability of results from an analytical study. Outbreaks were classified into two groups: those with a public health impact across regions within a country and requiring national coordination (level 3) and those with a severe or catastrophic impact requiring direction at national level (levels 4 and 5). Investigations in Europe published between 2003 and 2013 were reviewed. We identified 86 papers for review: 63 level 3 and 23 level 4 and 5 investigations. Time intervals were ascertained from 55 papers. The median period for completion of an analytical study was 15 days (range: 4–32) for levels 4 and 5 and 31 days (range: 9–213) for level 3 investigations. Key factors influencing the speed of completing analytical studies were outbreak level, severity of infection and study design. Our findings suggest that guidance for completing analytical studies could usefully be provided, with different time intervals according to outbreak severity.

Introduction

The International Health Regulations (2005) stipulate that each State Party is required to ensure they have the capacity to respond 'promptly and effectively to public health risks', such as outbreaks of communicable diseases [1]. The timeliness of outbreak investigations is vital for containing outbreaks and preventing further cases, minimising the impact of an outbreak on both patients and health services, yet despite this, no guidance or standards currently exist regarding what might be considered a timely investigation.

A national Field Epidemiology Service (FES) was formed within Public Health England (PHE) in April 2013, following reforms to the health system in England under the Health and Social Care Act 2012 [2]. The FES aims to improve the consistency of high-quality epidemiological investigations. Hence its formation prompted the consideration of whether specific guidance on the timeliness of outbreak investigations was feasible and, if so, what should be recommended.

Current guidance from PHE [3] states that outbreak reports should be completed within 12 weeks of the formal closure of an outbreak, a common standard for outbreaks within England classified as level 2 or above (Table 1). Such outbreak reports are compiled for internal purposes, to detail the steps within and results of an outbreak investigation, they may or may not include an analytical study (case–control or cohort, for example) and will not necessarily lead to publication in a peer-reviewed journal. No further guidance or standards currently exist to inform what might be considered high quality in terms of timeliness.

We sought to review specific time intervals within epidemiological investigations, those from declaration of an outbreak to hypothesis generation and hypothesis generation to the availability of analytical results to inform the actions of relevant authorities. This review aims to summarise these time intervals in published outbreak investigations with cross-regional, national or international implications (using PHE definitions for level 3, 4 and 5 outbreaks, as in Table 1) to assess the feasibility of developing PHE guidance for the timeliness of analytical studies in outbreak investigations and whether separate standards for different outbreak levels would be appropriate. Such guidance or standards could be used to inform service improvement and/or monitor performance in England and could be similarly developed in other countries.

Methods

MEDLINE, Embase and *Eurosurveillance* were searched using the search terms 'outbreak', 'case-control' and 'cohort' to identify outbreak investigations in Europe published between 2003 and August 2013 and which included an analytical epidemiological study. Papers were included if they met the following criteria: they reported on an outbreak occurring within Europe; were published since 2003 and the outbreak occurred in 2000 or later; were deemed to be level 3 or above (Table 1); were available in English, French, Spanish, German, Greek or Italian; and an analytical study was carried out (e.g. a case–control or cohort study) (Box).

Time intervals from outbreak declaration to hypothesis generation and from hypothesis generation to availability of analytical results were ascertained from peer-reviewed publications retrieved by our search. If the intervals were not explicitly stated, estimations were made, where possible, based on the dates reported. The date of commencing an analytical study was assumed to be within one day of hypothesis generation (given an analytical study cannot commence without a hypothesis having been defined). Analytical results were assumed to be available one day following the end of the analytical study period, i.e. the period over which data collection was reported to have occurred and following which results would be available to inform action and control measures. PHE outbreak level definitions were applied to all reviewed outbreaks: judgement of the outbreak level was based on the geographical spread of cases, the involvement of national agencies in the investigation and the potential severity of population impact. In England, PHE local centres are responsible for establishing outbreak control teams and leading investigations that affect their local population, with support from the FES. Investigation into nationwide outbreaks or outbreaks with wider impact or greater severity are led nationally by the National Centre of Disease Surveillance and Control or the FES, working as part of a team with local PHE centres and other agencies as relevant.

Outbreaks of gastroenteritis infections were classified into mild to moderate or severe according to the causative organism. Severe infections were those with a recognised risk of serious long-term complications or death. Hypothesis generation and analytical study time intervals were compared by outbreak level, study design, type of infection and number of cases. The median number of days was calculated for each time interval considered. Pearson's correlation coefficient was calculated for the association between the number of cases identified and time intervals within the investigation.

The search and analysis of papers was carried out by one researcher (EV) with regular communications with both co-authors to discuss assumptions and categorisation of studies. Where more than one study related to the same outbreak, the investigation that gave a more complete overview (i.e. more cases) was selected for inclusion.

