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Outbreak of NDM-1-producing *Enterobacteriaceae* in northern Italy, July to August 2011

P Gaibani[1,2], S Ambretti[1,2], A Berlingeri[1], M Cordovana[1], P Farruggia[3], M Panico[3], M P Landini[1], V Sambri (vittorio.sambri@unibo.it)[1]
1. Operative Unit of Clinical Microbiology, S. Orsola-Malpighi University Hospital, Bologna, Italy
2. These authors contributed equally to this paper
3. Bellaria Hospital, Bologna, Italy

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Between July 2011 and August 2011, the New Delhi metallo-beta-lactamase 1 (NDM-1) gene was detected in *Klebsiella pneumoniae* and *Escherichia coli* isolates obtained from six patients hospitalised in four healthcare facilities in northern Italy. The patient who had been hospitalised in New Delhi, India, from February to May 2011 and subsequently in the Bologna area, Italy, from May to July 2011, may have been the source of the outbreak. Our findings suggest ongoing spread of this carbapenem-resistance gene in Italy and highlight the need for intensive surveillance.

Outbreak description

On 2 July 2011, we isolated *Klebsiella pneumoniae* harbouring the New Delhi metallo-beta-lactamase gene (bla_{NDM}), cultured from the urine of a patient (Patient 1) who was admitted to a nursing home (Facility A), in Bologna, Italy. In the same period, two bla_{NDM}-positive *K. pneumoniae* isolates were identified in patients in two hospitals (Facilities B and C) in the Bologna area on 8 July (Patient 2) and 13 July (Patient 3), respectively. Patient 2 had been previously admitted to the same nursing home (Facility A) as Patient 1. Subsequently, two further bla_{NDM}-positive *K. pneumoniae* isolates were identified on 18 and 22 July from Patients 4 and 5, respectively, who were in the same nursing home as Patient 1. Retrospective analysis of the hospital records indicated a possible epidemiological link between Patients 1, 2, 4 and 5 since the timing of the stays of Patients 2, 4 and 5 in healthcare facilities overlapped with that of Patient 1 (from June to July 2011) and four of these five patients (Patients 1, 2, 4 and 5) had been admitted to the same nursing home. Patient 3 had been in the same hospital (Facility C) as Patient 1 in the second week of July.

In addition, an *Escherichia coli* harbouring bla_{NDM} was isolated on 8 August from a patient (Patient 6) who was hospitalised in a fourth facility, a tertiary hospital (Facility D) in the same geographical area. Epidemiological investigations suggested that this patient was probably the source of the outbreak: this patient had been hospitalised from February to May 2011 in New Delhi, India, and then, after arriving in Italy, in a fifth facility (Facility E) from 25 May to 11 July. During the stay in Facility E and before the detection of an NDM-producing *E. coli* in August, *E. coli* had been cultured from four urine samples (the first on 26 May). These isolates showed an elevated level of resistance to carbapenems: the antimicrobial susceptibility of these four isolates was very similar to that of the isolate bearing NDM that we subsequently isolated. Unfortunately, we did not have the opportunity to test for the presence of NDM in these first four isolates from this patient, as this routine diagnosis was carried out in another laboratory. It should be noted that the culture from the fourth sample also led to the isolation of a *K. pneumoniae* strain with reduced susceptibility to carbapenems.

It is noteworthy that Patients 1 to 5 had no reported history of travel to or hospitalisation in an NDM-1 endemic area. It was not possible to identify a direct epidemiological link between Patient 6 and the other five patients. Patient 6 had been hospitalised in the same hospital (Facility C) as two other patients in this outbreak (Patients 1 and 3). From the information currently available, it is not possible to identify a possible link between Patient 6 and Patients 2, 4 and 5.

The dates of the stays of Patients 1–6 in the healthcare facilities are shown in the Table.

Background

Carbapenems are the preferred treatment for severe infections caused by multidrug-resistant Gram-negative bacteria producing an extended-spectrum beta-lactamase (ESBL). For this reason, the increasing and rapid spread of mobile genetic elements that determine acquired resistance to carbapenems and all other beta-lactams in *Enterobacteriaceae* [1] is of great concern. In the last few years, the considerable spread of carbapenem-resistant *K. pneumoniae* strains harbouring the *K. pneumoniae* carbapenemase (KPC)

gene (bla_{KPC}) has been reported in Europe [2] and has greatly affected Italy [3,4].

Recently, an increase in the spread of a novel acquired carbapenemase, New Delhi metallo-beta-lactamase 1 (NDM-1), which can be produced by several *Enterobacteriaceae* species, has been reported in Europe: a total of 77 cases were reported from 13 countries from 2008 to 2010 [2]. In Italy, NDM-1-positive isolates were first described earlier this year [5]: NDM-1-positive *E. coli* was found in a patient with an indirect epidemiological link to NDM-1-endemic areas. Transient colonisation was apparently seen in another patient linked to the index case.

Laboratory investigations

The carbapenem-resistant strains were collected from four different Italian healthcare facilities in the Bologna area. Routine determination of minimum inhibitory concentrations (MICs) was performed by using a VITEK2 automated system (bioMérieux, France) and the results were interpreted according to the European Committee on Antimicrobial Susceptibility Testing [EUCAST] guidelines [6]. Isolates that showed reduced susceptibility to ertapenem (≥0.5 mg/L) were further evaluated in order to investigate the mechanism of resistance. This phenotype is thought to arise from the production of carbapenemase or metallo-beta-lactamase (MBL) or ESBL associated with porin loss. As a phenotypic confirmatory test for carbapenemase production, the modified Hodge test [7] and a disc-diffusion synergy test (ROSCO Diagnostica, Denmark) were performed.

Between 1 March and 30 August 2011, a total of 44 *Enterobacteriaceae* isolates that showed reduced susceptibility to carbapenems and in which the bla_{KPC} gene was not detected were screened for the presence of an MBL-resistance mechanism. The disc-diffusion synergy test indicated MBL production (inhibition of carbapenemase activity by dipicolinic acid) for the six isolates (five *K. pneumoniae* and one *E. coli*).

Polymerase chain reaction (PCR) amplification of the bla_{NDM-1} gene and direct cloning and sequencing of the PCR product was performed as previously described [8]. The sequences obtained were compared using BLAST (basic local alignment search tool) [9]. In accordance with the phenotypic results, this molecular testing confirmed the presence of the bla_{NDM-1} gene in all six isolates, with 99.9% identity with bla_{NDM-1} gene present in GenBank (JF714412.1). In addition, all the isolates contained the bla_{TEM-1} gene.

