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Controlling *Salmonella* along the food chain in the European Union - progress over the last ten years

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Salmonella has long been recognised as an important food-borne zoonotic pathogen of economic significance in animals and in humans. The main reservoir of *Salmonella* is the intestinal tract of a wide range of domestic and wild animals, which may result in contamination of a variety of foodstuffs of both animal and plant origin. This risk has been taken seriously by food business operators (FBO) and policy makers in the European Union (EU). The incremental implementation of an integrated legislative approach to monitor and control *Salmonella* along the food chain, from primary production to consumption, over the last ten years has thus brought about important progress, however, challenges remain as a paper by Kinross et al. about an ongoing EU-wide outbreak of *S.* Stanley in this issue demonstrates [1].

Animal and human surveillance of food-borne diseases in the European Union

In the EU, surveillance of food-borne salmonellosis in humans is mandatory [2, 3]. Food-borne outbreaks need to be thoroughly epidemiologically investigated [4]. Zoonoses and zoonotic agents, including *Salmonella*, are consistently monitored in food-producing animals and food thereof in EU countries [4]. Data on humans, animals and food are compiled and analysed jointly by the European Food Safety Agency (EFSA) and the European Centre for Disease Prevention and Control (ECDC) and presented annually in the EU Summary Report on trends and sources of zoonoses, zoonotic agents and foodborne outbreaks.

The 2012 report showed that, as in previous years, *S.* Enteritidis, *S.* Typhimurium and monophasic *S.* Typhimurium 1,4,[5],12:i:- were, by far, the serovars most frequently associated with human illness (Figure 1), followed by *S.* Infantis. *S.* Stanley was the causative pathogen in 0.8% and 1.4% of the human cases in 2011 and 2012, respectively [5]. Human *S.* Enteritidis cases are most commonly associated with the consumption of contaminated eggs and poultry meat, while *S.* Typhimurium cases are mostly associated with the consumption of contaminated pig, poultry and bovine meat [5].

Salmonella has been isolated from a wide range of foodstuff, but typically from various types of meat and meat products. In 2012, the highest proportions of *Salmonella*-positive single samples were reported for fresh broiler meat and turkey meat at an average level of 5.5 %, while in fresh pig and bovine meat, the proportions equalled 0.7 % and 0.2 %, respectively, for the group of reporting countries [5].

National control programmes of *Salmonella* in poultry

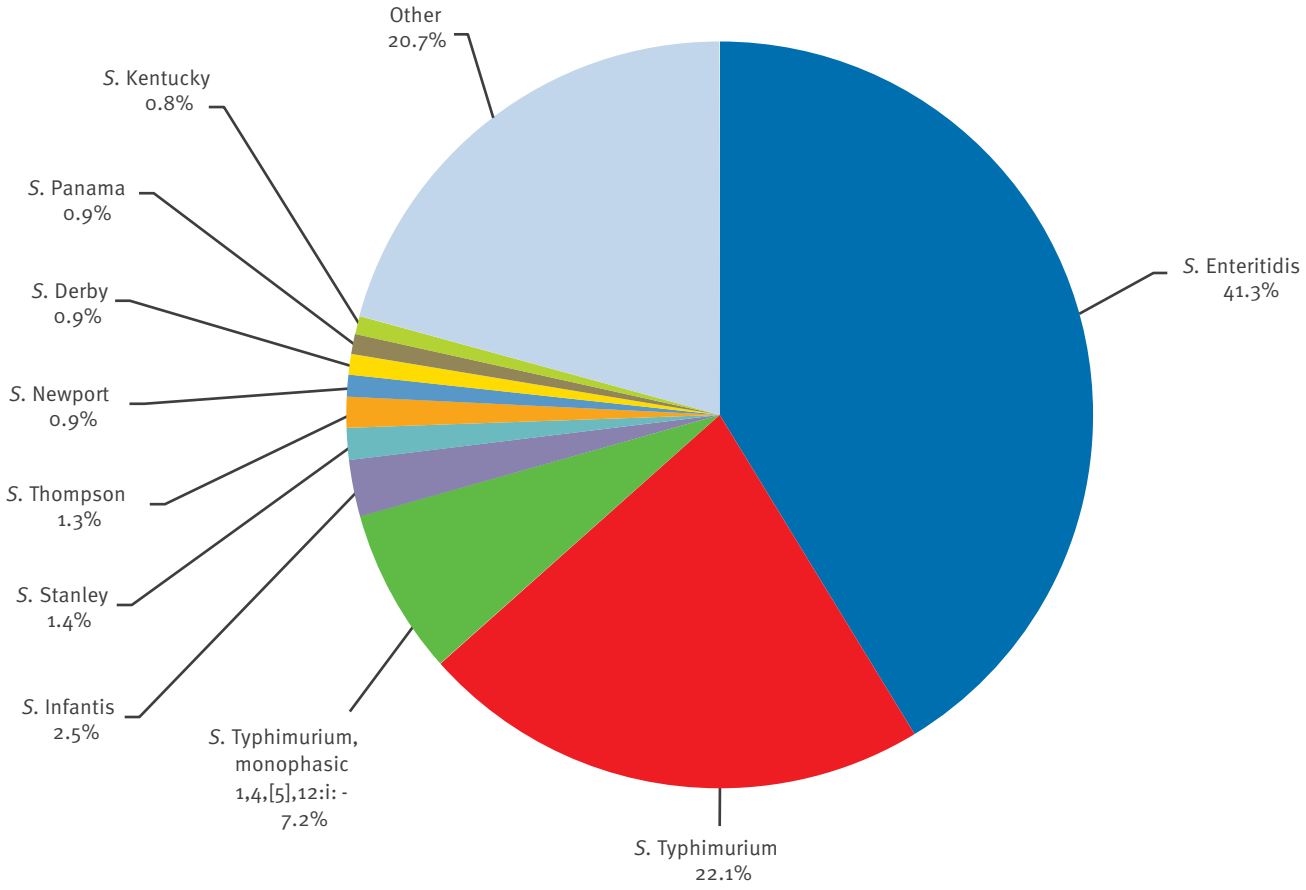
In animals, in particular in poultry, *Salmonella* causes mostly sub-clinical infections and the organism may easily spread between animals in a herd or flock without detection; animals can become intermittent or persistent healthy carriers. The prevalence of *Salmonella* in poultry populations is considered as the main risk factor for presence of *Salmonella* in table eggs and poultry meat. In order to control *Salmonella* in various production types of domestic fowls and turkeys, and to limit the risk of contamination of poultry products, national control and surveillance programmes (NCP) of *Salmonella* have been implemented in the countries in accordance with the EU legislation [6].

NCP targeting several *Salmonella* serovars deemed to be of particular public health significance were set up in selected poultry populations, such as breeding flocks of *Gallus gallus*, laying hens and broilers, as well as breeding and fattening turkeys based on the evidence that these populations have the highest risk of transmitting *Salmonella*. The target *Salmonella* serovars include *S.* Enteritidis, *S.* Typhimurium, *S.* Hadar, *S.* Infantis and *S.* Virchow in breeding flocks of *Gallus gallus* and *S.* Enteritidis and *S.* Typhimurium in the additional poultry populations covered by the programmes. *S.* Typhimurium also includes monophasic *S.* Typhimurium 1,4,[5],12:i:-.

NCP may vary to some extent between countries; nevertheless, they are based on the same principles and aims. NCP typically include systematic implementation of preventive measures of flock infection with *Salmonella*, thorough surveillance of the *Salmonella* status of flocks, and once a *Salmonella* infection is detected, implementation of control measures to

Figure 1

Distribution of the 10 most common *Salmonella* serovars in humans in the European Union, 2012 (N=82,409)



Source: [5]

prevent spread of infection. Poultry flocks are tested for the target *Salmonella* serovars at fixed stages of production at farms or hatcheries using harmonised sampling plans and standardised analytical methods.

With the exception of breeding flocks of *Gallus gallus*, EU *Salmonella* targets were set by the European Commission (EC) in consultation with EU Member States following EU-wide prevalence surveys [6]. The specific *Salmonella* control programmes and the reduction targets were progressively set up from 2005 onwards [7-14]. In the case of breeding and fattening turkey flocks, the mandatory NCPs for *Salmonella* came into effect on 1 January 2010 [8, 14, 15] and were reconfirmed in 2013[16].

EFSA monitors whether EU targets for *Salmonella* prevalence reduction have been met by the countries and follows the progress made. Most countries met their *Salmonella* reduction targets for poultry in 2012, and the prevalence of the target *Salmonella* serovars is significantly declining or remaining stable in poultry populations at the EU level [5].

Hygiene rules for *Salmonella* control in foodstuffs

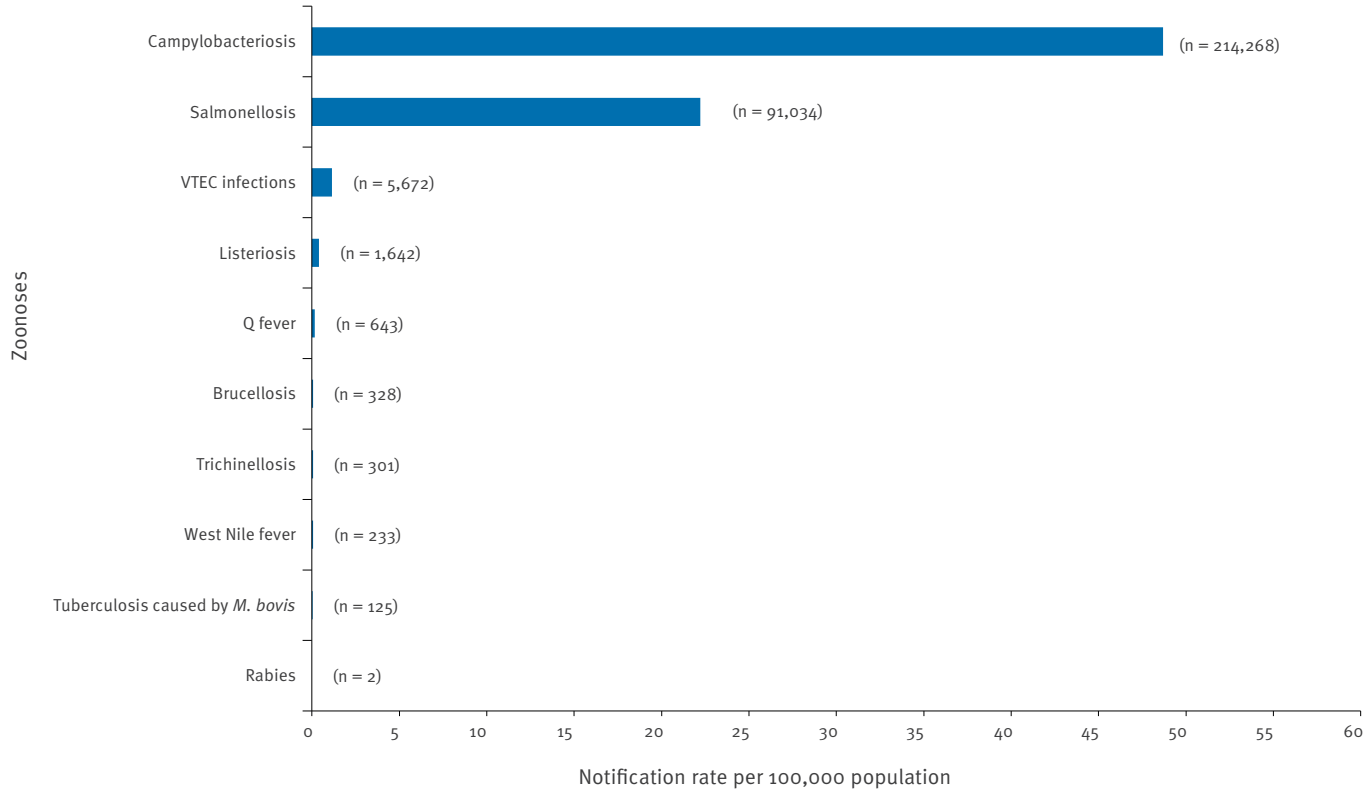
FBO are committed to general requirements on hygiene of foodstuffs, such as implementing procedures based on Hazard Analysis and Critical Control Points (HACCP) and good hygiene practices [17], and specific hygiene requirements with regard to unprocessed and processed products of animal origin, including poultry meat and meat products [18].

Furthermore, FBO should comply with specific food safety criteria for *Salmonella* in minced meat and meat preparations, in particular from poultry. These criteria define the acceptability of foodstuffs placed on the market. Complementary process hygiene criteria for *Salmonella*, notably on carcases of broilers and turkeys, set an indicative value above which corrective actions are required in order to maintain hygiene during processing [19].

Finally, official controls on products of animal origin intended for human consumption ensure that the legal framework for hygiene conditions is implemented correctly by FBO [20].

Figure 2

Reported notification rates of zoonoses in confirmed[a,b] human cases in the European Union, 2012



VTEC: verocytotoxin-producing *E.Coli*

Source: [5]

Note: Total number of confirmed cases is indicated in parenthesis at the end of each bar.

[a] Exception West Nile fever where total number of cases were used.

[b] Due to the restricted nature of the present report, the 2012 human notification rates for yersiniosis and echinococcosis were not produced but will be available in the "Annual Epidemiological Report 2014 - Reporting on 2012 surveillance data and 2013 epidemic intelligence data, ECDC 2014" (In preparation). The 2011 rates for these diseases were reported in the "The European Union Summary Report on Trends and Sources of Zoonoses, Zoonotic Agents and Food-borne Outbreaks in 2011; EFSA Journal 2013;11(4):3129".

Success of *Salmonella* National Control Programmes

In 2007, salmonellosis was the second most commonly reported zoonotic infection in the EU, with 151,995 human cases and a statistically significant decreasing trend in the notification rate in the EU over the past four years. [21]. The number of notified salmonellosis cases in humans in the EU continued to decrease in 2012, to 91,034 cases (Figure 2).This decline is part of the significant declining trend of 30 % observed over the past five years. [5]. It is assumed that the observed reduction in salmonellosis cases in humans is mainly the result of successful *Salmonella* control programmes in fowl (*Gallus gallus*) populations particularly resulting in a lower occurrence of *Salmonella* in eggs, though other control measures might also have contributed to the reduction.

These results indicate that FBO and veterinary public health authorities have continued to invest in *Salmonella* control and that this work is yielding improvements even though challenges remain.

Challenge through possible prevalent serovars in poultry production sectors

Notwithstanding the positive developments, other *Salmonella* serovars, than the major targeted ones, may be occasionally implicated in food-borne outbreaks. In this issue of *Eurosurveillance*, Kinross et al. report about a cross-border outbreak of an unusual strain of serovar *Salmonella* Stanley that occurred in 2011-12 with more than 700 non-travel related human cases reported in 10 EU countries [1]. This number probably only represents the tip of the iceberg because additional cases might have not been captured by the surveillance systems in different countries. The investigations undertaken by affected countries, and subsequently coordinated by the European Commission ECDC and EFSA, suggested the turkey production chain as the source of the outbreak. More recently, further human cases of salmonellosis due to a *S.* Stanley strain exhibiting similar microbiological characteristics (i.e. resistance to ciprofloxacin) were detected and also linked to turkey meat in Austria in April 2014,

suggesting that the outbreak may still be continuing with one or several similar sources [1, 22].