Box

Inclusion criteria for selection of peer-reviewed publications containing epidemiological outbreak investigations

Inclusion criteria

- European outbreak
- Published since 2003 and outbreak occurring in 2000 or later
- Level 3 outbreak or above (cross-regional, national or international outbreak), according to Public Health England definitions.
- Available in English, French, Spanish, German, Greek or Italian
- Analytical study performed (e.g. case–control or cohort study)

Results

The search yielded 1,522 publications, which were reduced to 1,208 following removal of duplicates. After a review of the abstracts, 290 full-text papers were selected for further screening. Application of the inclusion and exclusion criteria led to 86 studies being

Table 1

Public Health England incident levels

Level	Description	Authority to assign response level
1	Local with limited public health impact.	Public Health England (PHE) Centre Director/Leader of Local Health Protection Service
2	Local with limited public health impact but greater than can be managed by one PHE centre.	PHE Regional Director (in consultation with the Director for Health Protection if appropriate)
3	Public health impact across regional boundaries or national. May require national coordination.	PHE Director of Health Protection and/or Duty Director in consultation with the Chief Operating Officer (COO)
4	Public health impact severe. Requires central direction and formal interaction with the Government.	PHE Director for Health Protection in consultation with Chief Executive Officer (CEO) and/or Duty Director and COO
5	Public health impact catastrophic. Requires central direction and extensive commitment of resources.	PHE CEO and/or Duty Director

Source: [3].

selected for this review [4-89]. Of the selected results, 63 were classed as level 3 outbreaks, 22 level 4 and one level 5. Given the small number of level 5 outbreaks, these were combined with level 4 outbreaks for the analysis.

Distribution by country

The countries with the highest number of outbreaks, with peer-reviewed reports meeting the inclusion criteria were the United Kingdom (UK), Germany and the Netherlands (Table 2).

A total of 19 outbreaks occurred across the UK (eight across two or more countries within the UK, four in Scotland, three in England, three in Wales and one in Northern Ireland). These were led by the Health Protection Agency (now Public Health England), Health Protection Scotland, the National Health Protection Service for Wales and the Communicable Disease Surveillance Centre for Northern Ireland, as appropriate.

Germany was the location of the level 5 outbreak investigation that was reviewed, which related to an outbreak of *Escherichia coli* O104 infection in May 2011 [22]. Investigations of outbreaks in Germany were all led by the Robert Koch Institute. All investigations of outbreaks occurring in the Netherlands were supported or led by the Dutch National Institute for Public Health and Environment (RIVM).

Reporting of time intervals

Date of outbreak declaration was reported in 75 papers and at least one time interval was available from 55 of the 86 included papers. The hypothesis generation interval was more frequently available (50 papers) than the analytical study interval (28 papers). Of the 50 studies providing the hypothesis generation interval, 26 also included the analytical study period. Both intervals were available from nine of the 23 level 4 and 5 outbreaks and from 17 of the 63 level 3 outbreak investigations. A further two studies only reported the interval from hypothesis generation to availability of analytical results and three studies only reported the total time from outbreak declaration to availability of analytical results.

Time intervals by outbreak level

The median hypothesis generation and analytical study time intervals were shorter in level 4 and 5 outbreaks (median: 3 days; range: 1–21 and median: 7 days; range: 1–26 respectively) compared with level 3 outbreaks (median: 12 days; range: 1–168 and median: 19 days; range: 7–59 respectively). Overall, analytical results for level 4 and 5 outbreaks tended to be available around two weeks following the outbreak declaration (median: 15 days; range: 4–32), with 20 of 22 completed within 28 days. Analytical results for level 3 outbreaks tended to be available around a month following outbreak declaration (median: 31 days; range: 9–213) and 9 of 10 were completed within 65 days (Figure, Table 3).

Time intervals by study design

The most common study design was a case–control study (n=52). The proportion of case–control studies by outbreak level was similar in level 3 (38 of 63) and level 4 and 5 outbreaks (14 of 23). Approximately a third (n=18) of all case–control studies reported using matched controls. Cohort studies were carried out in 26 of the selected papers, with similar proportions across outbreak levels (19 of 63 level 3 and 7 of 23 levels 4 and 5). The median interval from outbreak declaration to hypothesis generation was shorter in level 4 and 5 outbreaks than in level 3 outbreaks, and the total investigation period (from outbreak investigation

Table 2

Number of selected papers, by country and outbreak level, in peer-reviewed publications containing epidemiological outbreak investigations (n=86)

Country of outbreak	Level 3[a]		Levels 4 and 5[b]		Number of papers
	Number of papers	Source	Number of papers	Source	
United Kingdom	14	[4-6,9-11,14-21]	5	[7,8,12,13,72]	19
Germany	11	[24-31,33,35,89]	3	[22,32,34]	14
The Netherlands	8	[36-43]	2	[44,45]	10
France	6	[59,69,78,79,81,84]	2	[51,58]	8
Norway	6	[48,61,64,67,77,85]	1	[53]	7
Italy	5	[62,76,80,82,83]	1	[49]	6
Denmark	4	[23,57,63,70]	1	[50]	5
Spain	1	[52]	2	[65,73]	3
Sweden	1	[46]	2	[47,75]	3
Other European countries	7	[54,56,60,66,68,86,88]	4	[55,71,74,87]	11
Total number of papers selected	**63**	–	**23**	–	**86**

[a] Cross-regional or national impact with national coordination.

[b] National or international outbreak with potentially severe or catastrophic public health impact requiring national direction.

to availability of analytical results) was shorter in cohort studies than in case–control studies (Table 4). Unfortunately, however, the number of outbreaks reporting time intervals by study design was too small to make robust comparisons.