The six bla_{NDM}-positive isolates showed MICs of >8 µg/mL for ertapenem, while for imipenem, the MICs ranged from <1 to >32 µg/mL and for meropenem from 2 to 4 µg/mL. Furthermore, they had a high resistance rate to other classes of antimicrobials, such as fluoroquinolones and aminoglyocosides. The only drugs that showed a good level of antimicrobial activity against all six isolates in vitro were tigecycline and colistin, with MICs of ≤ 2 µg/mL and ≤ 1 µg/mL, respectively. The antimicrobial susceptibility profiles of the six isolates are listed in the Table.

Discussion

After the first identification of NDM-production in *K. pneumoniae* and *E. coli* isolates in a Swedish patient of Indian origin in 2009, NDM has been detected in all continents [10]. *Enterobacteriaceae* that carry carbapenemase-producing genes, including bla_{NDM} and bla_{KPC}, are considered an important public health problem because of ability of these genes to spread [1] and the considerable clinical impact of this type of

Table

Minimum inhibitory concentration of selected antimicrobial agents against NDM-1-producing *Enterobacteriaceae* isolates, northern Italy, July–August 2011

Patient	Sample collection date (2011)	Patient's healthcare facility	Dates of stay in healthcare facility (2011)	Isolate	Sample	Minimum inhibitory concentration (µg/mL)											
						AK	AMC	CAZ	CIP	CL	EPM	IPM	MPM	GM	TZP	TYG	SXT	CTX
1	2 Jul	A C	1 Jul–12Jul 12 Jul –20 Jul	*Klebsiella pneumoniae*	Urine	16	>32	>64	>4	0.5	>8	≤1	2	16	>128	1	>320	>64
2	8 Jul	A B	21 Jun–4Jul 4 Jul–20 Sep	*K. pneumoniae*	Bile	16	>32	>64	>4	1	>8	≤1	4	16	>128	2	20	>64
3	13 Jul	C	7 Jun–27 Jul	*K. pneumoniae*	Sputum	2	>32	>64	>4	0.5	>8	4	2	8	>128	1	>320	>64
4	18 Jul	A	11 Jul–13 Aug	*K. pneumoniae*	Urine	16	>32	>64	>4	0.5	>8	8	2	16	>128	1	20	>64
5	22 Jul	A	20 Jun–19 Aug	*K. pneumoniae*	Urine	16	>32	>64	>4	0.5	>8	>16	4	8	>128	2	>320	>64
6	8 Aug	E C D	25 May–11 Jul 11 Jul–29 Jul 29 Jul–9 Aug	*Escherichia coli*	Urine	64	>32	>64	>4	0.5	>8	>16	4	16	>128	0.5	>320	>64

AK: amikacin; AMC: amoxicillin/clavulanic acid; CAZ: ceftazidime; CIP: ciprofloxacin; CL: colistin; CTX: cefotaxime; EPM: ertapenem; GM: entamicin; IPM: imipenem; NDM; New Delhi metallo-beta-lactamase; MPM: meropenem; SXT: sulfamethoxazole/trimethoprim; TYG: tigecyclin; TZP: piperacillin/tazobactam.

antimicrobial resistance on the management of healthcare-associated infections.

This study reports an outbreak of NDM-producing *Enterobacteriaceae* colonisation or infection in Italy, where previously there had been only one report of NDM in isolates from two patients, in a different part of the country [5]. As at the time of microbiological diagnosis, the six patients in our study were hospitalised in four different healthcare facilities: epidemiological investigations suggested a likely link between five of the patients (Patients 1–5). For the sixth patient, it was not possible to identify a possible direct link between this patient and all the other patients. Nevertheless, Patient 6 could be the possible source of this outbreak because of the patient's history of previous hospitalisation in New Delhi before admission to a healthcare facility in the Bologna area, where NDM-positive isolates had not been previously reported. We can consequently hypothesise that the NDM-producing bacterial strains were transmitted nosocomially to other patients.

The detection of the NDM-1 gene in five strains of *K. pneumoniae* and one *E. coli* strain confirms that for this resistance mechanism, the risk of spread is not only among clonally related strains of the same species: this gene can also be efficiently spread to other bacterial species. The rapid spread of this gene is not unexpected [10,11] and has been already described among several *Enterobacteriaceae* species, mainly *K. pneumoniae*, in the United Kingdom [12]. Further molecular studies are currently in progress in order to better define the correlation between these NDM-positive strains identified in our study.

Given our findings, it will be extremely important to apply strict measures of surveillance and infection control in order to limit the spread of carbapenem-resistance genes in *Enterobacteriaceae* into other areas of Italy.

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National outbreak of *Salmonella* Java phage type 3b variant 9 infection using parallel case–control and case–case study designs, United Kingdom, July to October 2010

M Gobin (Maya.Gobin@hpa.org.uk)[1], N Launders[2], C Lane[2], G Kafatos[3], B Adak[2]
1. Health Protection Agency South West Regional Office, Health Protection Agency, Gloucester, United Kingdom
2. Gastrointestinal, Emerging and Zoonotic Infections Department, Centre for Infections, Health Protection Agency, London, United Kingdom
3. Statistics, Modelling and Bioinformatics Department, Centre for Infections, Health Protection Agency, London, United Kingdom

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Between July and October 2010, a national outbreak comprising 136 cases of *Salmonella* Java phage type 3b variant 9 was identified by the Health Protection Agency. Most cases were female. Cases had a median age of 39.5 years and lived in London, the South East and East of England. Parallel case–control and case–case study designs were undertaken to test the generated hypotheses. The case–case study aimed to examine if the infection was associated with eating food items purchased from commercial catering settings, and the reference group comprised non-travel related cases of *S*. Enteritidis infected during the same time period as the cases. The case–control study was designed to examine if the infection was associated with specific food items purchased from commercial catering settings, and recruited case-nominated controls. However, in response to poor recruitment we adapted our methods to investigate food exposures in the same way. Results of epidemiological investigations are compatible with salad vegetables as the potential source, but no common suppliers of salad were identified and no organisms were isolated from environmental and food samples. Limitations in the case–control study highlight the potential value of using a combination of epidemiological methods to investigate outbreaks.

Introduction

Salmonella enterica Paratyphi B variant Java shares the same somatic and flagellar antigens as other *S*. Paratyphi B variants, but utilises d-tartrate as a carbon source. *S*. Java is thought to be less virulent than non d-tartrate utilising *S*. Paratyphi B, with infections characterised by watery diarrhoea, abdominal pain and fever. However, infection can also be invasive, producing typhoid-like clinical symptoms [1].