In March 2012, EFSA adopted a Scientific Opinion on an estimation of the public health impact of setting a new target for the reduction of *Salmonella* in turkeys [16]. It concluded that control measures in turkeys have contributed to a considerable reduction in the number of turkey-associated human salmonellosis cases compared with the situation in 2007. The target focusing on *S.* Enteritidis and *S.* Typhimurium, including monophasic *S.* Typhimurium, was therefore confirmed by the legislation for the period starting in 2013 onwards [14]. In addition, complete serotyping was required to inform on the diversity of serovars, other than the targeted ones, prevalent in flocks. Where necessary, targeted control of *Salmonella* serovars other than *S.* Enteritidis and *S.* Typhimurium in turkey should be guided by the prevalence and public health impact in each individual country. If sufficient information becomes available to reliably identify particular strains of public health significance, the inclusion of such strains as part of the EU-wide targets should be considered.

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Multidisciplinary investigation of a multicountry outbreak of *Salmonella* Stanley infections associated with turkey meat in the European Union, August 2011 to January 2013

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Between August 2011 and January 2013, an outbreak of *Salmonella enterica* serovar Stanley (*S.* Stanley) infections affected 10 European Union (EU) countries, with a total of 710 cases recorded. Following an urgent inquiry in the Epidemic Intelligence Information System for food- and waterborne diseases (EPIS-FWD) on 29 June 2012, an international investigation was initiated including EU and national agencies for public health, veterinary health and food safety. Two of three local outbreak investigations undertaken by affected countries in 2012 identified turkey meat as a vehicle of infection. Furthermore, routine EU monitoring of animal sources showed that over 95% (n=298) of the 311 *S.* Stanley isolates reported from animal sampling in 2011 originated from the turkey food production chain. In 2004–10, none had this origin. Pulsed-field gel electrophoresis (PFGE) profile analysis of outbreak isolates and historical *S.* Stanley human isolates revealed that the outbreak isolates had a novel PFGE profile that emerged in Europe in 2011. An indistinguishable PFGE profile was identified in 346 of 464 human, food, feed, environmental and animal isolates from 16 EU countries: 102 of 112 non-human isolates tested were from the turkey production chain. On the basis of epidemiological and microbiological evidence, turkey meat was considered the primary source of human infection, following contamination early in the animal production chain.

Introduction

In Europe, between 2007 and 2011, *Salmonella enterica* serovar Stanley (*S.* Stanley) was relatively rarely reported in humans, with 2,647 *S.* Stanley cases reported to the European Surveillance System (TESSy) during the five-year period [1]. Reporting of all *Salmonella* cases is mandatory within the European Union (EU). Of the 2,044 cases with information on probable country of infection, 1,498 (73%) were acquired outside the EU, of whom above 80% had recorded travelling to south-east Asia in the days before symptom onset; nine cases per month were autochthonous [2,3].

In 2004–10, there were eight reports per month of isolation of *S.* Stanley from food, animals and feed by EU Member States [2,3]. In the past 10 years, only two reports of *S.* Stanley outbreaks in Europe have been published: in 2001, an international outbreak (involving Australia, Canada and the United Kingdom) due to the consumption of imported peanuts [4] and in 2007, an outbreak in Sweden linked to alfalfa sprouts [5].

There is no indication that the clinical presentation of *S.* Stanley cases differs from that of other non-typhoidal *Salmonella* infections, especially in terms of severity [6].

On 29 June 2012, the Belgium National Reference Centre for *Salmonella* reported the detection of 20 autochtonous cases of *S.* Stanley infection in the first half of 2012, compared with 3, 6 and 19 cases detected in 2009, 2010 and 2011, respectively. *S.* Stanley isolates from the 20 cases in 2012 were all nalidixic acid resistant and 18 of them had an indistinguishable *Xba*I pulsed-field gel electrophoresis (PFGE) pattern. On 3 July 2012, Germany reported a twofold increase in the number of cases of *S.* Stanley infection in the first half of 2012 compared with the number in same period the previous years, with 34 domestic and nine travel-related cases. On 11 July 2012, Hungary also notified an increase in the number of cases of *S.* Stanley infection, with 63 cases in 2012 compared with the 2 to 10 cases expected annually. On 17 July 2012, the Belgium National Reference Centre for *Salmonella* confirmed the PFGE pattern of isolates from the Hungarian cases was indistinguishable from the Belgian pattern. On 6 August 2012, Austria reported an increase in the number of cases of *S.* Stanley infection (n=37) with a nalidixic acid mono-resistant profile observed between April and July, compared with eight cases in the first quarter that year.

As more information from the food sector became available, the European Commission asked the European Centre for Disease Prevention and Control (ECDC) and the European Food Safety Authority (EFSA) for technical assistance in the evaluation of information collected during the outbreak investigation. Rapid outbreak assessments were initiated by ECDC in collaboration with EFSA, the European Reference Laboratory for *Salmonella* (EURL-*Salmonella*) and affected EU/European Economic Area (EEA) countries to identify outbreak-related cases, describe the outbreak size and progression and provide evidence supporting the implementation of control measures. ECDC provided the first assessment of this information on 27 July 2012 [2], an update on 29 August and a further update jointly with EFSA on 21 September 2012 [3]. To our knowledge, this is the first large multicountry outbreak of *S.* Stanley infection, investigated through both epidemiological and microbiological investigation coordinated at the EU level.

Methods

Epidemiological and microbiological information for risk analysis was shared through the Epidemic Intelligence Information System for food- and waterborne diseases (EPIS-FWD) [7].

European Union outbreak case definition

A probable case was defined as a person with *S.* Stanley infection with an onset of symptoms after August 2011, and no travel history outside the EU in the seven days before the symptom onset, to focus the investigation on likely sources of infection within the EU. The definition's date restriction was chosen as the increased incidence in Hungary was observed from this time.

A confirmed case was a probable case with isolates showing an *Xba*I-PFGE pattern indistinguishable from the outbreak strain first detected in Belgium. Cases from whom isolates were tested by *Xba*I -PFGE and results patterns were different from the outbreak strain were excluded.

The case definition did not include antimicrobial sensitivity information. A 'case' refers to probable and confirmed cases, unless otherwise specified. A country reporting at least one confirmed case was considered affected.

From 1 October 2012, a monitoring phase was initiated: EU/EEA countries were asked to provide ECDC with their aggregate monthly number of non-travel-associated cases of *S.* Stanley infection. ECDC removed its recommendation on PFGE confirmation, which was costly and time consuming, to monitor the overall trend.

Epidemiological investigations

Data on cases were collected by national public health institutes. Baseline incidence was established by reviewing surveillance reports of human *S.* Stanley infection since 2007 (ECDC) and reports of *S.* Stanley infection in animals, food and feed since 2004 (EFSA). Population data were obtained from the 2010 Eurostat population dataset [8] and the incidence ranges per million population were determined using the geometrical interval classification method (ArcGIS v.10.2).

Investigators in Austria and Hungary created hypothesis-generating questionnaires, which served as a basis for the development of a standard EU questionnaire for interview of retrospective and prospective cases. The questionnaire focused on selected exposures in the seven days before symptom onset, and was shared with countries on 4 September 2011.

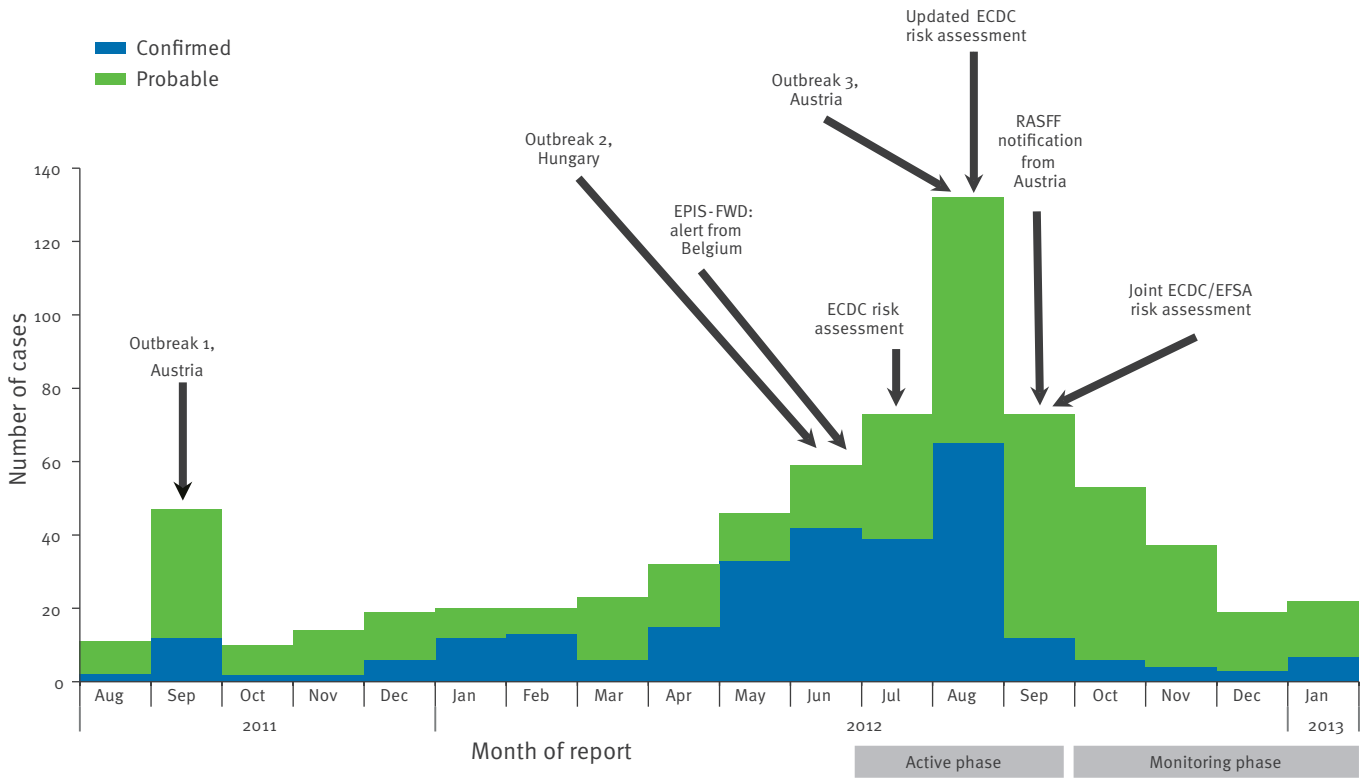
Microbiological investigations

For the microbiological investigations, the outbreak strain was defined as the first *S.* Stanley strain detected in Belgium in 2012. Outbreak isolates were isolates with an indistinguishable *Xba*I-PFGE pattern to the outbreak strain; no single band differences were accepted.

ECDC, EFSA and EURL-*Salmonella* jointly prepared a laboratory testing protocol for human, food and animal isolates, requesting PFGE analyses of selected *S.* Stanley isolates using the PulseNet protocol and *Xba*I [9]. The clonality of the *Xba*I-PFGE outbreak strain was further analysed using a selection of human, animal, food and environmental isolates from Austria, Belgium and Hungary through use of a second restriction enzyme, *Bln*I. EU/EEA public health institutes were

Figure 1

Confirmed and probable cases of *Salmonella* Stanley infection in humans by month of report in affected European Union Member States, August 2011–January 2013 (n=710)[a]



ECDC: European Centre for Disease Prevention and Control; EFSA: European Food Safety Authority; EPIS-FWD: Epidemic Intelligence Information System for food- and waterborne diseases; RASFF: Rapid Alert System for Food and Feed.

[a] Of the 710 isolates reported, 281 were confirmed to be the outbreak strain.

requested to share with ECDC PFGE typing results of isolates from patients meeting the EU outbreak case definition; animal health and food safety authorities were requested to share with EURL-*Salmonella* the PFGE typing results of *S.* Stanley-positive isolates with the outbreak strain from animal, food and environment sampling.

EU/EEA veterinary and food reference laboratories were requested to share PFGE typing results from isolates from food, feed, environment and animals since 2007 and to perform PFGE typing on stored *S.* Stanley isolates from January 2011 onwards, and on new isolations.

Quality assessment of the shared PFGE gel pictures was performed according to the PulseNet international protocol PNQ01 [10]. Cluster analysis was performed using Bionumerics V6.6 (Applied Maths, Sint-Martens-Laten, Belgium) with tolerance and optimisation set at 1.5%. Analysis of the pattern variation within the clusters was reassessed setting the optimisation and tolerance thresholds at 1%. A cluster was defined as a group of isolates of *S.* Stanley with indistinguishable *Xba*I-PFGE patterns.

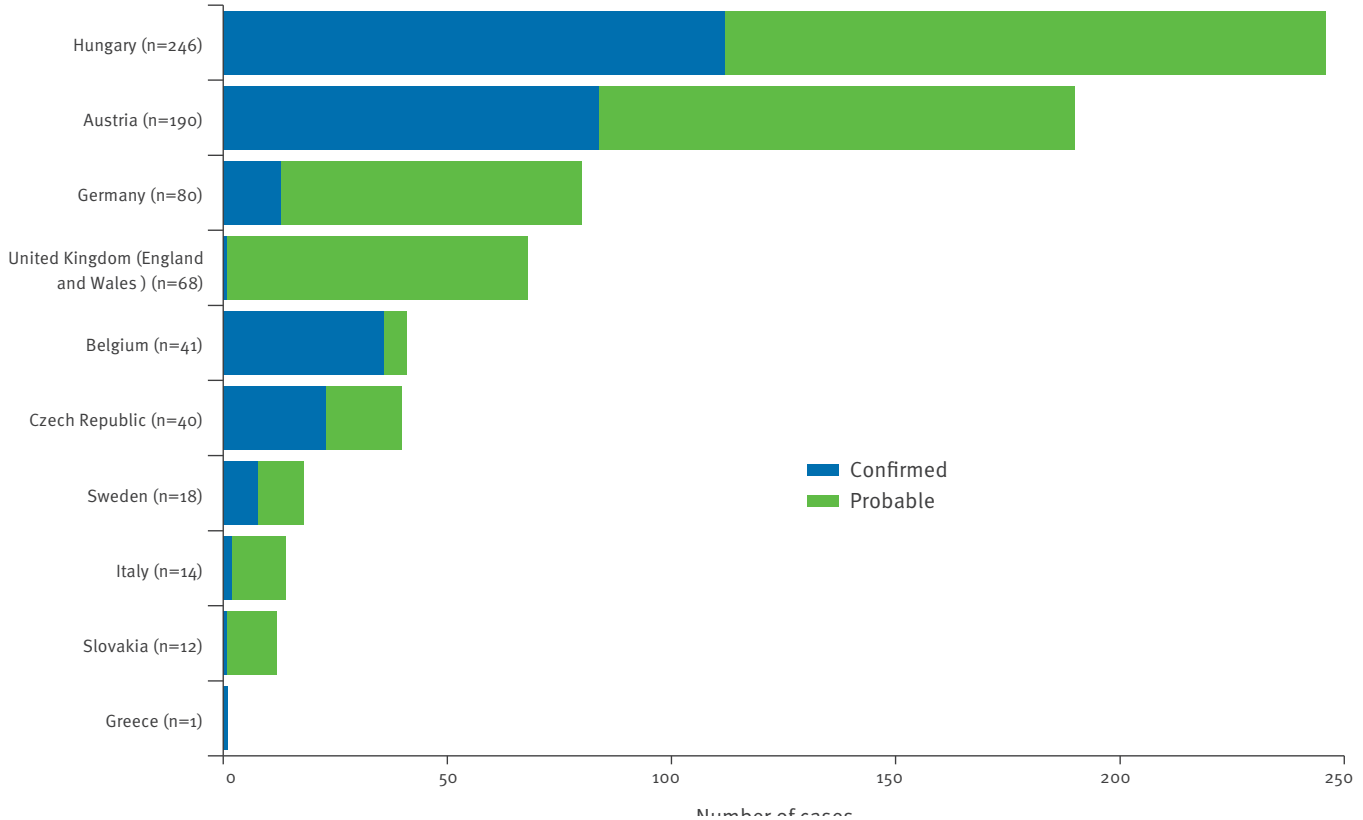
The PulseNet Europe PFGE database hosted at ECDC was used to assess the genetic diversity of historical European *S.* Stanley isolates and to compare outbreak isolates' patterns with those of the 21,748 isolates of *Salmonella* spp. imaged between 1994 and 2008. In addition, ECDC consulted the EU Member States to determine whether they had identified the outbreak strain between 2008 and 2011. The Hunter–Gaston index was used to calculate the discriminatory power of the *Xba*I-PFGE typing [11].