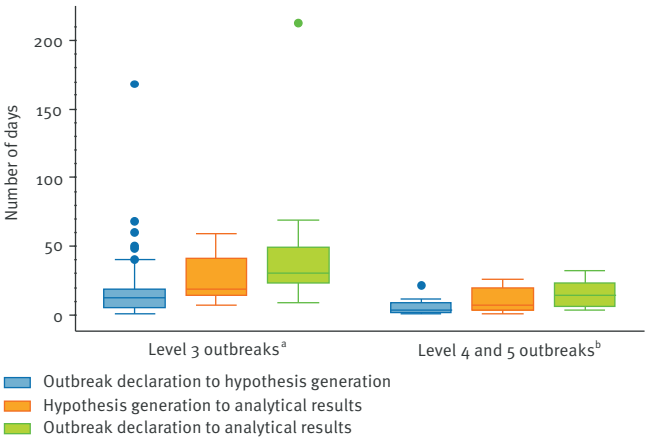
A small number of studies used other study designs, including case–case [44] and case series [16], or a combined approach of case–control and cohort [11,18,28,33,46,47]. One level 4 outbreak used a mixed case–control and cohort design [47]. This investigation was of a large-scale outbreak of *E. coli* infection with 135 linked cases and was completed around a week from outbreak declaration. The speed of this investigation is likely to have been aided by mandatory surveillance information gathered on cases in the two months before recognition of the scale of the outbreak, when a rise in the number of cases had been noted but no common source or *E. coli* subtype identified. Environmental samples were also pivotal in the testing of the hypothesis and prompt withdrawal of the implicated product from the market.

Time intervals by type of infection

The majority of papers (n=65) related to outbreaks of gastroenteritis. Where such outbreaks were suspected or known to be due to more severe infections (i.e. verotoxin-producing *E. coli* (VTEC), Shiga toxin-producing *E. coli* (STEC), *Shigella sonnei*), investigations appear to have been completed more rapidly than mild to moderate infections. The median investigation period (from outbreak declaration to availability of analytical results) for level 3 outbreaks of mild to moderate gastroenteritis was 31 days, compared with 10 days for level 4 and 5 outbreaks of severe gastroenteritis (Table 4).

Figure

Time intervals of outbreak investigations by outbreak level in selected peer-reviewed publications containing epidemiological outbreak investigations (n=55)



Boxes represent the interquartile range (IQR) and the median. Whiskers incorporate values within 1.5 times the IQR from quartile 1 and 3 (Q1 and Q3). Where maximum and minimum values lie within Q3 + 1.5 × IQR or Q1 –1.5 × IQR, the end of the whiskers represent the maximum and minimum values.

Outliers are less than Q1 – 1.5 × IQR or greater than 3 + 1.5× IQR and are represented by dots.

[a] Cross-regional or national public health impact with national coordination.

[b] National or international outbreak with potentially severe or catastrophic public health impact requiring national direction.

Table 3

Time intervals of outbreak investigations by outbreak level in selected peer-reviewed publications containing epidemiological outbreak investigations (n=55)

Time interval	Outbreak level							
	3[a] n=63			4 and 5[b] n=23			Total (3 to 5) n=86	
	Number of papers reporting interval	Source	Median number of days (range)	Number of papers reporting interval	Source	Median number of days (range)	Number of papers reporting interval	Median number of days (range)
Between outbreak declaration and hypothesis generation	38	[6,9,11,17,18,19,20, 21,23,26,27-31, 33,35,38,40-43, 48,52,54,56,57, 59-64,66-70]	12 (1–168)	12	[7,8,22,32,45,47, 49,50,53,55,58,65]	3 (1–21)	**50**	**9 (1–168)**
Between hypothesis generation and availability of analytical results	19	[6,9,11,17,18,20,21, 23,25,29-31, 37,38,42,52,54,56,57]	19 (7–59)	9	[7,8,22,45,47, 49,50,53,55]	7 (1–26)	**28**	**15 (1–59)**
Between outbreak declaration and availability of analytical results	22	[5,6,9,11,17,18,20,21, 23,25,29-31,36-38, 42,43,52,54,56,57]	31 (9–213)	10	[7,8,22,45,47, 49-51,53,55]	15 (4–32)	**32**	**28 (4–213)**

[a] Cross-regional or national public health impact with national coordination.

[b] National or international outbreak with potentially severe or catastrophic public health impact requiring national direction.

Table 4

Time intervals of outbreak investigations by outbreak level in selected peer-reviewed publications containing epidemiological outbreak investigations (n=55)

Variable by outbreak level		Total number of papers	Time interval								
			Between outbreak declaration and hypothesis generation			Between hypothesis generation and availability of analytical results			Between outbreak declaration and availability of analytical results		
			Median number of days (range)[a]	Number of papers	Source	Median number of days (range)[a]	Number of papers	Source	Median number of days (range)[a]	Number of papers	Source
Study design											
Level 3[b]	Case–control	38	15 (1–168)	22	[6,9,17,20,23,27, 29-31,38,40,42, 43,48,52,54,56, 57,64,68-70]	16 (7–59)	16	[6,9,17,20,23, 25,29-31,37,38, 42,52,54,56,57]	30 (9–213)	19	[5,6,9,17,20,23, 25,29-31,36-38, 42,43,52,54,56,57
	Cohort	19	6 (2–40)	12	[19,21,26,35,41, 59-63,66,67]	NA	1	[21]	NA	1	[21]
	Other	6	8 (2–28)	4	[11,18,28,33]	NA	2	[11,18]	NA	2	[11,18]
Levels 4 and 5[c]	Case–control	14	3 (2–12)	7	[7,8,22,45, 53,55,65]	15 (3–26)	6	[7,8,22,45,53,55]	19 (6–32)	6	[7,8,22,45,53,55]
	Cohort	7	2 (1–21)	4	[32,49,50,58]	NA	2	[49,50]	6 (4–16)	3	[49,50,51]
	Other	2	NA	1	[47]	NA	1	[47]	NA	1	[47]
Severity of infection											
Level 3[b]	Mild to moderate gastroenteritis	40	11 (1–168)	27	[6,9,11,17,18,20, 21,27,30,31,33, 35,38,40-42, 52,54,56,57, 60-64,68,70]	20 (7–59)	16	[6,9,11,17,18,20,21, 30,31,37,38, 42,52,54,56,57]	31 (21–213)	17	[6,9,11,17,18,20, 21,30,31,36-38, 42,52,54,56,57]
	Severe gastroenteritis	6	16 (2–19)	3	[23,59,67]	NA	1	[23]	NA	2	[5,23]
	Other	17	17 (1–68)	8	[19,26,28,29, 43,48,66,69]	NA	2	[25,29]	49 (9–69)	3	[25,29,43]
Levels 4 and 5[c]	Mild to moderate gastroenteritis	5	NA	2	[7,55]	NA	2	[7,55]	NA	2	[7,55]
	Severe gastroenteritis	13	3 (1–21)	9	[8,22,32,45,47, 49,50,53,58]	5 (1–26)	7	[8,22,45,47, 49,50,53]	10 (4–28)	8	[8,22,45, 47,49-51,53]
	Other	5	NA	1	[65]	NA	0	–	NA	0	–