S. Java has an animal reservoir. It is present in poultry flocks in the European Union and is the most common serovar reported in poultry in the Netherlands [2,3]. A recent increase in the incidence in poultry has also been reported in Germany [4]. Outbreaks of *S*. Java have been reported in the past, associated with salad vegetables, goat's milk cheese, poultry, reptiles and tropical fish aquariums [4-8]. *S*. Java is an uncommon cause of salmonellosis in the United Kingdom (UK), with 151, 112 and 130 cases reported in 2007, 2008 and 2009 respectively according to the national database.

In 2007, a multi-country outbreak of *S*. Java phage type (PT) 3b variant 9 (var9) involved cases in Denmark, Finland, the Netherlands, Norway, the UK and the United States (US). Epidemiological evidence suggested an association with salad vegetables [9].

Outbreak description

Between 27 July and 1 October 2010, 136 cases with *S*. Java PT 3b var9 were reported for the UK by the Laboratory of Gastrointestinal Pathogens (LGP) at the Health Protection Agency (HPA), compared to five in 2009 and one in 2008 (Figure). The LGP routinely receives isolates of *Salmonella* species for testing from local laboratories in England and Wales, and this is the basis of routine national surveillance. The outbreak strain was fully susceptible to the LGP panel of antimicrobial agents and had the pulsed-field gel electrophoresis (PFGE) profile SPTJXB.0001.

Cases were non travel-related. Isolates had been submitted to the LPG from most regions, with predominance in the East of England, London and the South East. The majority of cases were female (82/130) and the median age was 39.5 (interquartile range: 24–53). The on-going and widespread nature of the outbreak

indicated exposure to the outbreak strain of *Salmonella* through a widely distributed source. The outbreak of Java PT 3b var9 was notified by the LPG on 18 August 2010 and an immediate investigation was launched to identify the source.

Methods

Microbiological investigation

Local clinical microbiology laboratories referred all presumptive isolates of *S. enterica* to the LGP in the HPA Department of Gastrointestinal, Emerging and Zoonotic Infections (GEZI) for confirmation and characterisation. Isolates were sero-typed, phage-typed and screened for antimicrobial susceptibility. Pulse Field Gel Electrophoresis (PFGE) was performed on all *S.* Java PT 3b var9 isolates to reveal if the strain type identified was the same in all isolates.

Epidemiological investigation

Hypothesis generation

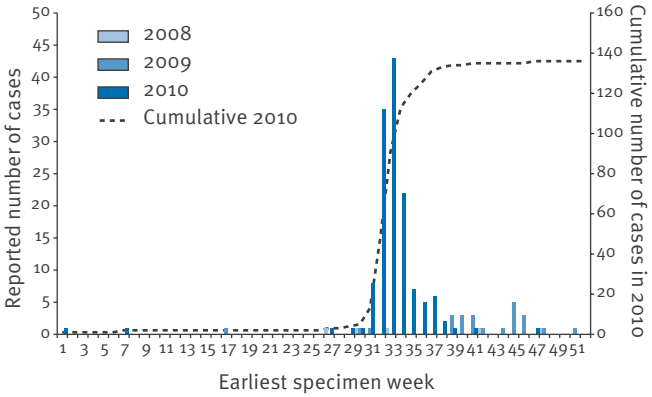
Trained interviewers (medical registrars and epidemiological scientists) based at the HPA Centre for Infections (CfI) interviewed 11 non travel-related cases of fully sensitive *S.* Java PT 3b var9, using a detailed standard *S. enterica* trawling questionnaire between 20 and 24 August. The 29 page long trawling questionnaire conducted over the phone collected an extensive food history for the five days before the onset of illness and comprised also detailed questions about salad vegetables, including sprouted seeds, herbs, salad dressing and pickles. Any exposures reported by eight or more cases were considered eligible for inclusion in an analytical study.

Analytical epidemiology

The generated hypotheses were tested using a case–control study with case-nominated controls. A parallel case–case study was also carried out using laboratory-confirmed cases of *S.* Enteritidis infected at the same time period as the *S.* Java PT 3b var9 cases.

Figure

Weekly reported cases of non-travel related fully sensitive *Salmonella* Java phage type 3b variant 9 from 2008 to 2010 and cumulative incidence for 2010, United Kingdom, 1 January 2008–31 December 2010



The two strategies were developed to test different aspects of the generated hypotheses. The case–case study was designed to examine if the risk of infection was associated with eating food obtained from commercial catering settings referred to as 'eating away from home', while the aim of the case–control study was to examine if the infection was associated with the consumption of specific food items eaten away from the home.

A secondary aim of undertaking the case–control and case–case studies was to compare and contrast the usefulness of these two methods in recruiting controls for the investigation of national outbreaks.

Case definition and controls

For the analytical epidemiological investigation a case of *S.* Java PT 3b var9 was defined as a primary non travel-related symptomatic adult of 18 years of age or older, resident in England, infected with *S.* Java PT 3b var9 (PFGE: SPTJXB.0001) confirmed by LGP since 27 July 2010 and fully sensitive to the LGP panel of antimicrobial agents.

Note that the study was restricted to people aged 18 years and older to reflect the age distribution of cases (less than 15% of all cases were under 18 years old).

Case-nominated controls were sought, and were defined as case-nominated individuals 18 years or older, and who had not: (i) experienced an episode of gastrointestinal illness in the seven days before interview, (ii) travelled outside the UK in the seven days prior to the date of the interview, (iii) shared a household with an individual with any gastrointestinal illness.

A *S.* Enteritidis case was defined as a primary non travel-related symptomatic adult of 18 years of age or older, infected with *S.* Enteritidis as confirmed by LGP since 27 July 2010, and resident in England.

Note that *S.* Enteritidis cases were used as a comparison group because there is no reason to believe that the eating habits of *S.* Enteritidis cases are different to those of the general population and it is unlikely that the exposures of interest would be under- or over-represented in these cases.

Case–case and case–control questionnaires

Standard structured case–control and case–case questionnaires were designed and administered to all subjects by telephone interview. The case, case–control and case–case questionnaires contained questions related to the same exposures identified in the hypothesis generation.

All cases were interviewed by trained staff from CfI and all interviewers were fully briefed on the questionnaire and interviewing technique. Up to three attempts to contact subjects were made at different times of the

day or evening. One case-nominated control and one *S*. Enteritidis reference cases were sought per case.

Statistical analysis

The case–control and case–case studies were analysed separately. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for all exposure associations with the outcome variable (caseness) tested in univariable analysis using the Chi-squared and Fisher's exact tests. Exposures were tested singularly and also grouped into broader categories.