International food safety notifications inside and outside the EU

ECDC liaised with the Rapid Alert System for Food and Feed (RASFF) of the European Commission to facilitate identification of internationally distributed products contaminated with *S.* Stanley. The International Food Safety Authorities Network (INFOSAN) issued an alert on 20 July 2012 to identify cases outside the EU/EEA.

Figure 2

Distribution of cases of non-travel-related *Salmonella* Stanley infections (probable and confirmed cases) by European Union Member State, August 2011–January 2013 (n=710)



Results

National outbreaks

Austria investigated two local outbreaks. The first occurred in September 2011, before the multicountry alert [3] (Figure 1). A descriptive epidemiological study identified that all 32 cases (of whom five were confirmed) ate at a turkey kebab stand. No turkey meat remained for testing, but a sauce sample and dishcloth from the stand tested positive for *S.* Stanley. Both *Xba*I- and *Bnl*I-PFGE analyses of the human, food and environmental isolates from this cluster were indistinguishable from that of the Belgian outbreak strain. The second outbreak occurred in August 2012 with 62 cases (of whom 54 were confirmed) following a local community event in Upper Austria [3]. Descriptive and analytical epidemiological investigations by the national Agency for Health and Food Safety (Agentur für Gesundheit und Ernährungssicherheit, AGES), assisting the local public health authorities, identified an association between the disease and consumption of a potato salad prepared by a person subsequently identified to have had an asymptomatic infection with the *S.* Stanley outbreak strain [3].

In Hungary, health authorities investigated an outbreak that occurred in June to July 2012 in a summer camp [3]. Its two confirmed cases both reported eating meatballs containing turkey meat. Leftover meatballs were not available for testing, but frozen turkey meat from the batch used to prepare the meatballs was positive for *S.* Stanley with the outbreak PFGE profile. Environmental isolates taken in August 2012 at the factory that processed this turkey meat also had a PFGE pattern indistinguishable from that of the outbreak strain. Isolates from the farm and slaughterhouse that supplied this contaminated meat tested positive for *S.* Stanley repeatedly during routine investigations in 2012, although no PFGE results were available.

European Union investigation

Descriptive epidemiology

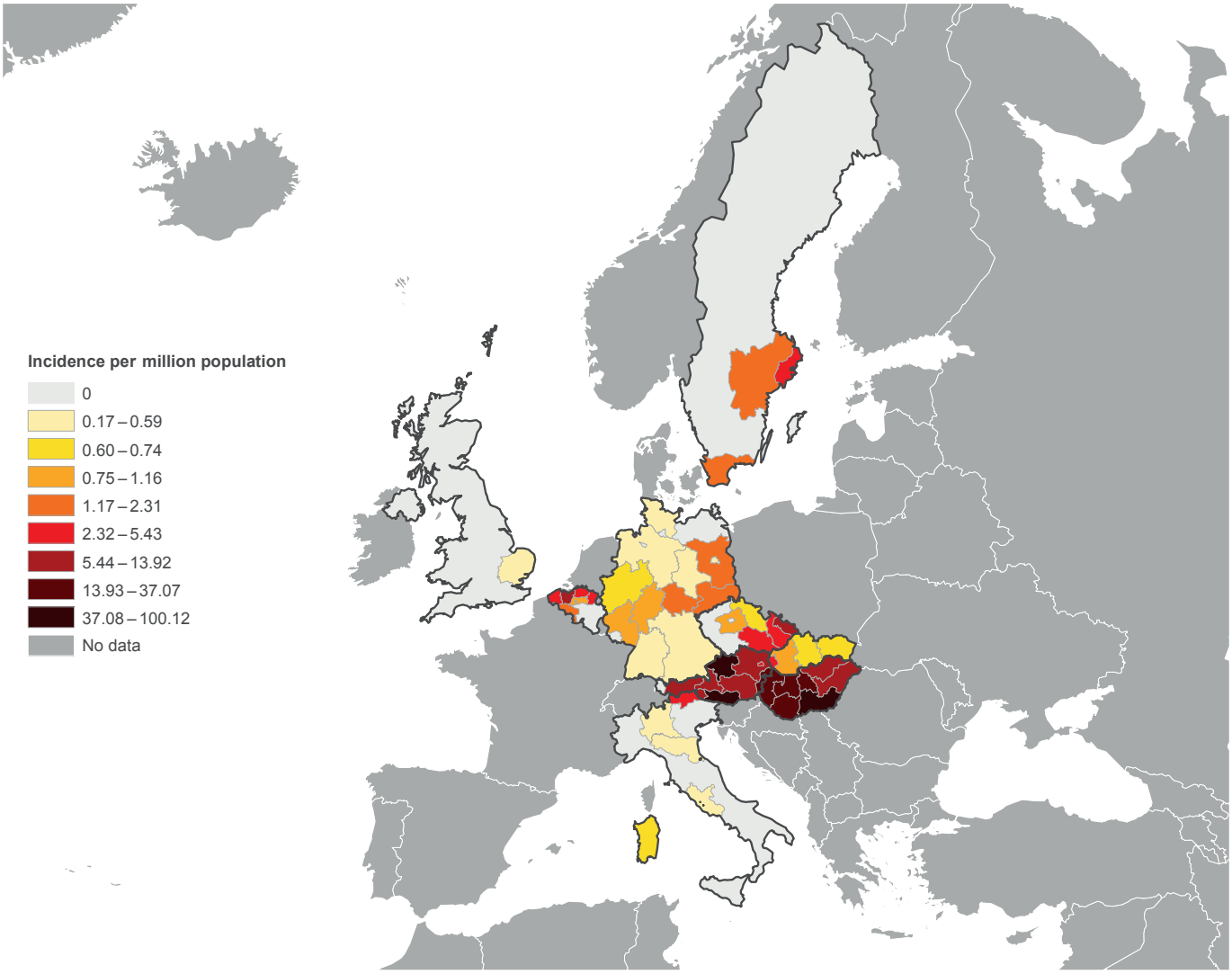
Between 1 August 2011 and 31 January 2013, 710 human cases of *S.* Stanley infection were reported in 10 EU Member States: Austria, Belgium, Czech Republic, Germany, Greece, Hungary, Italy, Slovakia, Sweden and the United Kingdom. Of these, 281 (40%) were confirmed cases (Figures 1 and 2). PFGE testing was not performed on the remaining 429 probable cases.

The median age, for the 493 cases with available information, was 16 years (range: 0–89). Of the 497 cases with available information on sex, 259 (52%) were male.

A total of 20 EU/EEA countries reported no unusual increase in the number of *S.* Stanley infections or no

Figure 3

Incidence rates of confirmed and probable cases of *Salmonella* Stanley infection by European Union Member State region, 1 August 2011–22 October 2012[a] (n=498)[b]



NUTS: nomenclature of territorial units for statistics.

[a] The map was generated once the outbreak investigation had moved to its monitoring phase.

[b] Cases for whom geographical information was available.

Population data were obtained from the 2010 Eurostat population dataset [9] and the incidence ranges per million population were determined using the geometrical interval classification method (ArcGIS v.10.2). The incidence rate in Austria, Belgium, Czech Republic, Hungary and Slovakia are represented at NUTS2 level; in Germany and the United Kingdom, at NUTS1 level.

cases associated with the outbreak. No cases were identified as a result of the INFOSAN alert [3].

Geographical clusters were observed in three countries: Belgium's cases were reported from the northern, Flemish part of the country; Sweden's cases clustered in the southern and south-eastern population centres; Austria's cases clustered in Upper Austria and Carinthia (Figure 3), partially due to two large outbreaks.

The monthly incidence at the EU level increased incrementally from February (n=20) until August 2012 (n=132), decreasing each month thereafter until December 2012 (n=19).

European Union standard questionnaires

By 29 October 2012, ECDC had received 43 questionnaires from five countries: Belgium (n=1), Czech Republic (n=24), Greece (n=1), Hungary (n=11) and Slovakia (n=6). Three questionnaires were excluded from the analysis due to incompleteness.

Meat was eaten by 39/40 respondents. Products explicitly labelled as turkey (e.g. roast turkey and turkey ham)

were reported to have been eaten by 10/40 overall. Two of these 10 cases ate barbequed 'back-yard' turkey.

Control measures

The European Commission's arranged ad hoc teleconferences to ensure communication between the competent authorities and trace-back/trace-forward investigations to more accurately determine the source of the outbreaks. Control measures were coordinated at the national level and communicated between countries, e.g. in a RASFF notification from Austria [12].

Microbiological investigation of human, food and veterinary samples

Of the 21,748 entries in the PulseNet Europe PFGE surveillance database between 1994 and 2008, 91 (0.4%) were *S.* Stanley. A total of 72 different PFGE types were identified; none matched the 2011–12 outbreak PFGE profile (Figure 4). Additional comparisons with national PFGE databases from EU Member States confirmed that the outbreak profile had not been identified among isolates of *S.* Stanley from humans in the EU before August 2011.

In 2011, 311 *S.* Stanley serovar isolations from routine monitoring of food and animals were reported to EFSA by EU Member States, Norway and Switzerland, of which 96% (n=298) were from turkey fattening flocks, turkey breeding flocks and turkey meat [3]. By comparison, between 2004 and 2010, *S.* Stanley was isolated on 55 occasions but not from turkeys or turkey meat [3].

S. Stanley was first identified in turkeys in January 2011 in Hungary, in breeding flocks. The animals had been imported as day-old chicks from a German hatchery, having tested negative for *Salmonella* spp. on arrival. Later that year, *S.* Stanley also appeared in turkey fattening flocks in Hungary (data not shown); however, no PFGE results were available for these isolates.

Austria's turkey hatchery received regular consignments of hatching eggs from a turkey parent flock in Hungary. Animal samples (boot swabs) from that parent flock were sent to the Austrian hatchery as part of its self-monitoring: they tested positive for nalidixic acid mono-resistant *S.* Stanley on several occasions from June 2011 onwards. Samples from the Austrian hatchery, taken in March 2012, also tested positive for the outbreak strain. In 2012, the Austrian hatchery distributed day-old chicks to fattening farms in Austria and 10 other countries, some of which reported confirmed human cases (Czech Republic and Hungary) and some that did not report any human cases (Croatia, Poland, Serbia and Slovenia). Subsequent to the detection of *S.* Stanley with the outbreak PFGE profile in a 'turkey stick' produced in Austria, the Austrian food authorities issued a RASFF notification on 10 September 2012 [12].

In 2012 in Hungary, 24 turkey holdings were found to be infected with *S.* Stanley (no PFGE results were available). Hungary isolated *S.* Stanley from 13 food samples from January to September 2012; all but one were from turkey meat; one sample was from broiler chicken meat (no PFGE results were available).

During the investigation, ECDC received PFGE profiles of 488 *S.* Stanley isolates from human and non-human samples from 15 EU/EEA countries (Austria, Belgium, Czech Republic, Germany, Denmark, Greece, Finland, France, Hungary, Italy, Norway, Poland, Slovenia, Slovak Republic and the United Kingdom). A total of 464 PFGE profiles were included in the analysis, as 24 profiles were excluded for quality reasons. *Bnl*I-PFGE profiling of a selection of human, animal, food and environmental isolates from three countries (Austria, Belgium and Hungary) confirmed the clonality of the *Xba*I-PFGE outbreak strain. The *Xba*I-PFGE outbreak profile was identified in 346 of the 464 profiles analysed.

For the isolates from human cases, ECDC received PFGE profiles of 234 isolates indistinguishable from the outbreak profile, from 281 reported confirmed cases. These 234 isolates with the outbreak profile were received from eight EU countries and showed that the first isolate from a human case was from Austria, from July 2011.