NA: not applicable.

[a] Median and range are not included where the number of papers reporting the time interval was less than three.

[b] Cross-regional or national public health impact with national coordination.

[c] National or international outbreak with potentially severe or catastrophic public health impact requiring national direction.

The time it takes to complete an epidemiological investigation may in part be affected by the natural history of infectious diseases, namely the incubation period. Where incubation periods are longer, it will take longer for cases to be detected, given the longer period until symptoms develop in exposed individuals, and there is therefore an increased risk of recall bias. This may lead to delays in the identification of the source of an outbreak and may present greater challenges in identifying additional linked cases, given the increased potential for the movement of cases. Unfortunately, the number of studies of non-gastroenteritis outbreaks in this review was relatively small (n=22) and with few of them reporting time intervals (n=9), it was difficult to identify patterns related to specific infections or incubation periods.

In this review, level 4 and 5 outbreak investigations, with time intervals reported, included infections of STEC, VTEC, *Shigella sonnei*, *Salmonella* and hepatitis A. Level 3 reports, with time-intervals reported, included infections of *E. coli*, *Cryptosporidium parvum, Campylobacter*, *Giardia lamblia*, hepatitis A, *Legionella pneumophila*, *Leptospira*, norovirus, *Pseudomonas aeruginosa*, *Salmonella*, meningitis due to echovirus or coxsackievirus, *Coxiella burnetii* and *Yersinia pseudotuberculosis*. Only one report of a nosocomial outbreak was included in this review (due to *P. aeruginosa* infection) [48]. This nosocomial outbreak took 68 days from outbreak declaration to form a hypothesis and no other time intervals were reported.

Time intervals and number of cases

There was no correlation between the number of suspected and confirmed cases reported in an outbreak and the number of days from outbreak declaration to hypothesis generation (r^2=0.0007). There was also no correlation between the number of cases and the number of days to completion an analytical report (r^2=0.00001).

Discussion

This review found considerable variation in the speed of generating a hypothesis and obtaining analytical results following declaration of an outbreak with cross-regional, national or international public health impacts. The analytical study period following declaration of an outbreak tended to be shorter for outbreaks classified as level 4 or 5. This is likely to be due to a greater amount of resources being quickly mobilised following identification of an outbreak of this nature. By definition, such outbreaks are deemed to have the potential for severe or catastrophic public health impact and direction by national agencies will bring with it the ability to command greater resource deployment.

It should also be noted that the categorisation of outbreak level was based on definitions used by PHE and applied to outbreaks across Europe. Countries outside England may use different criteria to assess the potential impact of an outbreak, which may affect the level of response and timeliness of investigations. Therefore, conclusions regarding the timeliness of outbreak investigations by level should be drawn with caution.

The outbreak investigation period, which has a major influence on the timeliness of controlling an infectious disease outbreak, is just one part of a bigger picture. Whether an investigation period of 15 days for levels 4 and 5 and 31 days for level 3 from outbreak declaration to the availability of analytical results is acceptable needs to be considered alongside delays in outbreak recognition and notification, as well as how swiftly the required control measures are implemented following availability of the analytical results; all of which will affect the resulting population impact.

The study design appears to be one factor influencing the speed of completing analytical investigations; however, choice of study design is likely to be limited by the context of the outbreak. The longer time intervals in case–control studies may be due to challenges of identifying cases speedily and difficulties in selecting and recruiting appropriate controls. Hypothesis generation in cohort studies is likely to be swifter given the investigation starts with an identified population cohort. The factor that identifies the group as a cohort will itself provide clues to the source of the outbreak. In contrast, case–control studies often involve the identification of additional cases over time, which is likely to increase the time taken to define a hypothesis. While control selection methods for such studies was outside the focus of this review, some points are worth noting. Details of control selection methods were often lacking or sparse in the reviewed outbreak reports. Random digit dialling within specific postcode districts or other geographical areas was used in a number of investigations for which analytical results were available within three weeks of the outbreak being declared [6,20,25]. In one investigation, which was completed in 22 days, cases were asked to nominate a number of controls (given relevant criteria) [9]. A detailed description of control selection methods used by researchers at RIVM in the Netherlands was provided by Whelan et. al. [38] in a report of a level 3 case–control study, which had an analytical study period of 16 days (the median for this level in our analysis). RIVM receives each year a randomly selected list of 500 residents from each municipality (based on a unique reference number), totalling about 20,000 individuals per year. From this, a simple random sample of 300–500 individuals are invited to take part in an annual 36-question survey. The survey covers demographics, symptoms, travel history and risk factors in the previous 30 days. Completed surveys are used for enhanced surveillance of food-borne and respiratory infections and can be used in outbreak investigations, reducing the reliance on additional manpower for control selection and interviews [38].