Exposures with an estimated OR>1 and a p<0.2 were deemed eligible for inclusion in the multivariable analyses: multivariable logistic regression analysis for the case–case study and a multivariable conditional logistic regression analysis for the case–control study. Age and sex were controlled for in the multivariable analysis.
This conservative inclusion criterion for the multivariable analysis was selected to avoid the exclusion of exposures that are falsely non-significant.

Results

Epidemiological Investigation

Hypothesis generation

Analysis of the trawling questionnaires identified the following common (identified in eight or more cases) exposures: contact with domestic cats, eating food obtained from commercial catering settings (i.e. eating away from home), eating lettuce/salad leaves, tomatoes, cucumbers and prawns/scampi, buying food from a given supermarket chain "F".

On the basis of this evidence, analytical epidemiological studies were designed to test the null hypotheses that infection with *S*. Java PT 3b var9 was not associated with:

- Contact with domestic cats,
- Eating food obtained from commercial catering settings (restaurants: table and take away, hotels, pubs etc),
- Eating lettuce/salad leaves,
- Eating tomatoes,
- Eating cucumbers,
- Eating prawns/scampi,
- Buying food from a given supermarket chain "F";
- Buying lettuce/salad leaves from a given supermarket chain "F".

Analytical Investigation

One hundred and thirty six cases with the outbreak strain *S*. Java PT 3b var9, PFGE profile SPTJXB.0001, were reported by the LGP. Of these, 11 were interviewed during trawling and therefore excluded from the analytical investigation. A further 29 cases did not meet the case definition (12 were too young, nine were not resident in England, seven had a history of foreign travel and one case was a secondary case). Of the remaining 96 cases, four did not want to participate, contact could not be made with 25 cases and a further 19 were awaiting follow up information from local Health Protection Units including confirmation of name and contact details and consent for inclusion in the study.

Forty eight cases of *S*. Java were successfully interviewed, the median age was 44.5 years (interquartile range: 31–53), 34/48 cases were female. The median age of individuals who met the case definition but did not participate in the study (excluding cases already interviewed for the hypothesis generation) was 36 years (interquartile range: 22–56) and 29/48 were female. There was no difference in the age distribution of the two groups (p=0.52).

The most common symptoms in the cases were diarrhoea (48/48 of cases questioned), abdominal pain (42/48) and fever (37/48) and eight cases questioned were hospitalised during their illness. The date of onset of illness for interviewed cases ranged from 10 July to 31 August with the majority cases reporting an onset date between 16 and 22 August.

Twenty nine case-nominated controls were successfully interviewed, the median age of 49 years (interquartile range: 33–56 years) was similar to that of cases and 20/29 were female.

One hundred and twenty two cases of *S*. Enteritidis were identified for the same time period. Fifty cases were travel-related, 33 could not be contacted and 10 cases did not meet the eligibility criteria; the remaining 29 were interviewed. The median age of *S*. Enteritidis cases was 45 years (interquartile range: 29.5–59 years), 17/29 cases were female.

We initially intended to carry out the case–control and case–case study designs to investigate different hypotheses. In response to the poor recruitment of case-nominated controls however, we adapted our methods to investigate food exposures in the same way.

Statistical analysis

Case–control study

Based on the results of the crude analysis, no exposure was found to satisfy the criteria of an odds ratio higher than 1 and p<0.2 and so multivariable analysis was not undertaken. Furthermore, no grouped exposure satisfied these criteria. The exposures with OR>1 were 'eating out – cucumber' (OR: 1.65, 95% CI: 0.53–5.06) and 'takeaway – salad leaves'(OR: 1.81, 95% CI: 0.58–5.55).

Case–case study

Single variable analysis found 12 single and seven grouped exposures that had an odds ratio higher than 1 and p<0.2 (Table 1 and 2 respectively).

The multivariable analysis of single exposures from the case–case study indicates a significant association

between symptomatic infection of *S.* Java PT 3b var9 and eating out at restaurants, eating pre-packaged mixed salad leaves at home as well as consumption of salad leaves from takeaway restaurants (Table 3).

The multivariable analysis of the grouped food exposures from the case–case study indicates the only exposure associated with being a *S.* Java case was 'eat home or out – any salad leaves' (Table 3), whereas there was no evidence of association for 'eat home or out – scampi' (OR: 7.38, 95% CI: 0.70–78.38, p=0.057).

Discussion

On 27 July 2010, a national outbreak of *S.* Java PT 3b var9 took place in the UK and an investigation was initiated on 18 August. The cases were distributed across the country with initial analysis of stool samples undertaken by independently operated local clinical microbiology laboratories. *Salmonella* isolates were then referred to the HPA LGP reference laboratory for further typing. There is a necessary delay between a patient experiencing symptoms and the HPA becoming aware of the case. This delay is dependent on how quickly a case presents to healthcare, how quickly samples are taken and the isolation, referral and typing of *Salmonella* samples. However, the centralised laboratory and national surveillance system provided prompt identification of a nationwide increase in cases and enabled a timely nationally coordinated response.

The number of new cases of *S.* Java PT 3b var9 and *S.* Enteritidis diminished considerably over the course of the study restricting the recruitment of new cases and reference cases for the investigation and the outbreak control team closed the investigation on the 8 October 2010, 11 weeks after the first case was reported by LGP.

In total only half (48/96) of the eligible cases of *S.* Java PT 3b var9 were included in the analysis and there is

Table 1

Single variable analysis for single exposures with odds ratio>1 and p<0.2, case–case study, *Salmonella* Java phage type 3b variant 9 outbreak, United Kingdom, July–October 2010 (n=77)

Exposure	Exposed		Not exposed		Odds ratio	95% confidence interval	p-value
	Salmonella Java n (%)	*Salmonella* Enteritidis n (%)	*Salmonella* Java n (%)	*Salmonella* Enteritidis n (%)			
Travelling within United Kingdom	12 (26)	0 (0)	35 (74)	28 (100)	1.00	2.39–∞	0.003
Daytrips	7 (16)	1 (4)	37 (84)	27 (96)	5.11	0.76–∞	0.139
Cat at home	16 (34)	5 (17)	31 (66)	24 (83)	2.48	0.82–7.43	0.112
Other pets at home	9 (20)	2 (7)	35 (80)	27 (93)	3.47	0.77–∞	0.182
Eating out – restaurant	32 (67)	13 (45)	16 (33)	16 (55)	2.46	0.97–6.28	0.060
Eating out – salad leaves	17 (36)	4 (14)	30 (64)	25 (86)	3.54	1.09–11.3	0.039
Eating out – tomatoes	13 (28)	3 (10)	33 (72)	26 (90)	3.41	0.93–12.29	0.085
Eating out – cucumber	12 (26)	3 (10)	35 (74)	26 (90)	2.97	0.81–10.75	0.142
Takeaway – salad leaves	13 (28)	3 (11)	33 (72)	24 (89)	3.15	0.86–11.38	0.142
Eat at home – mixed salad	14 (30)	3 (11)	33 (70)	25 (89)	3.54	0.97–12.66	0.086
Eat at home – scampi	7 (15)	1 (3)	39 (85)	28 (97)	5.03	0.75–∞	0.141
Other supermarket chains than chain "F"	9 (22)	2 (7)	31 (78)	27 (93)	3.92	0.86–∞	0.104