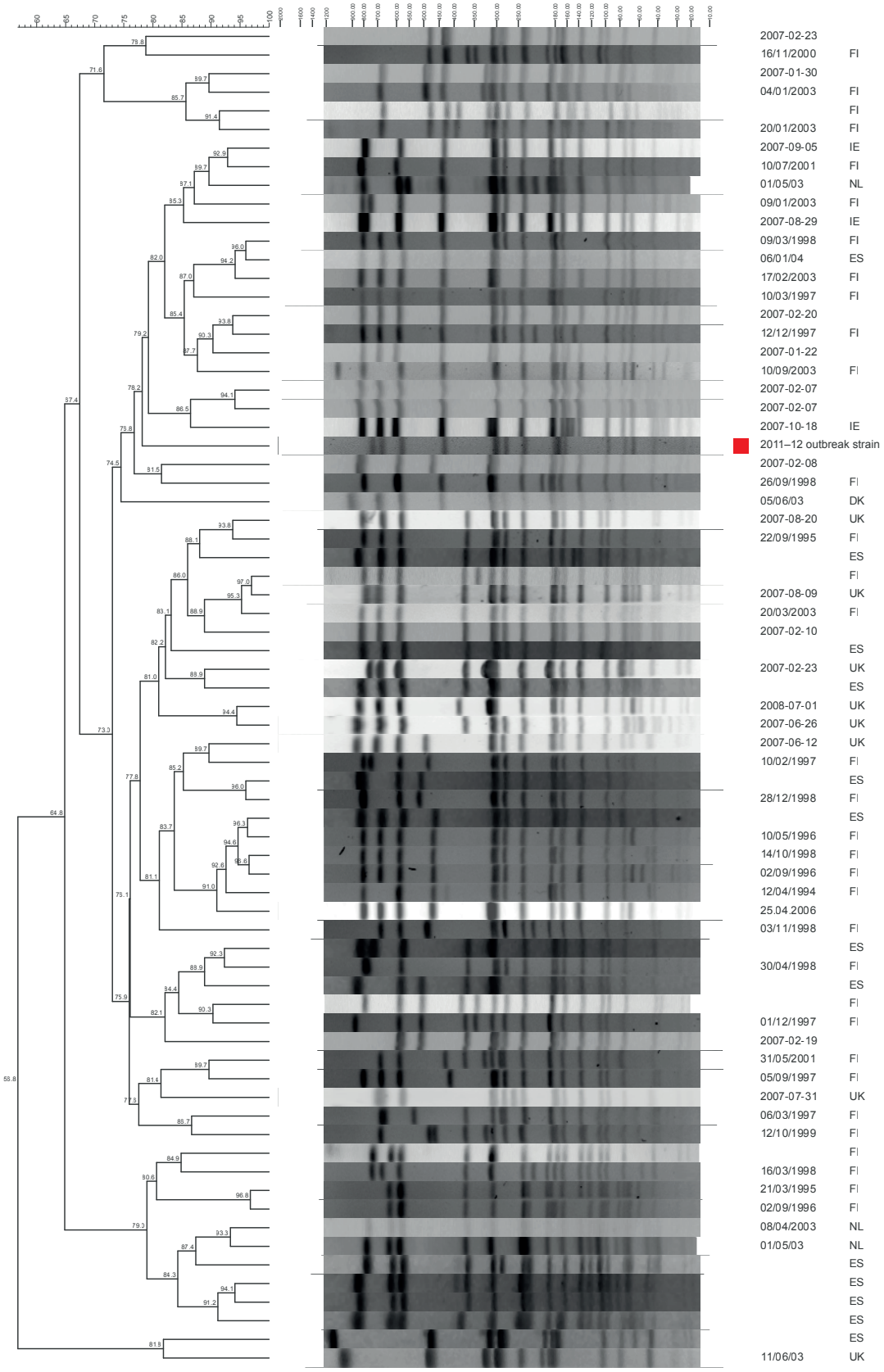
A total of 102 of 112 (91%) isolates from animals, food, feed and environment were related to the turkey industry (Table). Of these 102 isolates, 20 were from turkey and turkey fattening flocks, 50 were from turkey meat or turkey-containing products originating from eight EU countries, one was from feed (consisting of turkey by-products) for fur animals and 31 were from environmental samples. The seven non-turkey-containing food products containing isolates with the outbreak profile included poultry and beef. Turkey hatcheries and turkey farms were the origin of 31 of the 33 indistinguishable environmental isolates.

Discussion

This is the first reported multicountry food-borne outbreak of *S.* Stanley infection in the EU. More than a third of EU countries were affected between 2011 and 2012. Multisectoral investigation of the incidence and distribution of the outbreak resulted in strong evidence pointing towards the turkey production chain and confirming the emergence of a new microbial clone within the EU. The PFGE typing with a second enzyme supported this conclusion. The strong microbiological evidence for turkey being the main infection source was supported by food and animal investigations, most particularly the temporal correlation between the emergence of *S.* Stanley in the turkey production chain before the outbreak in humans and identification of the outbreak strain in a batch of turkey meat consumed by two cases in Hungary.

Figure 4

Dendrogram showing the similarity relationships of the 2011–12 European Union *Salmonella* Stanley outbreak strain among the different *Xba*I-PFGE types of *S.* Stanley isolates in the PulseNet Europe surveillance database (1994–2008)



DK: Denmark; ES: Spain; FI: Finland; IE: Ireland; NL: the Netherlands; PFGE: pulsed-field gel electrophoresis; UK: United Kingdom.

The *Xba*I-PFGE pattern of the 2011–12 European Union outbreak strain is marked with a red box.

The dendrogram was created with Bionumerics, with tolerance and optimisation set at 1.5%. Analysis of the pattern variation within the clusters was reassessed setting the optimisation and tolerance thresholds at 1%.

Table

Source of isolation of *Salmonella* Stanley isolates with an *Xba*I-PFGE profile indistinguishable from that of the European Union 2011–2012 outbreak strain (n=346, aggregated data)

Source of isolation	Number of Isolates
Human	**234**
Animal (boot swabs)	**21**
Turkey (undefined flock type)	12
Turkey fattening flock	8
Unknown	1
Food	**57**
Turkey	48
Turkey and beef	2
Chicken	2
Poultry	1
Other meat	4
Feed	**1**
Turkey-containing fur-animal feed	1
Environment	**33**
Turkey hatchery/farm (floor)	18
Turkey hatchery (breeding machine)	9
Turkey hatchery/farm (undefined)	4
Other (dishcloth and refrigerator)	2
Total	**346**

PFGE: pulsed-field gel electrophoresis.

Challenges in investigating a potentially widely distributed food source

This outbreak highlights the challenges in detecting and investigating food-borne events when contamination occurred early in the animal production chain, resulting in multiple vehicles of infection, contaminated over a long time period. Breaches in correct food handling resulted in sporadic cases and limited point-source community outbreaks in several countries.

Due to early contamination of the turkey production chain, subsequent cross-contamination of other foodstuffs may have occurred. Therefore, positive findings in other food items (e.g. broiler meat and beef) are expected and do not contradict the main conclusion of a contaminated turkey meat production chain being the primary source of infection.

Standard questionnaires for affected countries did not allow the identification of a specific food item as a common exposure for cases. The questionnaires were completed by 4% (11/246) of cases in Hungary and were not used in Austria, two countries with 61% (n=436) of all 710 cases; therefore, their representativeness was low. The development of the questionnaires was complicated by the sheer variety of meat choices, including national food specialties, within and between affected countries. Because of typing and reporting delays, many cases were interviewed long after their illness, increasing recall bias. Additionally, previous experience from a *Salmonella* outbreak in Germany suggested that assessment of turkey meat consumption using food consumption surveys is difficult, especially when the meat was in a composite food or labelled as 'poultry' (C Frank, personal communication, August 2012). These factors make it unlikely that a traditional case–control study at EU level would have provided strong epidemiological evidence. In such outbreaks, carefully performed retrospective analytical epidemiological studies on point-source sub-outbreaks would be more efficient in gathering epidemiological evidence. Detailed investigation, including analysis of recipes, shopping bills or loyalty card records may be effective additional tools if cases are identified and interviewed in a timely manner [6,13,14].

The distribution of the cases in the Flemish region of Belgium was surprising. Most likely this reflects different eating habits or food distribution channels between Flemish- and French-speaking Belgium. This epidemiological characteristic could not be further investigated as it would have required intense trace-back, which was not possible at the time.

The added value of molecular typing for outbreak investigation has been discussed previously [15,16]. The standard PulseNet PFGE method is still the gold standard molecular typing method for *Salmonella* isolates. In spite of PFGE being laborious, taking two to three days, and the quality being dependent on equipment and technicians' skills, the PFGE testing was not a limiting factor for implementation of control measures. However, the lack of an integrated PFGE typing database for human and non-human *Salmonella* isolates required time-consuming coordination efforts at EU level. Therefore, further work is needed to allow rapid comparison of PFGE patterns across laboratories.

Antibiotic resistance data provided supportive evidence during the investigation. The resistance profile was not included in the case definition due to variations in national testing panels and methods, as well as different interpretive standards for testing human and animal isolates, which precluded comparability.

This outbreak demonstrates the complexity of defining triggers for implementation of control measures. How much evidence is needed to incriminate vehicles/sources and launch appropriate control measures that could have positive protective public health effects but also financial consequences? At the European level, the role of ECDC and EFSA as risk assessment agencies is to provide all available evidence and critical analysis for risk managers at national and EU level so that appropriate control measures can be implemented. Feedback from risk managers on the implemented control measures supports the risk assessors in their continuous assessment of the event. Indeed, coordination of trace-back and trace-forward activities during large and complex multicountry outbreaks is crucial. This need was also underlined during a simulation exercise

in May 2013 attended by representatives from the public health and food safety sector from 29 EU/EEA countries, Croatia, Switzerland and Turkey, EU agencies, Health Security Committee Communicators' Network communication specialists, the European Commission's Directorate-General for Health and Consumers (DG SANCO) and the World Health Organization Regional Office for Europe [17].

The 2003 regulation of the European Parliament and Council and its implementing provisions requires countries to monitor *Salmonella* serovars of public health relevance in breeding hens, laying hens, broilers and turkeys in the EU [18]. Results must be known before slaughter to permit appropriate measures that reduce consumers' exposure. Although EU targets for the reduction of *Salmonella* in turkey flocks are set up for *S.* Enteritidis and *S.* Typhimurium only [19], control measures such as biosecurity measures at farms and hygiene at slaughter are common to all serovars [19]. Therefore, control of *Salmonella* contamination in turkey flocks should result in the control of *S.* Stanley. In 2013, the number of human cases reported in the EU decreased compared with the outbreak's peak in 2012, but was still higher than that observed in 2009 and 2010 [20] More recently, two outbreaks of infection with the *S.* Stanley outbreak strain were reported by Germany (December 2013) and Austria (April 2014): both were due to consumption of contaminated turkey meat [20]. This may indicate that *S.* Stanley is still circulating in the turkey production chain in some EU Member States in 2014.

Future directions

For this outbreak, a joint ad hoc molecular typing database for comparison of human, animal, food and environment isolates was established at EU level. ECDC has upgraded TESSy and EPIS-FWD with a capacity to collect and analyse molecular typing and epidemiological data to facilitate the rapid detection of emerging clones and dispersed food-borne outbreaks in humans. At present, the pilot project includes reporting of PFGE for *Salmonella* spp., Shiga toxin-producing *Escherichia coli* and *Listeria monocytogenes*, as well as multiple-locus variable-number of tandem repeats analysis (MLVA) data for *S.* Typhimurium. EFSA, in collaboration with relevant European reference laboratories, is establishing similar molecular typing data collection for isolates from food and animal sources. This outbreak of *S.* Stanley infection demonstrated the importance of agreeing on the use of comparable molecular typing methods in both sectors.

A new version of EPIS-FWD was launched in July 2013. It links to TESSy and so facilitates assessment of clusters detected though molecular surveillance of human isolates. The new platform also allows food and veterinary experts to be invited to join designated discussions, to promote the intersectoral sharing of operational information [7].

Following this outbreak, ECDC, EFSA and the European Commission have been jointly developing procedures to ensure coordinated investigation and cross-sector data exchange. ECDC's *Toolkit for investigation and response to food and waterborne disease outbreaks with an EU dimension* provides material for public health investigators that also aims to aid coordination of such outbreak investigations in Europe [21]. The outbreak investigation reported here highlights the importance of timely submission of molecular typing data. Routine molecular typing and the prospective analysis of these data on a European level can facilitate early outbreak detection, more efficient outbreak investigation and influence intervention decisions. The European Commission has also initiated extensive training within the 'Better training for safer food' programme [22], aiming at training multidisciplinary teams to investigate food-borne outbreaks.

Conclusions

The PFGE pattern of the outbreak strain was new and emerged in 2011 in the EU. As the outbreak was noted among persons without travel history outside the EU, exposure to contaminated vehicles presumably took place in the EU. The temporal distribution of cases indicated gradual spread and transmission originating from persistent common sources. The broad geographical distribution of cases and non-human isolates suggests contamination of widely distributed products in several EU countries.

Comparison of PFGE profiles from human, veterinary and food isolates pointed towards a common source: the turkey production chain. The emergence of *S.* Stanley isolates in animals and food preceded the large increase in the number of human cases by less than a year and emergence took place mostly within turkey production. Identification of the outbreak strain in turkey meat at farm, factory and fork level in a number of countries confirms that the contamination occurred early in the animal production chain.

This outbreak investigation was complex, highlighting the difficulties in performing coordinated multicountry investigations from farm to fork. Early collaboration across public health, veterinary and food sectors in a One Health approach will help the EU's reactivity to future multicountry outbreaks, for timely implementation of control measures.

Acknowledgments

We would like to acknowledge all national public health, food safety and veterinary institutes and laboratories in the affected Member States for their active participation in the international investigations; Rita Prager from the National Reference Centre for *Salmonella* and other Bacterial Enteric Pathogens in Germany for performing the PFGE typing and Christina Frank from the Robert Koch Institute for providing epidemiological data for Germany; ECDC surveillance team for providing background data from TESSy; ECDC GIS Team for providing the map; EPIET fellows in Austria, Belgium and Hungary for developing and piloting the EU trawling questionnaire.

Conflict of interest

None declared.

Authors' contributions

All authors have participated to the multicountry investigations and provided either epidemiological or microbiological or other food related information contributing to the response to the event. All authors have reviewed and provided substantial comments to the article.

Pete Kinross, Lieke van Alphen, Jaime Martinez Urtaza, Marc Struelens, Johanna Takkinen, Denis Coulombier and Céline Gossner (leader) were part of the ECDC outbreak response team which coordinated the investigations at the EU level.

Pia Mäkelä provided data collected by EFSA and its analysis. She also supported the collection of PFGE from food, animal and environmental samples.

Sophie Bertrand and Wesley Mattheus provided information for Belgium and posted the initial alert in EPIS-FWD; Daniela Schmid, Elisabeth Kanitz and Verena Rücker provided information for Austria; Katalin Krisztalovics, Judit Pászti, Zsuzsanna Szögyényi and Zsuzsanna Lancz provided information for Hungary; Wolfgang Rabsch, Beatrice Pfefferkorn and Petra Hiller provided information for Germany.

Kirsten Mooijman supported the collection of PFGE from food, animal and environmental samples.

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Investigating an outbreak of *Clostridium perfringens* gastroenteritis in a school using smartphone technology, London, March 2013

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On 22 March 2013, 150 of 1,255 students (13–17 years) and staff at a school in London reported gastrointestinal symptoms; onset peaked 8 to 12 hours after a lunch served in the school on 21 March. We performed a retrospective cohort study of all students and staff. We defined cases as school attenders on 20 and 21 March with onset of gastrointestinal symptoms between 20 and 23 March. We tested food, environmental and stool samples of cases for common pathogens and bacterial toxins. We administered an online questionnaire via email, encouraging the use of smartphones to respond, to measure risk of illness for food items eaten at school on 20 and 21 March. Survey response was 45%. Adjusted risk ratios were generated in a multivariable analysis. Those who ate chicken balti on 21 March were 19.3 times more likely to become ill (95% confidence interval: 7.3–50.9). *Clostridium perfringens* was detected in all 19 stool samples collected. Within eight school hours of its launch, 412 of 561 (73%) responders had completed the survey. Hygienic standards in the kitchen were satisfactory. The investigation was done rapidly due to smartphone technology and we recommend considering this technology in future outbreaks.