The number of cases may be considered an important factor in the speed of completing epidemiological investigations, both in terms of the public health importance of a large outbreak necessitating a speedy response, and the amount of information available from trawling interviews on which to base hypotheses. However, no association was found between the number of cases detected and the speed of completing an epidemiological investigation among the studies included in this review. A longer delay in detecting an outbreak is likely to lead to a higher number of cases and a greater risk of an outbreak escalating to a higher level. Unfortunately, delayed recognition of outbreaks could not be analysed in this review as any difference between the date the number of cases in the population reached outbreak levels and the date an outbreak was recognised and declared by authorities was rarely reported.

There will be additional factors influencing the timeliness of analytical epidemiological investigations that were not available from the published reports in this review, such as the local public health systems, the availability of resources for investigations, the quality of surveillance and effective public communications. The severe acute respiratory syndrome (SARS) outbreak in 2003 heightened governmental awareness of the risks and impacts of international outbreaks in the context of increased global travel; the timeliness of investigations and public communications appears to have improved somewhat since [90]. The use of electronic surveillance systems and algorithms to detect outbreaks has also improved the detection of outbreaks and the subsequent public health response in a number of countries [91-93]. Such surveillance systems should be regularly evaluated in order to ensure their ongoing usefulness and contribution to timely outbreak investigations [93]. In addition to effective, responsive surveillance systems, public communications regarding specific outbreaks can assist both in detecting outbreaks and in reducing the number of additional cases.

Publication bias is likely to have affected the findings of this study; not all languages were included in the review and there is likely to be a bias towards publishing reports where a source was identified. This may in part account for the large proportion of gastroenteritis outbreak investigations in this review; the short incubation times of these infections may reduce recall bias, leading to more reliable information on which to identify the source of the outbreak. There may also be some bias towards publication of swifter investigations that are considered unusual or highlight good practice. A previous review of published and unpublished food-borne gastroenteritis outbreaks found that few outbreaks reported to the Health Protection Agency (now Public Health England) led to peer-reviewed publication; those that were published had a bias towards more unusual outbreaks [94]. Therefore, a review of time periods within unpublished outbreak investigations would complement this report. It would also be interesting for future studies to compare the timeliness of investigations with identification of a source and implementation of robust control measures.

Timeliness in outbreak investigations is important for minimising the number of people affected and protecting public health. Our findings provide a first overview of timeliness of analytical outbreak investigations. Given the current lack of guidance, it will be useful to develop guidelines regarding what might be considered timely and how to improve the timeliness of outbreak investigations.

A key finding from this review is the need for more standardised reporting of time intervals in outbreak investigations so that the timeliness of investigations can be better understood. This will be required before firmer performance-monitoring standards can be developed. Our results suggest separate guidance and/or standards for the completion of analytical studies according to the severity of public health impact could be established.

While this review has provided useful material to inform discussions within PHE as to what might be considered as high quality in terms of timeliness, organisations within other countries may also find our results useful when considering factors influencing the speed of outbreak investigations and service improvements to ensure prompt completion of investigations. Separate recommendations for intervals from outbreak declaration to hypothesis generation and from hypothesis generation to completion of an epidemiological investigation could be considered; however, the number of studies reporting separate intervals is too small and the variation in timeliness too wide to draw firm conclusions from this review. The development of standards for performance monitoring requires further consideration. Such standards may assist investigation teams in getting organisational support for mobilisation of resources and lead to a more rapid public heath response. However, flexibility in applying standards to monitor the effectiveness of and improvements in outbreak investigations is advisable to allow for variation in the context and complexity of an outbreak. The introduction of such guidance or standards may usefully be accompanied by the development of tools to support prompt investigations. Robust routine surveillance systems and workforce capacity must also be maintained to enable prompt recognition of and response to outbreaks.

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Conflict of interest

None declared.

Authors' contributions

EV led the literature review, data extraction and analysis. All authors contributed to the study design and interpretation of data, all participated in drafting and revising the paper, and all approved the final draft for publication.

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The One Health approach for the management of an imported case of rabies in mainland Spain in 2013

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After more than 30 years without any reported cases of rabies in terrestrial carnivores in mainland Spain, an imported case was detected in June 2013 in Toledo. Although the infected dog was moved across different locations and had contact with humans and dogs, the incident was controlled within a few days. An epidemiological investigation was performed and rabies-free status in terrestrial carnivores in mainland Spain was restored six months after the incident. Key to the successful management of this case were the previous vaccination of susceptible animals in the affected area before the case was detected, the collaboration of different authorities in decision making, and the application of control measures according to national and international regulations and to the One Health concept.

Background

In the 20th century, mainland Spain suffered continuous outbreaks of rabies until 1966, when the country was declared free of rabies for the first time. In 1975, a new outbreak occurred in Malaga in southern Spain which was started by an infected dog owned by a tourist. The disease spread to 81 confirmed animal cases (dogs and cats), leading to the destruction of more than 10,000 dogs within one year. Rabies also caused three human deaths between 1975 and 1978 [1]. Since 1978, mainland Spain has been considered free of rabies in terrestrial carnivores; however, every year, the autonomous cities of Ceuta and Melilla report rabies cases, most imported from Morocco. In 2012, five cases were reported in these cities [2]. Some sporadic cases in bats have been reported since 1987 [3]. The eradication programme in Spain succeeded thanks to the elimination of suspicious animals and vaccination of susceptible animals.