Table 2

Single variable analysis for grouped exposures with odds ratio>1 and p<0.2, case–case study, *Salmonella* Java phage type 3b variant 9 outbreak, United Kingdom, July–October 2010 (n=77)

Exposure	Exposed		Not exposed		Odds ratio	95% confidence interval	p-value
	Salmonella Java n (%)	*Salmonella* Enteritidis n (%)	*Salmonella* Java n (%)	*Salmonella* Enteritidis n (%)			
Eating out – salad leaves	25 (56)	7 (26)	20 (44)	20 (74)	3.57	1.28–9.91	0.014
Eating out – tomatoes	18 (41)	6 (22)	26 (59)	21 (78)	2.42	0.83–6.98	0.106
Eating out – cucumber	19 (45)	4 (13)	23 (55)	26 (87)	4.20	1.29–13.47	0.019
Eat home or out – any salad leaves	40 (87)	14 (50)	6 (13)	14 (50)	6.67	2.19–20.18	0.001
Eat home or out – tomatoes	29 (67)	13 (45)	14 (33)	16 (55)	2.55	0.98–6.67	0.056
Eating home or out – cucumber	25 (57)	8 (30)	19 (43)	19 (70)	3.13	1.14–8.51	0.026
Eating home or out – scampi	13 (29)	3 (10)	32 (71)	26 (90)	5.28	1.2–∞	0.036

potential that the individuals who did not participate were systematically different from those who did. The age and sex distributions of the cases of *S.* Java PT 3b var9 included in the study were similar to the distributions in the total population of cases, however, it is possible that the study population was not representative of the total population of cases for reasons not considered in this study.

The recruitment of controls for both studies was also challenging, which may have resulted in biases in the individuals included in the study.

Comparison of case–control and case–case study designs

The case-nominated control design is considered a useful way of rapidly recruiting matched controls [10]; however, this method was not successful in this study for a number of reasons. Many cases were reluctant to provide contact details for friends and colleagues without prior consent from these individuals. In some instances, cases were willing to participate in the study but did not have any friends or colleagues to nominate as controls.

Four cases were only able to nominate controls from the same household, a potential for bias as the case and control may have shared the activities/exposures under investigation [11]. This may have resulted in the cases and controls being overmatched. There is also the possibility of recall bias amongst case-nominated controls that may have been aware of the hypothesis under investigation.

The finding that case-nominated controls may be hard to recruit is in keeping with experience from previous studies [12,13]. This suggests that other strategies need to be employed for selecting controls and that case-nominated controls should only be used where alternative methods cannot be readily identified.

The case–case comparison has previously been developed from the case–control methodology, and in this study we found that it was quicker and easier to recruit reference case–controls as compared with the case-nominated controls [14].

The case–case study was more advantageous than the case–control study in the investigation of this outbreak for a number of reasons. The demographic details of *S.* Enteritidis cases were already available from laboratory reporting, allowing the case–case study to be undertaken much faster than the case–control study.

The use of reference cases allows investigators to select controls randomly from the total population of controls as opposed to the selection of case-nominated controls which is prone to selection bias.

The inclusion of previously ill controls may introduce potential bias in the study and selection bias may have occurred with this study design if historical reference cases were recruited because exposures such as dietary habits and behaviour may have changed with time. This was avoided through the recruitment of reference cases that were infected in the same period of time as the *S.* Java PT 3b var9 cases.

There is the potential for overmatching of cases and reference cases in the case–case study design. This could lead to type II error i.e. high number of false negative associations. To avoid this, the choice of controls was carefully considered to ensure that the exposures under investigation would not be over-represented in the control group.

Conversely bias may be introduced if the reference cases selected are less likely to be exposed to food items under investigation. This can cause type I error i.e. false positive associations. However, given that *S.* Enteritidis has been isolated in a wide variety of food items we believe it is unlikely that reference cases can have different dietary patterns than the rest of the population.

For these reasons it is unlikely that the recruitment of reference cases would have produced a bias in the investigation of this outbreak.

Table 3

Multivariable analysis for single and grouped exposures with odds ratio>1 and p<0.05, *Salmonella* Java phage type 3b variant 9 outbreak, United Kingdom, July–October 2010

Variable	Multiple variable analysis		
	Odds ratio	95% confidence interval	p-value
Eating out – restaurant	3.72	1.03–13.39	0.038
Takeaway – salad leaves	6.92	1.08–44.2	0.021
Eat home – pre-packaged mixed salad	7.70	1.31–45.38	0.012
Eat home or out – any salad leaves	5.87	1.31–30.89	0.030

An odds ratio of one, and baseline 95% confidence interval were considered in the absence of exposure.

Salad vegetables

The results of the case–case study confirmed a significant association between symptomatic infection of *S.* Java PT 3b var9 and eating out at restaurants, eating pre-packaged mixed salad leaves at home, consumption of salad leaves from takeaway restaurants and eating any salad leaves either at home or purchased from commercial catering settings. Since salad is often used as a garnish in meals eaten in commercial catering settings, it is possible that the model underestimated the proportion of cases who consumed salad leaves away from home.

We cannot exclude the possibility that the study may have missed the right vehicle of the outbreak such as

sprouted seeds which have been implicated in two recent outbreaks in Europe [15,16]. It is likely that the consumption of smaller food items (seeds, sprouted seeds and herbs) in salads prepared by commercial caterers was not remembered or was not noticed by cases. None of the smaller salad items were found to be associated with cases during the hypothesis generation. It is possible that salad leaves were a confounding factor in this investigation and smaller, less memorable items should be considered in outbreaks where salad vegetables appear to be implicated.

Environmental investigations did not identify common suppliers of salad vegetables and the short shelf life of salad vegetables limited the ability to acquire any suspect foods for microbiological analysis.