Introduction

The incidence of *Clostridium perfringens* food poisoning presenting to general practice is estimated to be 0.24 per 1,000 persons per year in England and Wales [1,2]. Between 1992 and 2008, *C. perfringens* was identified as the cause of 10% of food-borne outbreaks [2].

C. perfringens causes a mild and short-lived gastrointestinal illness characterised by sudden onset of abdominal pain (80% of cases) followed by diarrhoea (>90%) [3,4]. The incubation period is usually 12 to 18 hours (range: 8 to 22 hours) [3,4]. Illness is due to an enterotoxin produced by *C. perfringens* type A strains [5]. Outbreaks often have a high attack rate and are usually associated with mass catering and a failure of adequate food preparation procedures, including inadequate cooking or inappropriate temperature control of food after initial cooking [6-8]. Meat, meat products and poultry are commonly implicated with inadequate cooking or storage allowing growth of vegetative cells [9,10].

The outbreak we describe involved a secondary school (for children aged 13 to 18 years) in London, with 358 staff members and 897 students. On Friday 22 March 2013 the local Health Protection Unit was notified that 53 students and 32 staff were ill with abdominal pain and diarrhoea. The onset of illness for the majority of cases was reportedly during the evening of Thursday 21 March and the early hours of Friday 22 March. All cases, both students and staff, appeared to have eaten lunch in the school dining hall at least once in the two days before becoming unwell.

On Friday 22 March, an outbreak control team (OCT) was convened to investigate the outbreak. Our investigation aimed to determine the size and nature of the outbreak, to determine the cause, to identify any factors associated as well as to recommend control measures to this outbreak and to prevent any recurrence in future.

Methods

Epidemiology

The study population was the staff and students at the school. The study design was a retrospective cohort study, including all students and staff (cleaning, teaching and kitchen staff) attending the school on

Wednesday 20 and/or Thursday 21 of March 2013. We defined a case as any student or member of staff with onset of gastrointestinal symptoms (any one of the following: diarrhoea, abdominal pain, nausea, vomiting) between 20 and 23 March 2013.

We developed an online structured questionnaire using SelectSurvey, an online commercial software used by Public Health England to develop surveys. A link to the questionnaire was distributed to all students and staff, after piloting, on Wednesday 27 March via email. All students and staff have school email accounts and the school uses these as the main route of communication between staff, students and the school senior management team. The questionnaire was also announced on the school's intranet site with a link.

We excluded those (i) with onset of gastrointestinal symptoms (as described above) in the seven days before 20 March, or (ii) who had a household member with gastrointestinal symptoms in the seven days before 20 March.

We described cases and compared risk of illness for various food items using risk ratios (RR) and 95% confidence intervals (CIs) and Fisher's exact test. We tested the association between eating the various food items and the risk of becoming ill subsequently (for example, in the analysis of exposure to food items eaten on 21 March, we excluded the cases with onset on 20 March). We did not consider in the analysis students or staff who had not attended school on that day.

We calculated attack rates for exposure to each food item on the overall number of responders for the question relative to that specific food item. We applied a robust Poisson multivariable analysis which included variables significantly associated with the occurrence of illness ($p<0.15$) to provide an adjusted risk ratio (95% CI). We chose the best model using the likelihood ratio test.

The questionnaire was structured so as to allow responders to report how much of each food item they had eaten (none, less than a portion, one standard portion, more than one portion). We analysed dose–response effect and tested the p value for interaction among strata with the likelihood ratio test.

Finally, we analysed the timing of responses to our questionnaire survey. All analyses were performed using Microsoft Excel and Stata 12.0.

Microbiology

We collected stool specimens on Friday 22 March from the 19 symptomatic cases who were available because they presented to the school's general practitioner (GP). We requested the GP to obtain samples from them and send them to the Public Health England Public Health Laboratory London, the designated laboratory for the outbreak investigation. Specimens were tested for a range of organisms, including *Campylobacter, Salmonella, Shigella, Escherichia coli o157, Staphylococcus aureus, C. perfringens, Bacillus cereus*, norovirus, adenovirus, astrovirus, sapovirus and rotavirus. The specimens were also tested for the presence of *C. perfringens* enterotoxin at the Public Health England Laboratory of Gastrointestinal Pathogens.

Environmental analysis

We conducted a kitchen inspection at the school on Monday 25 March. Detailed information was collected on the preparation, storage and transportation processes for the food, especially those dishes served at the school at lunch on Wednesday 20 March and Thursday 21 March. A sample of rice served on 21 March which had been kept refrigerated by the catering company was collected and analysed. A further visit on 26 March was made the following day to take hygiene control swabs, further review temperature recording charts for the main cooking pans and to take temperatures at various points in the main cooking pans while food was cooking. Food samples were collected from some of the herbs and spices used in cooking on 20 and 21 March (fresh mint, nigella seeds, dried oregano and ground cumin). On 28 March, samples of cinnamon, salt, black pepper, dried turmeric, dried star anise and coriander seeds were also collected. Other relevant foods were unavailable for sampling.

The rice sample was tested for Enterobacteriaceae, *E. coli, Salmonella, Listeria, S. aureus, C. perfringens* and *Bacillus* sp. The herbs and spices were tested for *E. coli, Salmonella* and *C. perfringens*.

Results

We received responses from 561 of 1,255 (45%) overall, of whom 398 of 897 (44%) were students and 163 of 358 (46%) were staff. We excluded 42 (7.5%, 30 students and 12 staff) based on the criteria described above. The overall attack rate was 19% (100/519) and was 16% and 27%, respectively, in students and staff ($p=0.006$). Attack rates were comparable among different staff groups (teaching, catering, cleaning, support staff; $p=0.228$).

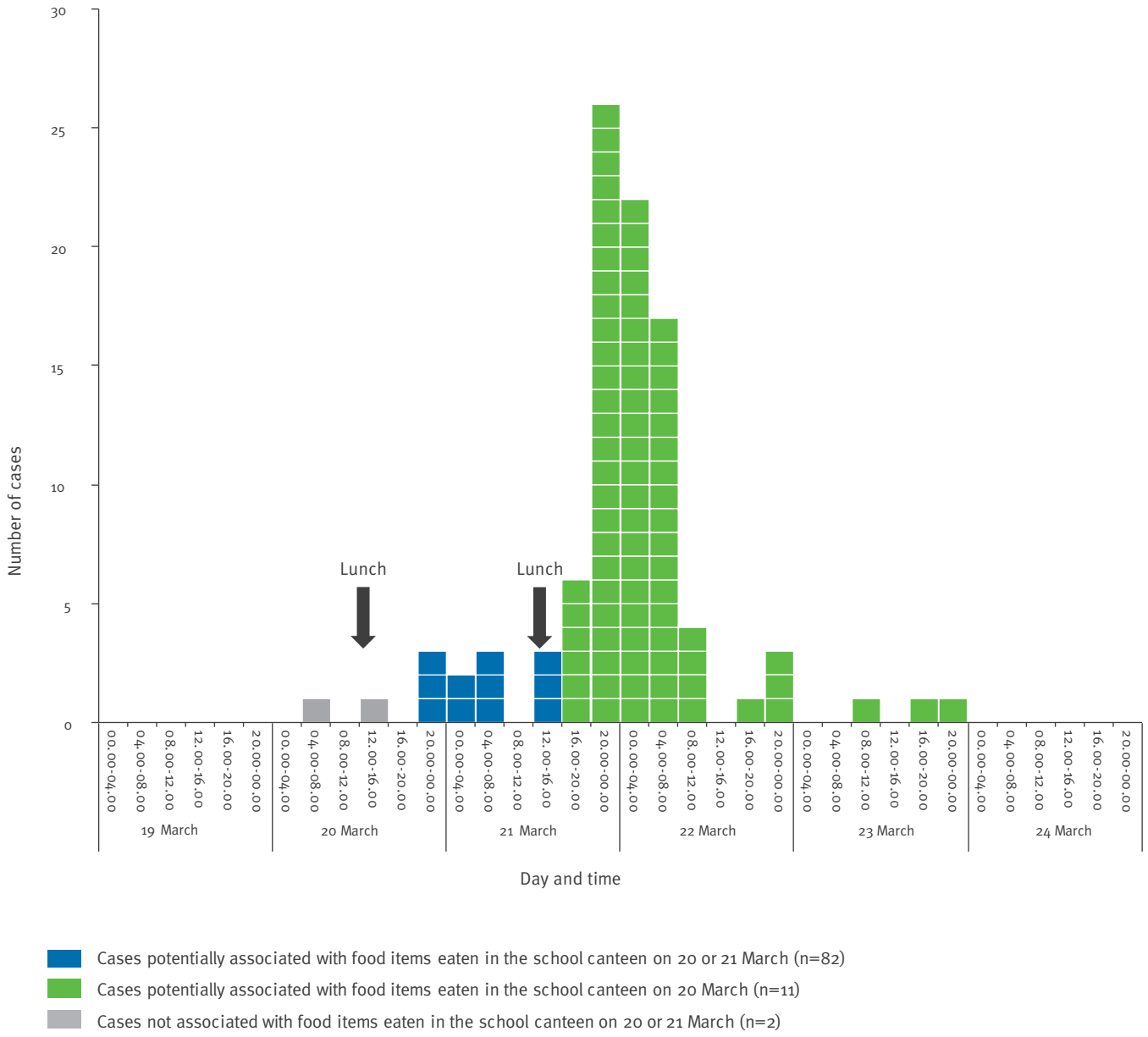
The majority of cases were ill between 16:00 on Thursday 21 March and 8:00 on Friday 22 March, with a peak at 8 to 12 hours after the lunch on 21 March (Figure 1).

The most frequently reported symptoms were diarrhoea, abdominal pain and nausea (90/100, 75/100 and 36/100, respectively); seven reported fever and three reported bloody stools. Symptoms were short-lived. Seventy-one of 100 cases reported symptoms for one day or less.

We had precise times of onset for 95 cases. Of these, two occurred before the lunch served on Wednesday 20 March (in grey in Figure 1), hence we only considered

Figure 1

Epidemic curve, *Clostridium perfringens* gastroenteritis outbreak, London, March 2013 (n=95[a])



[a] Precise time of onset was known for 95 of 100 cases.

the other 93 as potentially associated with the lunch served on 20 March (in blue and green in Figure 1). Those who had eaten in the school dining hall on 20 March were 2.5 more likely to be ill than those who had not (RR=2.5, 95% CI: 1.1–5.3, data not shown). No particular food item served on 20 March, however, was strongly associated with illness in the univariable analysis.

Ten cases had an onset after the lunch served on Wednesday 20 March and before the lunch served on Thursday 21 March (in blue in Figure 1), hence we only considered the remaining eighty-three cases as potentially associated with the lunch served on 21 March (in green in Figure 1). Overall, 425 of 435 responders declared that they had attended school on that day, and 10 responders declared that they had not. Eating in the canteen was strongly associated with increased risk of illness (p=0.001). All the cases with onset after the lunch on the 21 had eaten in the canteen that day (attack rate: 100%).

Those who ate chicken balti on 21 March were 16 times more likely to be ill (RR=15.9; 95% CI: 8.2–30.6) than those who did not, and those eating items served with the chicken (raw red onions, tomatoes and coriander

Table 1

Relative risk of illness (and 95% confidence intervals) for food items served on Thursday 21 March at school, *Clostridium perfringens* outbreak in a secondary school, London, March 2013 (n=425)

	Exposed			Not exposed			RR	95% CI	p value
	Cases	Non-cases	AR %	Cases	Non-cases	AR %			
Went to dining hall	**76**	**292**	**20.7**	**0**	**52**	**0.0**	**n.c.**	**n.c.**	**<0.001**
Ate at the dining hall	**76**	**284**	**21.1**	**0**	**58**	**0.0**	**n.c.**	**n.c.**	**<0.001**
Soup and Main course options									
Mushroom soup	**14**	**27**	**34.2**	**48**	**238**	**16.8**	**2.03**	**1.24–3.35**	**0.008**
Sliced bread	10	32	23.8	54	231	19.0	1.26	0.70–2.27	0.458
Beef lasagne	8	113	6.6	55	164	25.1	0.26	0.13–0.53	0.000
Vegetarian chili	0	15	0.0	63	244	20.5	0.00	n.c.	0.050
Chicken balti	**64**	**41**	**61.0**	**9**	**225**	**3.9**	**15.85**	**8.20–30.62**	**<0.001**
Coriander rice	**54**	**43**	**55.7**	**14**	**219**	**6.0**	**9.27**	**5.41–15.87**	**<0.001**
Jacket potato, fillings and pasta bar									
Jacket potato	1	27	3.6	63	236	21.1	0.17	0.02–1.18	0.026
Pasta (on pasta pod)	4	58	6.5	59	205	22.4	0.29	0.11–0.76	0.004
Baked beans	2	14	12.5	62	243	20.3	0.61	0.17–2.29	0.445
Tuna	1	12	7.7	62	248	20.0	0.38	0.06–2.56	0.273
Cheese topping	2	54	3.6	62	207	23.1	0.15	0.04–0.61	0.001
Tomato sauce	1	12	7.7	62	244	20.3	0.38	0.06–2.53	0.265
Salad bar									
Lettuce	6	33	15.4	58	230	20.1	0.76	0.35–1.65	0.482
Tomatoes	4	25	13.8	60	236	20.3	0.68	0.27–1.74	0.403
Cucumber	3	30	9.1	60	230	20.7	0.44	0.15–1.32	0.111
Hummus	3	9	25.0	60	248	19.5	1.28	0.47–3.51	0.637
Carrots	0	17	0.0	62	242	20.4	0.00	n.c.	0.038
Celery	0	8	0.0	63	250	20.1	0.00	n.c.	0.157
Desserts and fruit									
Peach crumble	24	89	21.2	41	175	19.0	1.12	0.71–1.75	0.625
Custard	16	50	24.2	47	208	18.4	1.32	0.80–2.17	0.289
Orange jelly	3	13	18.8	61	247	19.8	0.95	0.33–2.69	0.918
Lime jelly	2	10	16.7	61	254	19.4	0.86	0.24–3.11	0.816
Strawberry jelly	1	8	11.1	62	251	19.8	0.56	0.09–3.61	0.517
Yoghurt	7	22	24.1	55	242	18.5	1.30	0.66–2.59	0.462
Mango coulis	**5**	**5**	**50.0**	**58**	**253**	**18.7**	**2.68**	**1.38–5.20**	**0.014**

AR: attack rate; CI: confidence interval; RR: risk ratio; n.c.: not computable.
Individuals who did not attend school on that day were excluded.

rice), as well as soup and mango coulis were also more likely to be ill (Table 1). When asked whether they had eaten any chicken, 64 cases (77%) reported they ate chicken, nine reported they had not, and 10 did not respond.

In the multivariable analysis the only risk that remained was for chicken balti, with those eating it 19 times more likely to be ill, taking account of the other variables (Table 2).