Taking into account the distribution of rabies across the world according to data from the World Organization for Animal Health (OIE), summarised in Figure 1, it was essential for Spain and the European Union (EU) to use risk analysis for the potential introduction of domestic rabies. Several studies were conducted for this purpose [4-6]. This research concluded that the most vulnerable entry route would be the introduction of domestic dogs from Morocco [6]. When border surveillance is working correctly, the probability of importation of the disease decreases considerably, but the possibility of illegal entry of people and animals from Morocco should be taken into account. This is not surprising seeing as sporadic imported cases have been reported in other EU countries, for example recently in France and the Netherlands [7,8].

Since there is no clinical treatment for this zoonotic disease, and only prevention by vaccination is possible public and animal health authorities such as the OIE, recommend the vaccination of domestic animals to avoid the spread of rabies. However, in Spain, mandatory legislation about animal vaccination against rabies is the responsibility of the regional administration, not the national government. Some regions require mandatory vaccination of dogs, and in some places cats are also vaccinated. In some cases mandatory vaccination is annual, in others biennial, and in some autonomous communities it is not mandatory (Figure 2).

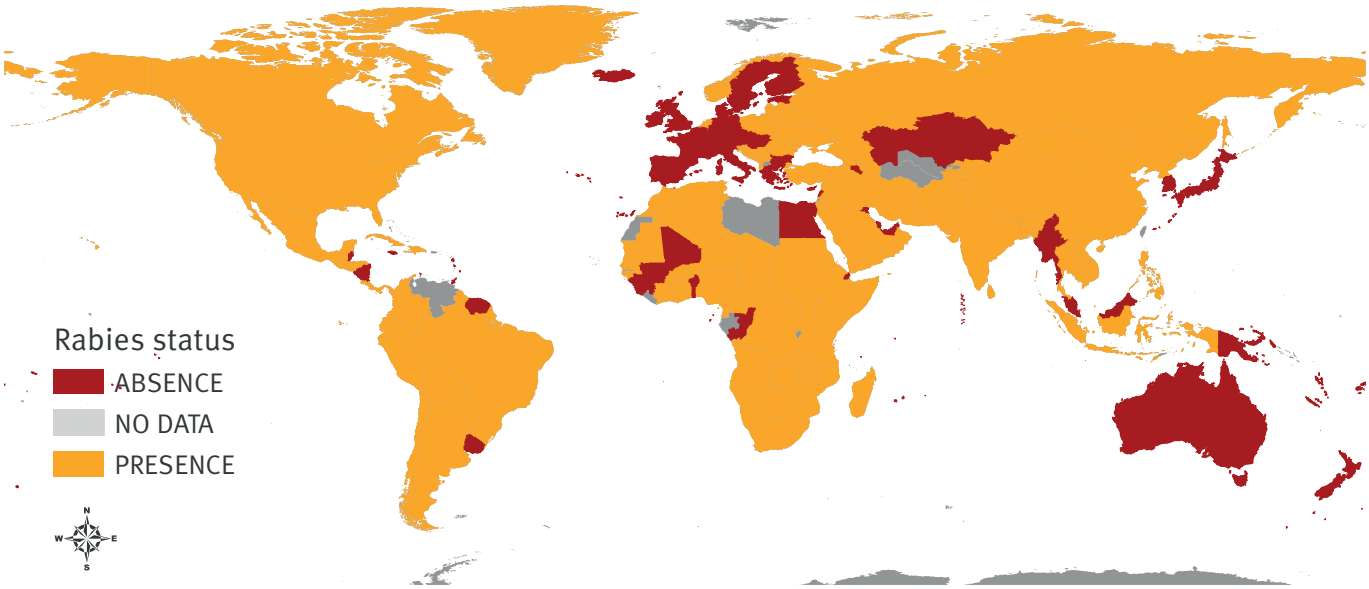
Chronology of the event

In Castilla-La Mancha, a region in mainland Spain, the vaccination programme has changed over time. Since 2002, when there were no rabies cases, vaccination has been voluntary, but in June 2012, the regional government introduced mandatory biennial vaccination [10]. In 2013 an imported case was detected in a dog in Argés, Toledo. The epidemiological investigation established the following sequence of events:

On 1 December 2012, the four year-old Spanish dog was vaccinated, for first time, against rabies with one dose of a polyvalent vaccine. On 12 December 2012, the dog travelled from Spain to an endemic area (Morocco). The time since vaccination was too short for immune protection to develop (the manufacturer's instructions describe the beginning of the immunity three weeks