The consumption of fresh and bagged salad vegetables across the globe has increased in the last twenty years. In the US there was a 9% increase between 1996 and 2005 as compared with the previous decade, however, outbreaks associated with these food items have increased by 38.9% during this the same time period [17]. In Europe there have been a number of country-wide and region-wide *Salmonella* outbreaks attributed to locally produced and imported salad greens [18].

The contamination of salad leaves and salad vegetables during their production and processing has been implicated in a number of geographically widespread outbreaks [19]. High risk practices during production and processing include the use of contaminated water either to irrigate the crops, to apply pesticides or other dressings, or to wash the crop once harvested; the use of human or animal sewage as a crop fertiliser; and the transport of the harvested crop in a contaminated vehicle/storage system, e.g. trucks previously used for transporting waste [20]. Crops growing in the field are also vulnerable to contamination from sources such as wild animals and birds [21].

The mild processing and packaging of these food items produce an environment that encourages the proliferation of bacteria transferred onto the vegetable surface during the growing period [22,23].

Gastrointestinal infection associated with salad vegetables may also be the result of cross-contamination from poultry, meat or meat products or contamination by the food handler during food preparation in the home or in catering establishments. A review of more than 2,000 general food-borne outbreaks from 1992 to 2006 undertaken by the HPA found that 4% of them were associated with prepared salads. The review found that most of the outbreaks linked to salads occurred in the catering sector and were associated with infected food handlers, cross-contamination and poor storage [24]. A study of sporadic cases of campylobacter infections in Wales found that infection was associated with specific salad vegetables because extensive handling required during preparation and use of a chopping board increased their likelihood of becoming contaminated [25].

The increase in illness and outbreaks associated with the consumption of fresh ready to eat salad vegetables indicates the ongoing need to improve methods in the production and preparation of these foods to reduce the potential for contamination with *Salmonella* and other enteric pathogens [26-28].

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Streptococcus pyogenes cluster in a care home in England April to June 2010

L M Milne (lorna.milne@hpa.org.uk)[1], T Lamagni[2], A Efstratiou[2], C Foley[1], J Gilman[1], M Lilley[1], S Guha[3], F Head[4], T Han[1]
1. Bedfordshire and Hertfordshire Health Protection Unit, Letchworth, United Kingdom
2. Health Protection Agency, London, United Kingdom
3. Bedford Hospital NHS Trust, Bedford, United Kingdom
4. NHS Bedfordshire, Bedford, United Kingdom

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Two fatal cases of *Streptococcus pyogenes emm* st22.6 bacteraemia occurred in a care home in England during April and June 2010, initiating a cluster investigation. The first case had left the home 13 days before the second case took up residence. We sought further cases and carriers. We swabbed throat and chronic skin lesions from residents and staff and examined these specimens for the presence of *S. pyogenes*. 61 specimens were taken from 18 of 19 residents and 39 of 39 staff. All results from swabbing were culture negative. We observed infection control practices and the environment at the care home for deficiencies. Issues were identified relating to the correct use of personal protective equipment, hand hygiene, clinical waste and laundry. Infection control practices were improved and training given. Infection control practices and the environment at a care home should be examined as part of the investigation of a *S. pyogenes* cluster. Screening for carriage of *S. pyogenes* should be done before antibiotic chemoprophylaxis is issued to care home residents and staff.

Introduction

Invasive infections due to *Streptococcus pyogenes* have been of increasing interest following upsurges in disease incidence in many countries [1-3]. The elderly have had the highest rates of infection [2,4,5] and those in care homes have been identified as being at risk [6-12]. A study in the United States found the incidence of invasive *S. pyogenes* infections among residents of long-term care facilities for the elderly to be almost six times higher than among elderly persons living in the community [10]. Furthermore cases in long-term care facilities were 1.5 times more likely to die compared to community cases affecting the elderly [10]. This population is more vulnerable due to older age and higher prevalence of underlying conditions such as congestive cardiac failure, and also at higher risk due to the potential for transmission of *S. pyogenes* within the care home setting [5,8,10,11].

There has been particular concern about clusters or outbreaks due to *S. pyogenes* occurring in care homes for the elderly as optimal management in this vulnerable group has not been well defined and has had several aspects [7-12], described below. There is a need for clear guidance, as there has been a lack of uniformity in control measures to be taken for residents and staff to prevent ongoing transmission and further cases of invasive disease occurring in such settings [4,7-9,11,12]. *S. pyogenes* may be transmitted by direct person -to -person contact [4,5] and by fomites in the environment [4,12]. Control measures used in various combinations have attempted to disrupt these modes of transmission in care homes. The management of clusters or outbreaks in care homes has included isolate typing [4,5,7-9,11], establishing the location of cases within a setting [9,13], maintaining vigilance for further cases [4,5], providing information for residents and staff about symptoms [4], identifying residents and staff who have symptoms compatible with *S. pyogenes* infection [4,11], screening residents and staff for carriage of *S. pyogenes* [4,5,9,11,14], review of infection control practices [4,5,9,11,13] and issuing targeted or mass antibiotic chemoprophylaxis to residents and staff without delay or after screening when one or more cases occur [4,8,9,11-13]. Management questions to be answered include the decision whether an investigation should commence after a single case occurs [11], the role of screening [11] and indications for antibiotic chemoprophylaxis [11].

We describe the management of a cluster of *S. pyogenes* in a care home.

Cluster description

Two residents developed *S. pyogenes* bacteraemia at an interval of 55 days apart in April and June 2010. Case 1 had a fall at the care home and developed swelling of the right thigh and calf. Hospital admission was arranged. There was right calf cellulitis, bilateral crackles on chest examination and bilateral consolidation on the chest X-ray. The patient's temperature was 38.2º Celsius. Culture of a blood sample taken on admission yielded *S. pyogenes*. The patient died in hospital eight days later and cause of death was streptococcal

pneumonia. Case 2 was admitted to hospital after one day of deteriorating consciousness. There were bilateral coarse crepitations on chest examination. Right-sided patchy consolidation was seen on the chest X-ray and pneumonia diagnosed. The patient's temperature was 39.7º Celsius. Culture of a blood sample taken on admission was positive for *S. pyogenes*. The patient died in hospital 12 days later and the cause of death was sepsis.

Epidemiological investigation

After the first case was notified in May 2010 by laboratory report to the local Health Protection Unit, care home staff were informed about the symptoms of *S. pyogenes* infection and asked to remain vigilant for 30 days for further possible cases [4]. On the day the second case was notified, we formed a cluster control team to decide on investigations and control measures. The team members were from the Health Protection Agency, the local National Health Service Hospital Trust and the local Primary Care Trust. Management at the home were unaware of additional earlier cases. Our Health Protection Unit routinely receives statutory notifications of invasive cases of *S. pyogenes* infection. We are satisfied there is no evidence to suggest additional cases occurred prior to the presentation of the two cases.