We found a strong dose–response effect for eating increasing amounts of chicken balti. The RR of illness went from 14.5 among those who reported eating less than one portion of chicken, to 19.2 among those who had a standard portion, up to 23.1 among those who had more than one portion (p for interaction <0.001; Table 3) after adjusting for the other food items considered in the multivariable model.

Finally, we found that 73% of the questionnaires (412/561) were completed during school hours on the day the survey was launched (Figure 2).

No new cases were reported after 23 March. By Monday 25 March, only nine students and one kitchen staff were still off sick, and by Thursday 28 March, symptoms had resolved in all those affected, and all had returned back to school or work.

All 19 stool specimens tested positive for *C. perfringens*. Isolates from 18 of 19 patients were found to have the enterotoxin gene, and all 18 enterotoxigenic isolates were undistinguishable by molecular typing (fAFLP CLP.39), which was indicative of a common

Table 2

Multivariable analysis showing final model and relative risk of illness for food items, *Clostridium perfringens* outbreak in a secondary school, London, March 2013 (n=425)

Food item	RR	95% CI	p value
Chicken balti	**19.32**	**7.33–50.89**	**<0.001**
Mango coulis	1.40	0.94– 2.08	0.095
Mushroom soup	0.89	0.58– 1.36	0.591
Coriander rice	1.02	0.56– 1.85	0.953

CI: confidence interval; RR: risk ratio.

source. Seventeen stool specimens also tested positive for *C. perfringens* enterotoxin. No other pathogens were detected in the stool samples.

On kitchen inspection, there was no evidence of poor hygiene or poor temperature control during the preparation of food. The temperatures of the pans used for cooking were reviewed and found to be satisfactory. The kitchen's logbooks for temperature recordings from the pans for Wednesday 20 and Thursday 21 March were reviewed and also found to be satisfactory.

No pathogens were isolated from the food samples examined (rice, herbs and spices). The hygiene control swabs were negative for *E. coli, Salmonella* and Enterobacteriaceae.

Discussion and recommendations

We found that eating chicken balti was the likely cause of this outbreak of *C. perfringens* in a large secondary school in London. Microbiological analysis confirmed that *C. perfringens* was the causative organism in this outbreak. We could not establish what factors may have contributed, as environmental investigations revealed satisfactory processes and procedures. The kitchen inspection and the review of the cooking pan temperature recordings revealed no evidence of poor hygiene or poor temperature control during the preparation of food. An inadequate temperature control of food after initial cooking may have contributed to this outbreak.

One of the main challenges in this investigation was the lack of appropriate food samples from food items served at the school on Wednesday 20 March and Thursday 21 March. Although it was not possible to conclusively identify underlying factors contributing to the outbreak, the epidemiological study was very useful to pinpoint the cause of the outbreak as the chicken balti dish.

The chicken balti was prepared on Thursday 21 in the morning. The chicken, which was delivered fresh on the same morning raw and pre-diced from the suppliers, was fried in a big kitchen pan with vegetables and sauce ingredients on the premises. It was kept hot in the pan until serving, and subsequently placed on the hot counter of the dining hall for serving. The garnish, including raw red onion, tomato, fresh coriander and nigella seeds, was added on top of the chicken balti before serving. Once serving started, the garnish would have mixed in with the chicken balti and it would have been unlikely that the two items would have been eaten separately.

Chicken was the likely source of the outbreak, as is often the case with *C. perfringens* outbreaks [5]. However, *C. perfringens* can also be found in spices and herbs sampled from production and retail premises in the United Kingdom [11-13]; spices and herbs have been linked to food poisoning outbreaks in the past [11]. The garnish, therefore, cannot be ruled out as the potential vehicle of the outbreak. The fresh coriander, in particular, was not available for sampling. The nigella seeds tested negative for *C. perfringens*.

We limited our investigation to the food items eaten in the school canteen on 20 and 21 March. From the information received from the school, we knew that the outbreak came from a point source, had an extremely rapid onset and symptoms were short-lived. This directed our suspicions towards a bacterial toxin or a

Table 3

Relative risk of illness associated with increasing amount of chicken balti eaten, *Clostridium perfringens* outbreak in a secondary school, London, March 2013 (n=339)

	Cases	Non-cases	AR %	RR[a]	(95% CI)
I did not eat chicken balti	9	225	3.8	1	Reference
I had a few mouthfuls	6	6	50.0	14.47	4.49–46.58
I had a standard portion	45	30	60.0	19.17	7.19–51.14
I had more than a standard portion	13	5	72.2	23.12	8.56–62.49

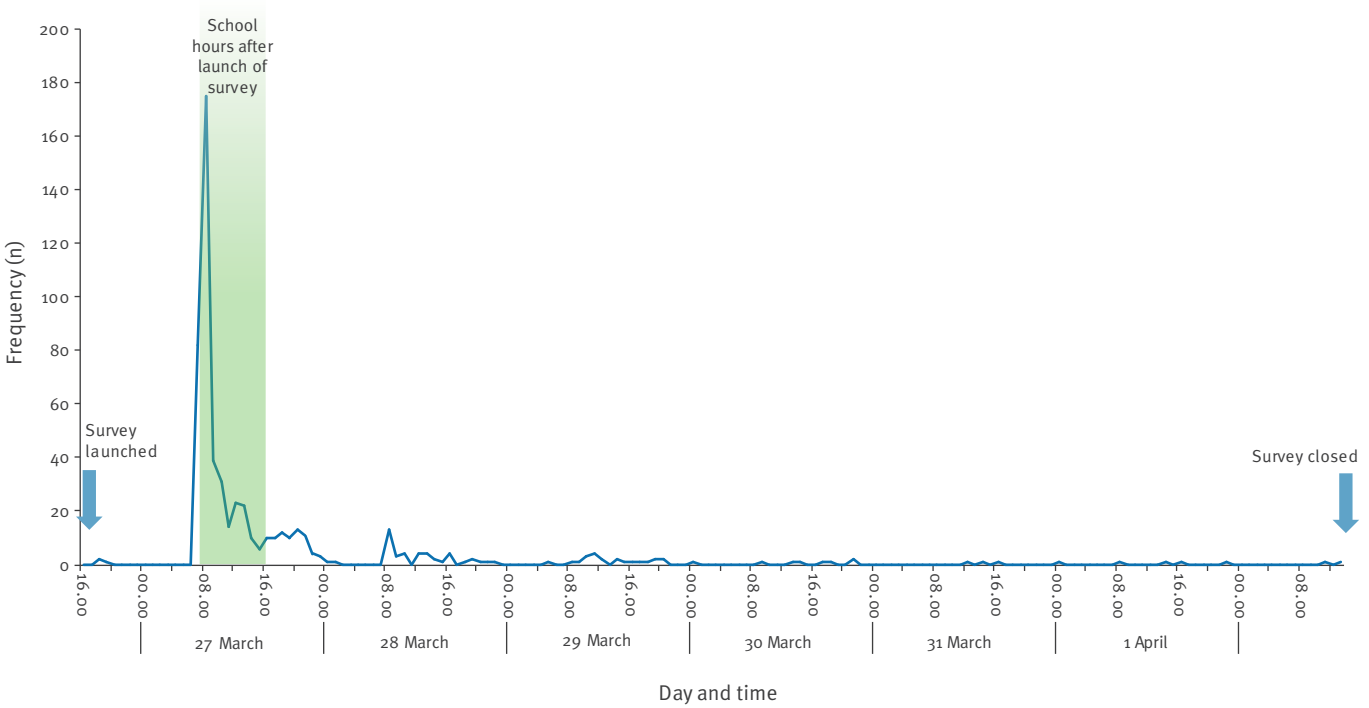
p value for interaction[b] <0.001.

AR: attack rate; CI: confidence interval; RR: risk ratio.

[a] RR adjusted by consumption of nigella seeds, coriander, mango coulis, beef chili topping and vegetarian chili.
[b] By likelihood ratio test.

Figure 2

Date and time of response to survey questionnaire: outbreak of *Clostridium perfringens* in a secondary school, London, March 2013 (n=561)



viral infection, all with short incubation periods. We felt that investigating food items eaten in the canteen over two days back in time would have rendered the questionnaire unnecessarily long, hindering response rates. We also considered that those responses would have been subject to considerable recall bias.

Our case definition included illness occurring on 20 March, and we did observe five cases who were ill on that day and eight who were ill during the evening or early hours of morning before the lunch on 21 March (Figure 1). We can speculate that respondents were ill for other reasons or that they recalled the days incorrectly. It is also possible that some of the food items consumed on 20 March might have been cross-contaminated in the kitchen by food to be served on 21 March. This notion is strengthened by the fact that one of the 19 positive faecal specimens came from a student who had been ill in the morning of Thursday 21 March and the strain isolated from this specimen was the same as that isolated from all the other specimens. This makes it highly unlikely that this early case was unrelated to the outbreak. It is also unlikely that this, or any other of the early cases, were responsible for contaminating the food. Students do not come in contact with food until it is served at the counter by catering staff. None of the catering or cleaning staff were ill before the afternoon of 21 March.

The strength of the outbreak investigation was defined by the rapidity required for the public health response and coordination across multiple organisations. The weakness of the investigation was the retrospective nature of the kitchen inspection which provided a limited picture of the food transport, storage and preparation processes that occurred on site on a specific day. A key strength was the speed with which the outbreak control team was set up and a meeting organised on the afternoon of Friday 22 March. This occurred within 60 minutes of the outbreak being notified to the local Health Protection Unit. In addition, the prompt collection of stool samples on Friday afternoon provided a rapid microbiological diagnosis.

An interesting aspect of the investigation has been the high rate of completion of the questionnaires using smartphones. Figure 2 shows how almost three quarters of the questionnaires were completed during school hours on the day the survey was launched. Currently, however, the tool we use to develop questionnaires does not have templates to build surveys specifically for smartphones, and responders had to scroll and zoom the questions on their phones in order to complete it. The survey could have been made more accessible and readable to the responders if a specific tool to develop questionnaires for smartphones had been available.

It would have been useful to have a question in the survey asking which device participants had used to complete the questionnaire. This is a limitation of the study. Anecdotal evidence, however, suggested that the majority of participants had used smartphones. No laptops or tablet computers are allowed in the school

for security reasons, and the Deputy Head reported to us that teachers had observed the students completing the questionnaires on their phones during lesson time and break time. The school has computer rooms, but they are supervised by teachers and are only open for private use at lunch time and after school. Our analysis showed that most questionnaires were completed in the morning. The teachers reported that approximately 30 to 40 students overall used the computer room on 27 March.

Our previous experience with similar school outbreaks is that it is very difficult to achieve a good response rate, and the process of data collection can take days and several reminders. This delay increases the potential for recall bias among late responders and reduces the possibility of setting up public health interventions. In the outbreak presented here, no reminders were necessary, and the responses collected in one day were sufficient to identify the cause of the outbreak.

This investigation evidenced the need of an assessment of smartphone technology, and of other technologies, as a data collection tool in outbreak settings. Survey participants use a range of devices to complete online questionnaires. Which device is being used is an important question that should be included, to assess which data collection tools and devices perform best under different outbreak circumstances and settings.

In view of the fact that we could not find any issues with the kitchen or the food preparation, but given that poor food preparation practices are the contributing factor in the majority of *C. perfringens* foodborne outbreaks [2], we felt it was still worthwhile recommending to the school/catering company (i) reviewing standards and procedures to ensure adequate heat penetration in bulk cooking processes and adequate temperature control of food after initial cooking, and (ii) reviewing the preparation, storage and serving of raw garnishes.

Our main recommendation for the Health Protection Agency (as of 1 April 2013 Public Health England) and other health agencies is to explore opportunities for using smartphone technology for distributing questionnaires. There is evidence that smartphones are being used for data collection and surveillance purposes with good effect [14,15]. As many people now have access to mobile devices such as smartphones this would provide an alternative distribution channel for questionnaires which may improve the speed and completeness of response rates in future epidemiological studies.

Finally, we recommend an assessment of the validity of different data collection tools, including smartphones, in different outbreak settings.

Conflict of interest

None declared.

Authors' contributions

Benedetto Simone and Christina Atchison conducted the epidemiological investigation and wrote the manuscript; Barbara Ruiz and Paul Greenop conducted the environmental investigation and contributed to the manuscript development; Jayshree Dave and Derren Ready conducted the microbiological investigation and contributed to the manuscript development; Helen Maguire contributed to the manuscript development; Barry Walsh and Sarah Anderson led the outbreak control team and supervised the manuscript development.

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Long-term control of carbapenemase-producing Enterobacteriaceae at the scale of a large French multihospital institution: a nine-year experience, France, 2004 to 2012

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In 2009, following the occurrence of several outbreaks of carbapenemase-producing Enterobacteriaceae (CPE), a programme for controlling the spread of CPE was implemented in the 38 hospitals of the Assistance Publique-Hôpitaux de Paris, a 21,000-bed institution. This programme included recommendations to isolate, and screen for CPE, patients previously hospitalised abroad, and bundled measures to control cross transmission (barrier precautions, dedicated staff and screening of contact patients). From 2004 to 2012, 140 CPE index cases were identified, 17 leading to outbreaks. After application of the programme, in spite of an increase in the number of CPE index cases epidemiologically linked with a recent stay or hospitalisation abroad, the proportion of cases followed by outbreaks, which was 40% (4/10) before 2009, decreased to 10% (13/130) (p=0.02), and the proportion of secondary cases among all CPE cases decreased from 69% (22/32) to 23% (38/168), (p<0.001). The number of secondary cases varied significantly depending on the speed and strength of the measures implemented around the CPE index case: quick (within two days of patient admission at the hospital) setting of nursing staff dedicated to the patient, quick setting of simple barrier precautions, or delayed measures of control (p=0.001). A sustained and coordinated strategy can lead to control CPE at the level of a large regional multi-hospital institution in a country where CPE are at an emerging stage.

Introduction

Carbapenemase-producing Enterobacteriaceae (CPE) are nowadays a major public health concern worldwide, since carbapenems represent the last line beta-lactam antibiotics for treating patients infected by multidrug resistant Enterobacteriaceae [1]. In 2011, the prevalence in European countries, as reported in percentage of carbapenem resistance among *Klebsiella pneumoniae*, varied significantly from high (e.g. >15% in Greece, Cyprus, or Italy) to extremely low (e.g. <1% in Nordic countries, United Kingdom, or Spain) [2]. High prevalence in *K. pneumoniae* and *Escherichia coli* has been recently reported in India and Pakistan and subsequently, a link between this high prevalence and the occurrence of CPE in hospitals in the United Kingdom has been demonstrated [3].

In France, resistance to carbapenems due to carbapenemases is so far uncommon among Enterobacteriaceae as shown by the European Antimicrobial Resistance Surveillance Network (EARS-net) [4]. Nevertheless, several outbreaks, the majority of which were limited in size, occurred in French hospitals in the past few years, most often involving patients with a history of hospitalisation abroad [5]. The first outbreak of CPE in France occurred in 2004, in one of the hospitals of Assistance Publique-Hôpitaux de Paris (AP-HP), the largest public health institution in France, and happened following the transfer of a patient from a Greek hospital [6]. This outbreak triggered the implementation of a long-term programme for surveillance and control of CPE in this institution. We describe here the results of this programme in AP-HP hospitals during a nine-year period, from 2004 to 2012.