Figure 1

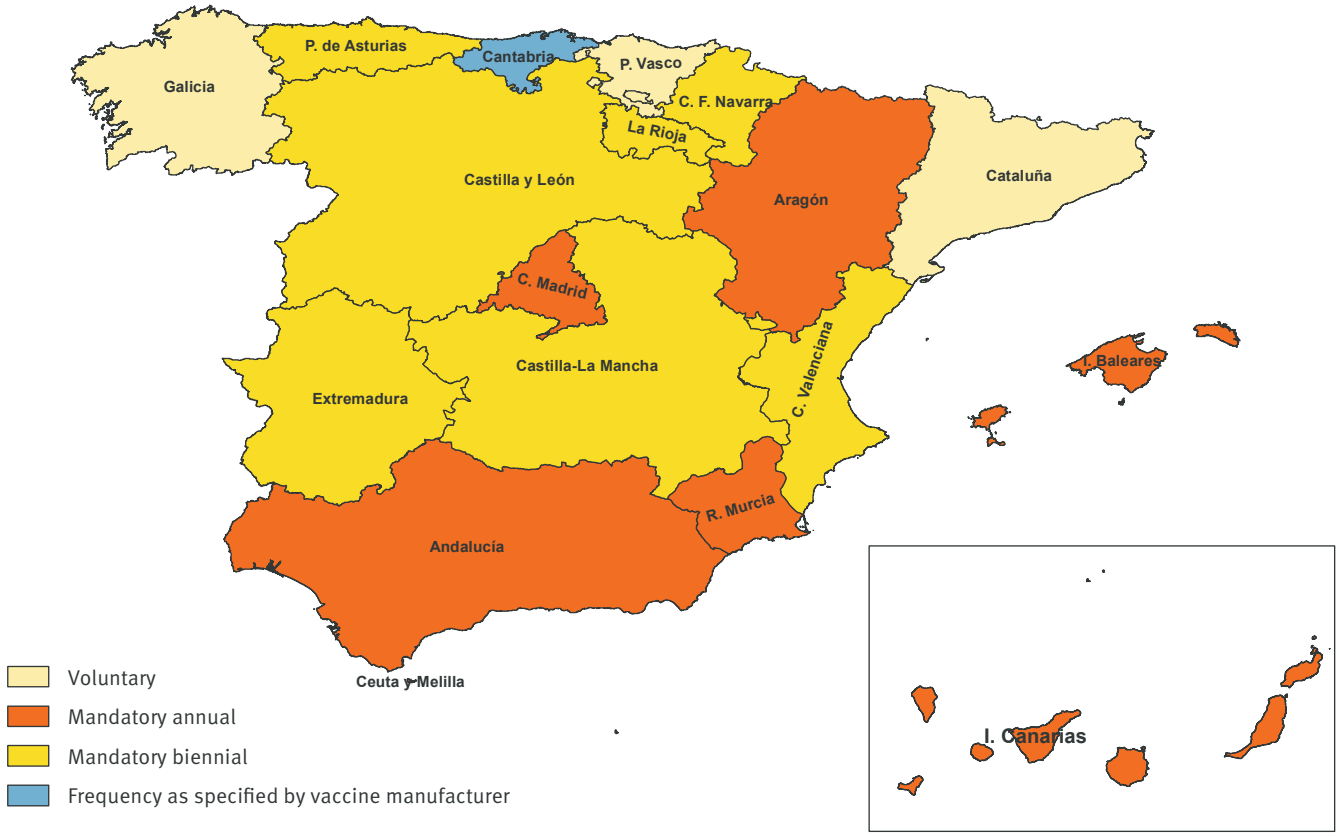
Rabies presence by country, 2012



The information includes only the data reported to the World Organization for Animal Health [9], therefore information was not available for all countries in 2012.

Figure2

Rabies vaccination strategy for dogs in different autonomous communities, Spain, 2012



after vaccination and the European regulation requires a period of thirty days between vaccination and seroneutralisation test [11]). On 12 April 2013, the dog returned to Spain. The entry route is unknown, but it is suspected that it was an illegal entry across the border at Ceuta [12]. Earlier, in February, the dog's owners had tried to cross the border legally, but were denied entry because the seroneutralisation assay according to EU regulation [11] had not been done before the trip to Morocco [13].

The dog's owners remained in Catalonia (Barcelona and Piera) until 5 May 2013, then continued to Huesca (Monzón), and returned to Catalonia (Banyoles y Porqueres) on May 18. From 20 to 22 May, they stayed in Barcelona and thereafter in Argés in Toledo province [14]. On 1 June, the dog escaped and attacked four children and one adult in different parts of Toledo. After several attempts to capture the dog and because of its aggressiveness, the police decided to shoot it. The body was retained and according to the protocol for suspicion of rabies, public health authorities sent the head to the national reference laboratory at the National Centre of Microbiology for diagnosis on 3 June 2013. On 5 June, rabies was confirmed by direct immunofluorescence and PCR. The laboratory further identified the genetic profile of the rabies virus as one of the strains circulating in in Morocco.

On 6 June, according to the Spanish contingency plan for rabies [5], a crisis committee was convened to evaluate and establish control measures which included mandatory vaccination of all susceptible domestic animals (dogs, cats and ferrets) in restriction areas; these were areas where the affected dog had been present during the virus excretion period and that were therefore defined as at risk of disease occurrence. Further control measures included restricted movement of susceptible animals, improved control of stray dogs, active surveillance of dogs and their correct vaccination and identification status, and rabies vaccination for people exposed to the infected dog and people who could have otherwise been exposed to the virus [5]. The virus excretion period was assumed to be from 8 May to 1 June, but to ensure the detection of all potential contacts, the period was extended back to 1 May. The four children and the adult that were attacked by the rabies-positive dog on 1 June received post-exposure treatment with human rabies immunoglobulin (HRIG) and rabies vaccine.

The case data, alert status, and adopted measures were reported to all veterinarians who might know about possible dog contacts. In Castilla-La Mancha, all dogs that were potential contacts were placed in an animal health authority facility on 8 June 2013, (nine dogs). All dogs that could have had contact with the infected animal were serologically examined to ensure their vaccination status. One immunosuppressed dog with insufficient protection against rabies was identified as a high risk for transmission. According to the contingency plan, the immunosuppressed dog was sacrificed on 21 June to prevent rabies dissemination [15].