The *S. pyogenes* isolates from the two cases were forwarded individually as they occurred to the United Kingdom (UK) Streptococcus and Diphtheria Reference Unit, Colindale, London for characterisation. The isolates obtained from blood cultures of both cases were *emm* type st22.6 and indistinguishable by *emm* typing [15-18].

The care home had 27 single bedrooms on three floors. We sought information from the management on environmental links between the two cases including location of their bedrooms and equipment shared by both. The two cases had had no direct contact as the first case had been admitted to hospital 13 days before the second case arrived at the care home. They had resided on the same side of a corridor in different bedrooms which were separated by an unused room and had not shared equipment of other items.

Active case finding

We informed residents, relatives of residents, staff and general practitioners of residents and staff at the care home by letter about the two cases and gave written information about signs and symptoms which might indicate *S. pyogenes* infection [19]. Recipients were advised to contact their general practitioners if they had any concerns about their health. When the management of the care home was asked about symptoms affecting residents and staff which could indicate colonisation or infection with *S. pyogenes* they were aware of one staff member who had a sore throat during the interval between the cases and two residents who had leg ulcers, one of whom had a leg ulcer prior to both cases.

Nineteen days after the second case was notified, we took a total of 61 specimens from throat and chronic skin lesions of residents, staff and visiting staff who had had close contact with residents (defined by us as face to face contact for longer than 15 minutes at any one time). They included throat swabs from 18 of 19 residents, swabs from leg ulcers of two residents and a swab from a blister of a third resident. It was not possible to obtain a throat swab specimen from one resident who was not cooperative. For staff and visiting staff, throat swabs were taken from 39 of 39 and an eczematous area from one staff member was swabbed.

Specimens were cultured to isolate *S. pyogenes* by inoculation onto blood agar and colistin nalidixic acid agar plates. Plates were incubated at 35-37º C in a CO2 incubator for 48 hours and examined for beta haemolytic colonies. Beta haemolytic colonies were Gram stained and colonies of Gram positive cocci in chains were examined using a streptococcal latex agglutination kit (Prolex TM Latex Agglutination). Lancefield group A streptococci (*S. pyogenes*) were not detected in any of the 61 specimens taken.

The staff was asked at the time of swabbing about recent sore throat or skin problems. Five members of staff gave a history of sore throat occurring during the period since the first case presented , two of the five in the interval between the cases and three of the five after case 2. We considered whether antibiotic chemoprophylaxis should be given to residents and staff to eradicate *S. pyogenes* from carriers who posed a risk of infection to others and from those who had newly acquired the invasive strain and who may themselves have been at risk [4,5]. It was decided not to issue antibiotic chemoprophylaxis before the availability of the swabbing results. No further cases of *S. pyogenes* infection occurred after the cluster control team was formed.

Infection control practices

We observed [20-22] infection control practices in the care home environment, i.e. the setting in which infection control practices were undertaken, during an on-site visit. This included obtaining information about the use of personal protective equipment (PPE), staff hand hygiene, management of clinical waste, arrangements for disposal of faeces and urine and management of laundry. Observations were recorded using a local audit tool which was a questionnaire (unpublished).

PPE was not conveniently placed and dirty laundry was handled without wearing PPE. Hand washing technique among staff was poor and wrist and finger jewellery worn. Liquid soap and paper towel dispensers were soiled. Clinical waste was carried through the home for disposal. No foot operated pedal bins were available at the point of care in bedrooms and there was no

central point for the collection of clinical waste on each floor. Commode pots and urinals were decontaminated by hand. Clean and dirty laundry was not separated on trolleys and in storage areas.

Following the identification of these deficiencies, the care home management made the following improvements: PPE was made available in bathrooms and toilets and staff were trained in the correct use of PPE using the Health Protection Agency DVD on infection control [23] and e-learning [24]. Staff received training in handwashing technique and new soap dispensers were installed. Foot-operated clinical waste bins were installed in all bedrooms and a central point for the collection of clinical waste was established on each floor. A room designated solely for the decontamination of commode pots and urinals was identified and upgraded sluice facilities planned. New bags for clean linen and new bins for dirty linen were introduced. Infection control was made part of the induction programme for new staff, an infection control programme was introduced, a champion for infection control in the care home was named, posters on hand hygiene were displayed and auditing of infection control practice was introduced.

Discussion and conclusions

The two cases presented at an interval of 55 days between them. No other cases of *S. pyogenes* infection have been reported at the care home (up to November 2011). It has been suggested that a heightened level of vigilance should be maintained for 30 days after a case occurs in a care home [4]. Invasive *S. pyogenes* cases in long-term care facilities have presented months apart. In 18 clusters investigated in long-term care facilities [10], 14 clusters consisted of two cases each and the other four clusters of three cases each. Similar to the interval in this outbreak, the median interval between the first and second case in these 18 clusters was 2.5 months (range 0.2-9.2 months). The factors that determine the interval between cases, hence the optimal period of enhanced vigilance, are still unclear.

Our cluster demonstrated the importance of typing isolates as has been noted during the investigation of other clusters [7,9,12,14,16]. Isolates from the two cases were indistinguishable, suggesting transmission had occurred within the home. Both isolates were identified as *S. pyogenes emm* type st22.6, a very uncommon type. In the UK during the period April to June 2010, less than 0.5% of all invasive *S. pyogenes* isolates belonged to *emm* 22. Seventy-two (1.65%) of all 4,353 isolates from a pan-European surveillance study during 2003–04 [16] and two of 262 (0.76%) Norwegian isolates in 2006–07 [17] were *emm* 22. *Emm* gene sequence typing identifies the M protein type which is an important *S. pyogenes* virulence factor [15]. *S. pyogenes* types vary over time and are very much dependent upon the geographic location [1-3,6] and income of a country [18]. Therefore, monitoring type distributions is essential to identify any changes in patterns of disease and to identify and investigate clusters and features of virulence [2,16].

With regard to transmission of *S. pyogenes*, case-to-case transmission by direct contact was excluded for our two cases because they were not present in the care home at the same time. It is interesting that the only environmental link we were able to identify between the two cases was that they had resided on the same corridor in different bedrooms which were separated by an unused room. This invites speculation that the close proximity of these bedrooms may have been significant in regard to transmission by fomites [12] although we have no indication that this occurred. Having to speculate about the causes of outbreaks of *S. pyogenes* is well described in the literature and occurs often [8,9,11-13].