Methods

Setting

AP-HP is a public health institution administering 38 teaching hospitals (22 acute care (AC) and 16

rehabilitation/long-term care (RLTC) hospitals, spread over Paris, suburbs and surrounding counties), with a total of 21,000 beds (10% of all public hospital beds in France) and serving 12 million inhabitants. AP-HP admits approximately one million inpatients per year, employs 22,000 physicians, 20,000 nurses and 30,000 assistant nurses. Local administrators and medical committees manage AP-HP hospitals, but decisions on large investments and medical developments are made by the central administration. In each hospital, a local infection control team (LICT) is in charge of prevention and surveillance of healthcare-associated infections, but decisions of foremost importance for the whole institution, e.g. multidrug resistance control programme, are coordinated by a multidisciplinary central infection control team (CICT), including one infectious disease physician, one bacteriologist, one epidemiologist and one nurse [7].

Case definitions

A case was defined as any patient infected or colonised with CPE. A contact patient was defined as any patient whose stay overlapped with the stay of a CPE case for at least one day in the same unit. An outbreak was defined as at least two CPE cases (i.e. one index case and at least one secondary case among the contact patients) occurring in a given hospital, with a clear epidemiological link (stay during the same period of time in the same unit) and involving indistinguishable CPE strain based on species, antibiotic susceptibility and carbapenemase enzyme. An event was defined as one index case, followed or not by secondary case(s).

Carbapenemase-producing Enterobacteriaceae control programme

In 2004, following the first CPE outbreak, every LICTs was asked to promptly report every new CPE case to the AP-HP CICT. For each CPE event, the following data were collected: the unit where the event occurred, the number of cases, the clinical status of the cases (infection or colonisation), the bacterial species and type of carbapenemase, the presence of an epidemiological link between the index case and a foreign country (any country outside France), and the nature of this link (e.g. direct transfer from a foreign hospital, previous hospitalisation abroad or previous stay abroad without hospitalisation, within the preceding year).

Moreover, for each CPE event, AP-HP CICT asked LICT to apply a bundle of measures to prevent cross transmission. These measures were based on the experience acquired to control the first CPE outbreak [6]:

i the day of CPE identification, barrier precautions around the CPE case had to be implemented; nursing staff, as far as possible, had to be dedicated to the case, the hospital administrator had to be alerted; transfers of the case and contact patients to other units of the hospital or to other hospitals had to be stopped; contact patients had to be screened for CPE by culturing rectal swabs;

ii the following days and until the discharge of index CPE case, CPE screening had to be extended to contact patients already transferred from the involved unit at the time of index case identification; screening of contact patients had to be pursued once weekly; hand hygiene had to be reinforced with the use of alcohol-based hand-rub solutions; the cleaning of the CPE patient's environments had to be reinforced using detergent-disinfectant product; antibiotics that could be used in case of serious infection due to the strain of the index case had to be identified;

iii if no secondary case was identified, the transfer of contact patients, if needed, was allowed providing that three consecutive rectal swabs, obtained on a weekly basis, were negative; screening of contact patients hospitalised in the involved unit had to be pursued until the discharge of index CPE case;

iv if a secondary case was identified, patients had to be cohorted in three distinct areas with dedicated nursing staff ('CPE patients' section, 'contact patients' section and 'CPE-free patients' section for newly admitted patients with no previous contact with CPE cases); and screening once weekly had to be maintained for all contact patients until the outbreak was considered under control, i.e. after all CPE cases had been discharged and after at least three consecutive negative rectal swabs in contact patients since their last contact with a case; screening of contact patients receiving antibiotics had to be resumed; transfer of contact patients after three negative rectal swabs was allowed provided they continued to be isolated and screened for CPE; antibiotics use was restricted; the list of cases and contact patients discharged from hospitals had to be maintained and an information system allowing to identify them in case of re-admission had to be implemented.

In 2009, after the analysis of the CPE events, occurring during the first years of surveillance had shown not only frequent delays in identifying the index case and subsequent implementation of measures, but also that most index cases (8/10, including 3/4 outbreaks) had been transferred from a foreign hospital, an institutional CPE programme was designed and coordinated by the AP-HP CICT. This programme included the above measures, which were detailed in an official document, and the recommendation to pre-emptively isolate (barrier precautions) and screen for CPE, every patient who had been hospitalised abroad within the preceding year. The programme emphasised the need of a rapid and stringent application of the measures, as well as the commitment of the hospital management. This programme was disseminated to all stakeholders, i.e. LICTs, medical managers and administrators of every hospital in the institution.

To stimulate the efforts made by the LICTs and administrators, the CICT (i) visited all the hospitals where an outbreak occurred, to help the local teams apply the CPE programme, (ii) prospectively recorded new cases, new outbreaks, and difficulties in implementing the programme, and (iii) regularly shared the results of this surveillance with hospitals and the central administration.

Microbiological methods

To screen patients for CPE carriage, rectal swabs were cultured on chromogenic agar targeting cephalosporin-resistant Enterobacteriaceae. Indeed, CPE strains are frequently resistant to cephalosporins due to the production of the carbapenemase itself or to the production of an additional extended spectrum beta-lactamase (ESBL). Cephalosporin-containing chromogenic agars are widely used in France for the surveillance of multiresistant bacteria targeting ESBL Enterobacteriaceae [8]. Screening for carbapenemase-producing strains without associated ESBL was performed using an ertapenem-containing agar [9].

Isolates from clinical specimens and rectal swabs were tested for susceptibility to antibiotics according to French guidelines [8]. In carbapenem resistant strains, carbapenemase production was detected using a set of phenotypic (e.g. synergy tests between carbapenems and carbapenemase inhibitors) and genotypic (carbapenemase gene amplification and sequencing) methods [9].

Statistical analysis

To evaluate the impact of the CPE programme, we compared the proportion of events resulting in an outbreak and the number of secondary cases occurring during these outbreaks in the period before (2004–2009) and after its implementation in 2009 (2010–2012).

Depending on whether the index case was identified/suspected upon admission or not, measures to prevent secondary cases (setting of nursing staff dedicated to the patient, or setting of simple barriers precautions) were quickly implemented (i.e. within two days of admission of the patient), or delayed for several days. We compared the proportion of events resulting in an outbreak and the number of secondary cases occurring during these outbreaks in these different situations.

The data were analysed with Stata. Quantitative variables were described using numbers and percentage or median and interquartile range (IQR). A chi-squared test and a Fischer exact test were used to compare categorical variables. A p value ‹0.05 was considered statistically significant.

Results

Carbapenemase-producing Enterobacteriaceae events and outbreaks

From January 2004 to December 2012, 140 CPE events occurred in AP-HP hospitals. The number of annual events, which was limited to one or two events per year before 2009 increased dramatically thereafter reaching 73 events in 2012, i.e. an incidence of 0.007 CPE events per 100 admissions in 2012. Among the 140 events, 118 (84%) involved patients with a history of hospitalisation or stay abroad within the past year. Seventy-four were directly transferred from foreign hospitals, 25 had been hospitalised in foreign hospitals during the last 12 months and 19 reported a recent stay (within one year) in a foreign country. Link with involved species and countries of travel are described elsewhere [10].

Seventeen of the 140 events (12%) led to outbreaks. Overall 200 cases were identified, among them, 123 (62%) were single cases (i.e. index cases not followed by secondary cases) and 77 (39%) were clustered in the 17 outbreaks (17 index cases and 60 secondary cases). The median number of secondary cases per outbreak was 1 (IQR: 1–4). The median duration of outbreaks was 22 days (IQR: 15–66). Three of these outbreaks have been already described in details [6,11,12]. One of them involved two AP-HP hospitals revealing inter-hospital spread of a strain of *K. pneumoniae* producing *K. pneumoniae* carbapenemase (KPC) [11].

The 140 events occurred in 25 distinct AP-HP hospitals (20 AC, and 5 RLTC hospitals) involving medical (n=63, 45%), intensive care (n=46, 33%) or surgical (n=31, 22%) units. Outbreaks occurred mainly in AC hospitals (n=16), involving intensive care (n=6), surgical (n=6) or medical (n=4) units; one outbreak occurred in a RLTC hospital.

Microbiology

The main species involved in events were *K. pneumoniae* (n=96, 69%), *E. coli* (n=36, 26%), *Enterobacter cloacae* (n=10, 7%), *Citrobacter freundii* (n=4, 3%), and *Enterobacter* spp. (n=4, 3%). In 10 events, two distinct species, generally *K. pneumoniae* and *E. coli*, were involved. *K. pneumoniae* and *E. coli* were involved in 15 and two outbreaks respectively.

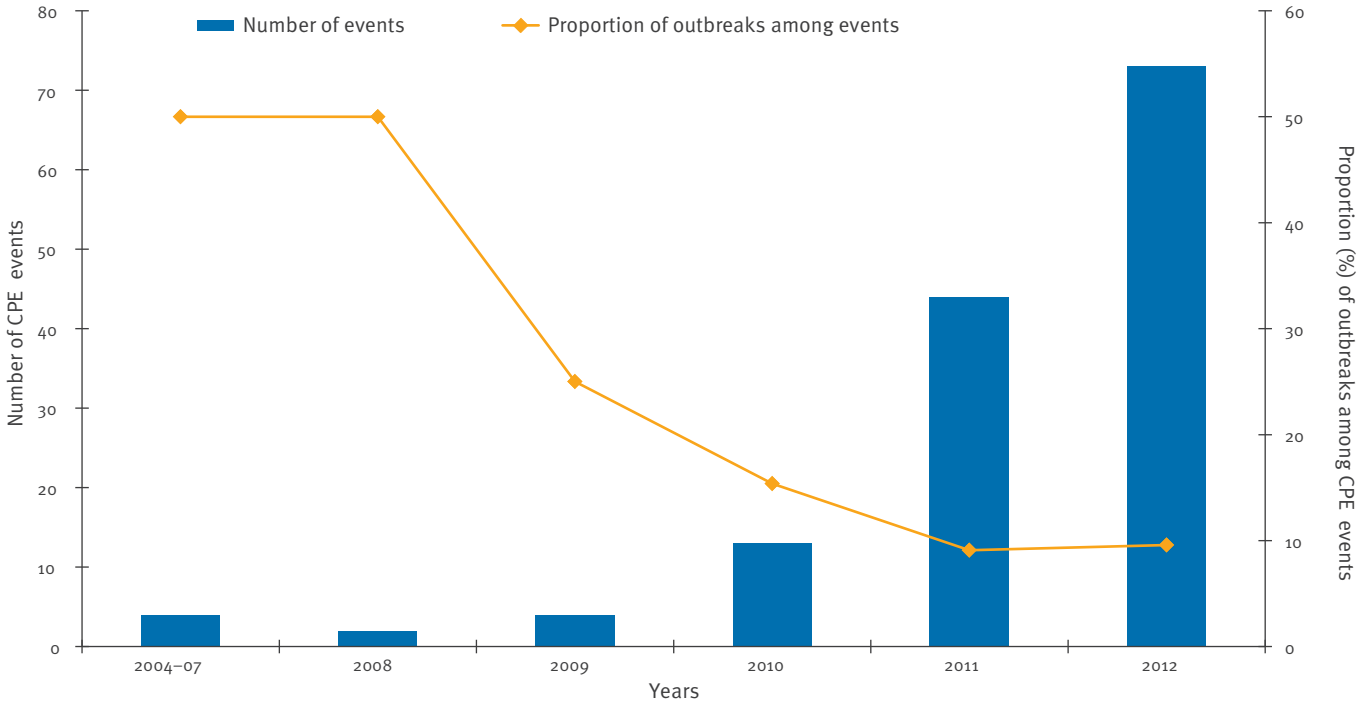
The carbapenemases identified were oxacillinase (OXA)-48 (n=82, 59%), KPC (n=31, 22%), New Delhi metallo-beta-lactamase (NDM)-1 (n=17, 12%), and Verona integron-encoded metallo-beta-lactamase (VIM) (n=10, 7%). KPC, OXA-48 and VIM were involved in eight, eight and one outbreaks, respectively.

Characteristics of carbapenemase-producing Enterobacteriaceae cases

Among the 200 case patients, 66 (33%) developed an infection: 27 (41%) were urinary tract infections, 22 (33%) bacteraemia, seven (11%) osteoarticular

Figure

Number of carbapenemase-producing Enterobacteriaceae (CPE) events (n=140) and proportion of outbreaks among these events at Assistance Publique-Hôpitaux de Paris, France, 2004–2012



A CPE event was defined as one index case (respectively defined as infected or colonised with CPE), followed or not by secondary case(s).

infections, six (9%) cutaneous infections, and four (6%) bronchopulmonary infections. Incidence of CPE infection was 0.004 per 1,000 hospital days in 2012. The crude case-fatality rate was 22% (43/200); 14 patients died with severe infection (bacteraemia or bronchopulmonary infections). The median length of hospitalisation, available for 176 patients, was 25 days (IQR: 12–53).

Impact of carbapenemase-producing Enterobacteriaceae control programme

The proportion of events leading to outbreaks decreased progressively from 50% (3/6) in the period between 2004 and 2008, i.e. before the full implementation of the institutional CPE programme, to 10% (4/44) in 2011, a level that was maintained in 2012. The Figure illustrates the evolution of number of events and the proportion of outbreaks among the events.

Moreover, the proportion of secondary cases among all the cases decreased significantly from 69% (22/32) in the period from 2004 to 2009 to 23% (38/168) in the period from 2010 to 2012, $p < 0.001$ respectively (Table 1). Also, while the number of index cases increased more than four times in the period after implementation of the CPE control programme, the number of additional secondary cases was less than one-fold higher.

The type and timeliness of measures implemented depended on whether the index case had been identified upon admission or not. If the index case was known to be a CPE carrier, dedicated nursing staff or at least barrier precautions, depending on availability of nursing staff, was implemented immediately after admission. If the index case was known to be at risk to be a CPE carrier, i.e. if the patient had been hospitalised abroad, simple barrier precautions were implemented, waiting the results of screening. If the index case was not known to be a CPE carrier and was not identified to be at risk at admission, implementation of control measures was delayed until the identification of CPE carriage, for example on a clinical specimen, several days or sometimes several weeks (range: 1–8 weeks), after admission. The important finding was that no outbreak occurred when dedicated nursing staff was implemented within two days following the admission of the index case, six outbreaks occurred despite barrier precautions implemented within these two days, whereas 11 outbreaks occurred when measures were delayed because the index case was identified several days after admission. Moreover, the proportion of secondary cases among all cases within a given event varied significantly from 0 (0%), to 19 (26%) and 41 (38%) respectively, depending on the speed and strength of the measures implemented (Table 2).