After six months without new cases, rabies-free status for terrestrial carnivores was restored in Spain in December 2013 [16,17]. Many authorities and institutions were involved in this crisis management. Some of them, such as the veterinary association, the Melilla Government or the Spanish Agency for Medicines and Health Products (AEMPS), were not initially included in the contingency plan (Table 1), but were crucial for the resolution of the incident.

In terms of risk perception, it is important to note that at the beginning of this rabies episode, the population reported many stray dogs, dog attacks, and suspicions

Table 1

Institutions and agents involved in rabies crisis management, Spain, 2012–13

Type of institution	Name	Foreseen in contingency plan	Field of work
National Administration	MAGRAMA	Yes	Animal health
	MSSSI	Yes	Public health
	National Reference Laboratory-ISCIII	Yes	Laboratory assays
Spanish Medical Agency	AEMPS	No	To ensure sufficient vaccine
Regional Administration (Castilla-La Mancha, Aragón, Cataluña and Madrid)	Department of Agriculture	Yes	Animal health
	Department of Health	Yes	Public health
	Melilla government	No	Advisor to authorities
Security agents	SEPRONA	Yes	Animal and proprietary identification
	Local police department	Yes	
Professionals and experts	Veterinary association	No	To report new data to veterinarians
	Private veterinarians	No	To detect potential contact
	VISAVET, other scientific experts	Yes	Advisor to authorities

AEMPS: Spanish Agency for Medicines and Health Products; ISCIII: Institute of Health "Carlos III"; MAGRAMA: Ministry of Agriculture, Food and Environment; MSSSI: Ministry of Health; SEPRONA: Nature Protection Service of the Civil Guard; VISAVET: Health Surveillance Centre.

of rabies after a dog's deaths. All these cases were analysed and no rabies was detected. The social alarm gradually decreased within a few weeks to a residual level similar to the one that exists when no case has been reported in years.

As a preventive measure, people at risk were vaccinated; in Castilla-La Mancha, about 300 people were considered at risk during the event surveillance period until the end of December 2013. Although only 12 people in Castilla-La Mancha could be considered at risk according to the World Health Organization (WHO) category III, 118 people received the complete post-exposure treatment of HRIG and vaccination in this region (Table 2).

Evaluation of management and recommendations

Although more than 15 different institutions, agents and authorities were involved, communication was immediate and complete from the moment disease was suspected. The effective communication allowed to prevent the potential spread of rabies in Spain, when consequences could have been as severe as in the outbreak of 1975 [1]. The successful collaboration underlines the importance of the One Health concept in preventing emerging disease and the spread of infectious animal disease that could have a significant impact on public health, animal health and national economics [18].

It is important to take into account that the animals involved in this rabies incident were pets. When working in animal health, one of the first measures is to restrict movement of susceptible animals and trade, and to review the most recent movements of the animal involved. When the disease affects pets, all these measures become far more complicated because in contrast to livestock, there is no registration system for the movement of pets. The Veterinary Association played an essential role in making information available to the general population and veterinarians, which underlines the importance of establishing an efficient collaboration system between public and private veterinarians and public health authorities.

One of the crucial points in the management of this imported case and its control was the mandatory vaccination ordered in 2012 in the most affected region Castilla-La Mancha, which led to most dogs in this region being vaccinated against rabies. All nine contact dogs in Castilla-La Mancha had been vaccinated in the twelve months previous to the rabies incident. Since vaccination is essential in the prevention of rabies [19,20], it is crucial to establish national legislation for this. It would be useful to require vaccination across the EU not only for movement purposes. Also, it is important to control the movements of pets and comply with the existing regulation, including rabies vaccination of all carnivores entering the EU, especially in areas that have been declared rabies free [4,21].

This case demonstrates how the One Health concept must enlist collaboration from different scientific disciplines [22]. Educating the general population about the importance of pet vaccination could prevent a mortal disease not only of animals but also of humans, and make them participants and collaborators in providing epidemiological data when an outbreak of an emerging disease happens. It is also crucial to educate the population about the risks related to the illegal introduction of pets to the EU and about the appropriate measures to take when travelling to endemic countries. Considering that the infected dog in this report was in fact vaccinated but travelled to Morocco before the immune protection was established, it is important that veterinarians emphasise the necessity to observe correct timing between vaccination and travel to endemic areas. Globalisation comes with the continuous movement of people, animals, products and, consequently, diseases. It is essential to stay alert for the potential risk of disease entry at all times. In the EU, border controls have become more important because a European citizen, once returned from a third country into the EU, could travel across the Schengen area without restriction.

Finally, it is relevant to note the importance of having reference laboratories with updated diagnostic assays and trained personnel who can respond to an alert within hours and provide relevant results.

Table 2

Exposure category of human contacts, and post-exposure protocol adopted in Castilla-La Mancha, Spain, 2012–13 (n=378)

	Number of people
WHO category	
Type I	321
Type I/II	37
Type II	8
Type III	12
Post-exposure treatment	
Vaccination	64
HRIG and vaccination	118
No treatment administered	188
No data available	8

HRIG: human rabies immunoglobulin; WHO: World Health Organization.

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Conflict of interest

None declared.

Authors' contributions

ACPD: wrote the outbreak report and collaborated in the field actions for management. MV, JM, AE: managed the outbreak, worked in decision making and collaborated to collect data for publication.

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