Staff at the care home had been unaware of the diagnoses of both hospitalised cases until contacted by the Health Protection Unit for each case, which is a situation other public health officials have reported [8]. Routine arrangements should be in place to protect care home residents when a cluster occurs although responsibility for protection will vary nationally. Distributing information about *S. pyogenes* infection to residents, staff and their general practitioners was essential in our investigation. The informal feedback received was that relatives and staff found the content of our information reassuring. This reaffirms the importance of communication [4,8].

When enquiring about recent symptoms compatible with infection due to *S. pyogenes*, asking staff members individually while their specimens were being obtained produced more information than asking the management. This approach should be taken when investigating future clusters.

Infections due to *S. pyogenes* are most often spread by aerosols produced in the nose and throat of infected people [7]. Screening of residents and staff for *S. pyogenes* carriage was conducted during the cluster investigation as others have done [7,11,13]. Practical problems encountered included the limited availability of infection control nurses in the community to take specimens and difficulty in taking throat swab specimens from residents with dementia. As no *S. pyogenes* were detected among residents and staff, there is no evidence of carriage within the care home was implicated in transmission to the two cases. As swabbing took place about three months after the first case presented, it is possible to speculate that transient carriers were missed from among the five members of staff who gave a history of sore throat occurring during the period since the first case presented.

If two or more cases of invasive *S. pyogenes* occur in a care home, targeted or mass antibiotic chemoprophylaxis for residents and staff should be considered [4,8,9,11-13]. Antibiotic chemoprophylaxis targeted

only at known carriers has been described [8,11,13]. Mass antibiotic chemoprophylaxis for all residents and staff before the results of screening for carriage of *S. pyogenes* are known has been done in other clusters [9,11,12]. The indications for targeted or mass chemoprophylaxis are not well defined [4,5,11] and we hope our experience will contribute to the debate. After a risk versus benefit assessment we did not proceed immediately to antibiotic chemoprophylaxis but decided to await the results of swabbing. There were five reasons for our decision. We were concerned about the unnecessary use of and possible side effects of antibiotics. There was no information about carriage within the care home. Chemoprophylaxis may not eliminate carriage of group A streptococci (in one study the eradication failure rate was 25% [25]). Comprehensive and prompt swabbing and reporting of results was achievable in this population. Staff were being vigilant about symptoms of *S. pyogenes* infection among residents in order to identify possible further cases without delay.

The negative results obtained from swabbing validated the decision not to proceed immediately to chemoprophylaxis. Our experience indicates that screening for carriage of *S. pyogenes* should be done before antibiotic chemoprophylaxis is issued to care home residents and staff.

We observed deficiencies in the infection control practices [20-24] that were in place in the care home. These were communicated to the management and subsequently addressed. Knowledge and understanding varied among staff. We agree with Schwartz et al. that the limited knowledge of infection control practices among staff [7] has made prevention of the spread of infection in care home settings more difficult. The cluster was an opportunity for the home to review
and improve infection control practice and the environment generally. *S. pyogenes* cluster or outbreak investigations need to include a detailed consideration of environmental aspects [5,9,11,13]. Benefits from doing this include optimising measures to decrease the transmission of *S. pyogenes* by fomites [4]. Certain practices were improved with immediate effect including availability and use of PPE, standards of hand hygiene, management of clinical waste disposal, the existing practice of decontamination of commode pots and urinals by hand, and handling and storage of clean and soiled laundry. Infection control practices at the home were revised simultaneously with relevant staff training [23,24] and this approach should be used in future outbreaks.

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The European Commission publishes call for proposals under the 2012 'Ideas' work programme of the 7th Framework Programme

Eurosurveillance editorial team (eurosurveillance@ecdc.europa.eu)[1]
1. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

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On 16 November 2011, the European Commission (EC) published a call for proposals under the 2012 'Ideas' work programme of the Seventh Framework programme of the European Community for research, technological development and demonstration activities (2007-2013) [1].

The title of the call is European Research Council (ERC) Advanced Investigators Grant. Information about the call, the work programme and guidance for applicants on how to submit proposals is available on the EC website [2]. The maximum grant will be EUR 2,500 000 for a five-year period.

The European Research Council (ERC) is a European funding initiative, designed to support the best scientists, engineers and scholars in Europe. Its mandate is to encourage top quality research in Europe through competitive funding and to support investigator-initiated frontier research across all fields of research, on the basis of scientific excellence. The ERC was established by the EC and consists of a Scientific Council and an Executive Agency. It is funded through the EU's Seventh Research Framework Programme. The direct link to the Guide for Applicants may be found on the ERC website [3].

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European Food Safety Authority evaluates public health risk of Shiga toxin-producing *Escherichia coli* (STEC) in seeds and sprouted seeds

Eurosurveillance editorial team (eurosurveillance@ecdc.europa.eu)[1]
1. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

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Tasked by the European Commission (EC), the European Food Safety Authority (EFSA) published a scientific opinion on 15 November 2011 evaluating the public health risk of Shiga-toxin producing *Escherichia coli* (STEC) and other pathogenic bacteria in seeds and sprouted seeds [1].

The EFSA Panel on Biological Hazards (BIOHAZ), author of the opinion, draws the conclusion that sprouted seeds are ready-to-eat foods with food safety concerns because certain pathogenic bacteria such as *Salmonella* and pathogenic *E. coli* (including STEC) can contaminate seeds and grow during sprouting.

Sprouted seeds have been shown to have the potential to cause serious and wide spread food-borne outbreaks. Although *Salmonella* and to a lesser extent pathogenic *E. coli* (including STEC) are the most commonly reported bacterial pathogens causing outbreaks associated with the consumption of contaminated sprouts, other bacterial pathogens (e.g. *Bacillus cereus, Staphylococcus aureus, Listeria monocytogenes* and *Yersinia enterocolitica*) have also been implicated with sprout-associated outbreaks, although very rarely.

As found for *Salmonella*, very low contamination levels of dry seeds, as little as four bacteria/kg, can cause sprout associated-outbreaks. Therefore is it very important to prevent contamination of seeds by pathogens during the production, storage and distribution stages.
Producers of sprouted seeds should aim to implement more stringent food safety management procedures, concludes the Panel, if these are not already in place. Additional measures include Hazard Analysis and Critical Control Point principles, Good Hygiene Practices, Good Agricultural Practices and Good Manufacturing Practices.

EFSA published a report on the public health risk of STEC in fresh vegetables earlier this year which outlined a fast-tracked risk assessment of the exposure of the consumer to STEC through eating raw vegetables [2].

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