Discussion

This prospective multicentre study, carried out in the largest French public multi-hospital institution, representing 10% of the public hospital beds in France,

Table 1

Number of carbapenemase-producing Enterobacteriaceae (CPE) outbreaks among CPE events and number of secondary cases among all CPE cases, before and after implementation of a CPE control programme at Assistance Publique–Hôpitaux de Paris, France, 2004–2012

	2004–2009	2010–2012	P value
Number of events	10	130	–
Number of outbreaks (proportion of outbreaks among events)	4 (40%)	13 (10%)	0.02
Number of cases	32	168	–
Number of secondary cases (proportion of secondary cases among total cases)	22 (69%)	38 (23%)	< 0.001

Over the whole period from 2004 to 2012 there were a total of 17 outbreaks among 140 CPE events and 60 secondary cases among 200 CPE cases.

aimed to assess the impact of an institutional control programme implemented for limiting CPE spread. The main result of the programme was the decrease over time in CPE outbreaks and in the proportion of secondary cases among all cases, in spite of the increase in CPE index cases. The increase in CPE index cases appears to be epidemiologically linked with a history of hospitalisation or stay abroad, a phenomenon also documented by French Health authorities [13]. To our knowledge, the present study reports the largest experience of a CPE control programme in a country where CPE are still at an emerging stage (sporadic hospital outbreaks, [14]). Indeed, data from the 2011 European survey antimicrobial resistance interactive database (EARS-net) show that the proportion of carbapenem-resistant isolates of *K. pneumoniae* and *E. coli* was <0.5% and almost 0%, respectively in France [4]. A specific early warning system organised by the French Health authorities at the national level to systematically collect information on CPE cases, reported 113 cases in 2011 for the whole country [13]. Bundle measures similar to those described in the present study have been associated with the limitation of CPE spread in Israel where CPE are endemic [15–17].

This study also highlights the importance of the type of measures and the way these are implemented to limit the number of secondary cases, in particular the speed of implementation of dedicated nursing staff. The type and timeliness of measures implemented after admission of the index case influenced significantly the number of secondary cases (Table 2): quick (≤2 days after admission) setting of nursing staff dedicated to the index case, quick implementation of simple barrier precautions or delayed (>2 days after admission) measures of control. Interestingly, as already reported by others [16], rapidly isolating index patients with barrier precautions was not always sufficient to avoid secondary cases and these occurred in six of 55 events (Table 2). Dedicated nursing staff is probably one of the most relevant measure to avoid cross transmission [15,17–19]. In the context of an epidemic, cohorting patients with dedicated nursing staff in three different groups (cases, contacts and newly admitted patients) was shown to be effective in controlling the outbreak [6,11,17]. The present study shows that dedicating staff to an index case carrying CPE also prevents the occurrence of outbreaks. However, limitation in nursing staff can present an obstacle to assigning several healthcare workers to a single case. Implementation of cohorting requires a strong and sustained involvement

Table 2

Occurrence of outbreak and number of secondary cases according to measures implemented around a carbapenemase-producing Enterobacteriaceae (CPE) index case at Assistance Publique–Hôpitaux de Paris, France, 2004–2012

Event[a] and related cases	Measures implemented within two days following admission of the index case		Delayed measures of control[b]	P value
	Dedicated nursing staff	Barrier precautions		
Number of events	18	55	67	–
Number of outbreaks (proportion of outbreaks among events)	0 (0%)	6 (11%)	11 (16%)	0.17
Number of cases	18	74	108	–
Number of secondary cases (proportion of secondary cases among cases)	0 (0%)	19 (26%)	41 (38%)	0.001

[a] An event was defined as one index case, followed or not by secondary case(s).

[b] Control measures were implemented but occurred later than two days after admission of the index case, because the patient was not identified as infected/colonised with CPE within the first days of admission.

of chief nurses and heads of departments, as well as administrators. Such measures already allowed to control the spread of vancomycin resistant enterococci in our institution [20].

Identification of patients transferred from or previously hospitalised abroad in the prior year was most likely crucial, as this allowed to rapidly screen these patients at risk to be colonised by a CPE strain and to implement pre-emptive barrier precautions to avoid transmission to other patients [21]. This recommendation has been subsequently extended at the national level by French Health authorities in August 2010 [22], a measure that could have contributed to improve adherence to organising early screening of such patients in our institution. The increase in CPE index cases in our institution, mainly in 2011 and 2012, reflects the worldwide spread of CPE, since 84% of cases in our study had a history of hospitalisation or stay abroad, within the past year. In certain regions of the world, the spread of carbapenemases (NDM-1 and OXA-48) occurs primarily in the community via the faecal-oral route, either by food or water-borne transmission [3,23]. In industrialised countries with safe water systems and good sanitation, CPE are up to now acquired almost exclusively in the healthcare setting [23]. In a country with low prevalence of CPE such as France, it appears essential to identify CPE carriers upon their admission in hospitals in order to further implement adequate control measures [22]. Indeed, in the present study, most outbreaks and secondary cases occurred following delayed identification of index case patients.

Screening contact patients to rapidly identify cross-transmission was likely also important to limit the spread of CPE in our study. Indeed, active screening of contact patients has been shown to be very effective to identify CPE carriers [24,25]. Stopping the transfer of CPE index or secondary cases and the transfer of contact patients within and between hospitals most likely contributed to decrease the risk of CPE spreading in our institution. Indeed, extensive transfer of KPC positive patients has been reported to account for a regional spread affecting at least 26 different healthcare facilities of four counties in the United States [26]. In brief, the earlier the index case is identified, isolated and cohorted, and contact patients are identified and screened, the lower is the risk of additional cross-transmissions [15].

Our study has potential limitations since it was not a randomised, controlled trial aiming at assessing direct causality between intervention and outcome. The occurrence of the first outbreaks in our institution and the rapid spread of CPE in neighbouring countries [4,15,27] triggered quick and strong actions to control this emerging problem, contraindicating randomised comparative studies. However, the fact that the strength and the nature of the enhanced measures implemented after 2009 markedly differed from those applied before 2009, as well as the length of the continuous and systematic surveillance of every CPE event, justify to consider this study as quasi-experimental with pre-test and post-test periods [28].

We checked that the differences in number of secondary cases observed between the types of measures were not due to bias in species, enzyme and type of ward where the index case was admitted. Indeed, the distribution of the two main species (*K. pneumoniae* versus *E. coli*), the two main enzymes (KPC versus OXA-48) and the three main types of wards (medicine, surgery or intensive care unit) did not differ for each category of measures (data not shown).

In conclusion, this study shows that, although the number of CPE index cases increased in our region due to admission and increased screening of carriers having been recently hospitalised or stayed abroad (Figure 1) [5], and although some secondary cases occurred, particularly when the implementation of control measures was delayed, the number of outbreaks and of secondary cases can be strongly limited by a specific control programme. Such a programme requires quick and sustained involvement of all stakeholders, particularly the infection control teams, medical and nursing staff, microbiologists and hospital administrators [15]. The strong commitment of the AP-HP institution, continuous coordination and support by the CICT, as well as a continuous feedback stimulated the efforts made in each hospital. Early detection of emerging drug resistant bacteria such as CPE and an active control programme must be developed and implemented at a national level to avoid CPE spread [15,29]. Institutional programmes, based on a coordinated policy, such as the one presented here, are efficient ways to bring together and motivate hospital staff and managers, and to promote quality and safety in healthcare.

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Conflict of interest

None declared.

Authors' contributions

Sandra Fournier participated in the design of the programme, performed the survey, analysed the data, and wrote the manuscript. Catherine Monteil performed statistical analysis. Margaux Lepainteur participated in the survey. Christian Brun-Buisson participated in the design of the programme and revised the manuscript. Christian Richard, from AP-HP Central administration, sustained the implementation of the programme. Vincent Jarlier participated in the design of the programme, in the data analysis and revised the manuscript. Members of the AP-HP Outbreaks Control Group implemented the CPE control programme in AP-HP hospitals and organised the laboratory-based survey and CPE

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Letter to the editor: Measles on the cruise ship: links with virus spreading into an emergency department in Southern Italy

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To the Editor:

Recently, Lanini et al. described an outbreak of measles that occurred on a ship cruising the western Mediterranean Sea, involving 27 cases among crew members and passengers between 20 February and 1 March 2014 [1]. Cases originated from different countries, six were from Italy. As highlighted by the authors, at the time of their preliminary report, the number of cases among passengers was likely to be underestimated, given that the incubation time for measles ranges from seven to 18 days, and the mean passenger time on board is seven days. Since the time on board is not long enough to develop symptoms in a susceptible exposed person, passengers might develop the diseases only after returning to their home country [1].

In the context of these circumstances and the possibility to further spread of measles, we would like to discuss the serious consequences that such an event could have in areas where pools of susceptible persons still exist.

On 27 February 2014, an unimmunised Italian teenager presented to the Emergency Department (ED) of a hospital in Brindisi province, Puglia region, Italy, with fever and rash; the patient was hospitalised and subsequently diagnosed with measles. The strain was confirmed to be identical to the outbreak strain reported by Lanini et al. (MVs/Tonbridge.GBR/5.14). In a letter to the Editor published in *Eurosurveillance* on 17 April 2014, Mandal et al. hypothesised that the index case of the cruise ship epidemic was likely to be symptomatic between 4 and 10 February 2014 [2], and our epidemiological investigation revealed that, between 6 and 13 February 2014, our patient had indeed been a passenger on the ship where the outbreak occurred.

This was the first measles case reported in Brindisi province since the beginning of 2014. By the end of April, we observed a sharp increase in the number of cases, developing into a rapidly spreading outbreak that was reaching its fifth generation [3]. As of 8 May 2014, 32 cases have been identified through the enhanced measles surveillance system and active contact tracing; 17 were female, the median age was 19 years (range: 0–39 years), and 25 were hospitalised. Of 32 cases, one had been vaccinated with one dose of measles-mumps-rubella vaccine (MMR); two cases received one dose as post-exposure prophylaxis during the epidemic.

Initially, there was no evident relationship between most of the affected subjects, but contact tracing by electronic medical records and individual interviews suggested that most cases were associated with the first reported case and, therefore, with the outbreak on the cruise ship. Our epidemic appears to be a secondary outbreak spreading in a hospital ED as a common setting of exposure.

The measles virus strain isolated from the 12 secondary cases that have been typed was indistinguishable from the outbreak strain on the cruise ship. Three of them were attending the ED for a different medical condition at the time when the cruise passenger was there for suspected measles, a time that is compatible with the measles incubation period. The other nine cases belonged to the second (two cases), third (one case), fourth (four cases) and fifth (two cases) generation of infections [3]. With the exception of four small family clusters (range: 2–5 cases), 12 of the 32 secondary cases had been exposed to a measles case in the ED or infectious disease ward of the Brindisi hospital during a time period compatible with their incubation period, either as visitors, patients or healthcare workers.

To contain the outbreak, immediate vaccination of close contacts was carried out, but the hypothesis of

a common exposure in the hospital setting was formulated late, and adequate control measures such as a separate waiting room for patients with symptoms compatible with measles, were only adopted after 15 April.

Our epidemiological investigation faced similar challenges of measles outbreak management as discussed in the paper by Lanini et al. Similar to a cruise ship, the waiting room of a hospital ED is a closed setting, with constant movement in and out of people with unknown vaccination status; the return to their home countries of passengers incubating the infection is analogous to the return of patients or visitors from the hospital to their own family. Compared with the cruise ship scenario, the risk related to the spread of measles in hospital settings could be even more severe, especially if the vaccine coverage among healthcare workers is low, their attitude towards vaccine uptake is negative [4], and control measures are not implemented early enough.

We believe that the specific characteristics of our outbreak can provide additional input to the measles elimination plan. It highlights the need to consider the risk of measles transmission in EDs, particularly among travellers, with urgent isolation of suspected cases, especially in contexts where vaccination coverage with MMR vaccine is less than 95% in newborns and lower still in adolescents and young adults. The accidental introduction of measles to healthcare facilities could generate dangerous consequences as in our outbreak where an infant under the age of one year and a woman in the third month of pregnancy were accidentally infected in the ED.

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Conflict of interest

None declared.

Authors' contributions

Vanessa Cozza acted as principal investigator, contributed to the concept and drafted the letter. Maria Chironna supervised the microbiological investigation and the sequencing. Carlo Leo carried out the epidemiological investigation. Rosa Prato acted as outbreak coordinator, contributed to the concept and edited the letter.

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Authors' reply: Measles on the cruise ship: links with virus spreading into an emergency department in Southern Italy

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To the Editor:

We thank Cozza et al. for their letter in response to our paper [1]. The letter is a timely report and a good opportunity to provide additional information about the outbreak and share some general considerations.

The Italian Ministry of Health has to date identified 29 confirmed cases of measles that occurred between 20 February and 10 March 2014 on the cruise ship in question. Of them, 23 were crew members and six were Italian passengers (data for non-Italian passengers are not available). These include three cases in addition to those reported before [2], one passenger with disease onset on 27 February and two crew members with onset on 1 and 10 March. Seven of the 29 confirmed cases developed symptoms at home after returning from the cruise. These cases included a young child (passenger) from Lazio, a young child (passenger) from Umbria, an adult passenger from Sardinia who needed admission to an intensive care unit, two cases from Lecce (an adult passenger and a crew member), an adult passenger from Bari, and the teenage passenger from Brindisi reported by Cozza et al [1].

The temporal distribution of symptom onset suggests that most cases may have been exposed to the same source of infection between 8 and 13 February 2014. In fact, 28 of the 29 cases clustered between 20 February and 1 March; this time frame is shorter than the maximum of 14 days expected after a simultaneous exposure, the minimum and maximum expected incubation time for measles being seven and 21 days, respectively [4,5]. The hypothesis of a unique source of infection is also supported by the results of molecular investigation which identified a single molecular variant in all infected patients who underwent phylogenetic analysis [2].

As we could not find any obvious common exposure on board, it is likely that 28 subjects may have been infected ashore while visiting one of the places where the ship stopped, i.e. Savona on 8 February, Marseille on 9 February, Barcelona on 10 February, Palma 11 February, or Civitavecchia on 13 February; on 12 February, the ship was at sea. In contrast, the case that occurred on 10 March is likely to have been infected on board. Molecular characterisation of the viral strains circulating in these locations within the first half of February will further clarify this point.

Cozza et al. raised another interesting issue with relevant public health implications: the contact tracing investigation pointed out that 12 of all 32 potential measles cases from Puglia were associated with exposure to measles within an emergency department [1]. Media news report that the Department of Health in Spain is investigating a large, still ongoing, measles outbreak in Catalonia, with about 102 cases in the first three months of 2014 [3]. It is noteworthy that about 24% of all reported cases in Catalonia occurred among healthcare workers [3]. Healthcare settings may play an important role both in spreading and in controlling respiratory infections. In particular, emergency departments may represent a significant site of transmission for respiratory pathogens due to close contact between cases and susceptible subjects, both patients and healthcare workers [6]. The experience from Puglia and the information provided by the Spanish Department of Health suggest that there is still a need to implement better procedures for infection control in emergency departments in Europe.

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