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Editorials

Salmonella Typhimurium: experiences from recent European outbreaks

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Salmonellosis is the second most common foodborne infection in the European Union (EU) with a notification rate of 34.6 cases per 100,000 population in 2006 [1]. The disease mainly causes gastrointestinal symptoms such as fever, diarrhoea, abdominal pain, nausea and vomiting but, depending on the strain and the vulnerability of the host, *Salmonella* infections can lead to septicaemia and sometimes death. Many efforts are therefore made to reduce the human burden of salmonellosis. As humans generally become infected by eating contaminated and insufficiently cooked food, the efforts are focused on EU-wide implementation of stricter control measures within the animal and food sectors. These have proven to be effective as the notification rates have been decreasing in the EU during the last years [1].

In this week's issue of Eurosurveillance, four European countries present recent outbreaks of *Salmonella* Typhimurium. *S.* Typhimurium is one of the two serotypes, the other being *S.* Enteritidis, accounting for the majority of salmonellosis cases in Europe (70-80% of the cases with known serotypes) [1]. The emergence of multidrug-resistant *S.* Typhimurium strains, like the definite phage type (DT) 104, in several EU countries is worrying. It is though debatable whether infections with these strains result in higher hospitalisation rates and/or case-fatality rates than infections with other *Salmonella* strains. In this issue, Doorduyn *et al.* [2] describes an ongoing *S.* Typimurium DT104 outbreak in the Netherlands where more than 20% of the cases were hospitalised. Also *S.* Typhimurium strains fully susceptible to antibiotics can still cause widespread outbreaks. This is presented by Schmid *et al.* [3], Grandesso *et al.* [4] and Ethelberg *et al.* [5] in this issue.

These four papers highlight the importance of molecular subtyping in outbreak investigations, which permits to compare strains within and between countries. In the investigations presented, phage typing, Pulsed Field Gel Electrophoresis (PFGE) and Multiple Loci Variable Number of Tandem Repeats Analysis (MLVA) have been used in different combinations. The results show not only that links exist between the countries, as in the outbreaks described by Switzerland [3] and France [4] and some cases in Denmark, which all seem to be caused by the same strain, but that also several outbreaks of the same serotype but different strains may be ongoing in one country simultaneously [2,3,5].

The impact of international food production and trade on infectious diseases is also worth mentioning in this respect. As shown by Schmid *et al.* [3] and Grandesso *et al.* [4] contaminated food products have the potential to cause widespread outbreaks in several countries. An even more illustrative example of that is the recent foodborne outbreak of *Salmonella* Agona linked to products intended primarily for consumption in the made-to-order sandwich trade. The outbreak resulted in over 160 salmonellosis cases in seven EU countries and had implications for additional European countries where the food product had been distributed [6,7]. In order to detect and minimise the extent of such international events, it is vital to ensure rapid communication between public health authorities in different countries and also with the food authorities. Within the human sector, the European Food- and Waterborne Diseases surveillance network (FWD), coordinated by the European Centre for Disease Prevention and Control (ECDC), has an important function as an informal network to assist in the detection of clusters or outbreaks with international dimensions. This network was used for information sharing in all four outbreaks described in this issue. Sometimes even a single case identified with the same strain in another country could be the key to finding the source, something which Doorduyn *et al.* [2] now will investigate in their case-control study.

Articles published in this issue also present a variety of innovative outbreak investigation methods. Doorduyn *et al.* [2] used food consumption studies differentiated by age groups to support the results of the case interviews in an outbreak primarily affecting children. Grandesso *et al.* [4] used case-case comparisons to identify the food items consumed by cases with a particular strain of *S.* Typhimurium compared to cases with other *S.* Typhimurium strains. Ethelberg *et al.* [5] used an even wider array of methods, including for example focus group interviews, matched case-control studies, cohort studies in point source sub-outbreaks, shopping list analyses, case-case interviews, extensive trace-back analysis including geographical analyses etc. Despite all these efforts, the sources of these outbreaks have not yet been identified although pork products are suspected in several of them. The Danish outbreak, which is still ongoing, is by now the largest salmonellosis outbreak recorded in Denmark since the present surveillance system was put in place in 1980. This shows the difficulties that may be encountered in investigating foodborne outbreaks and pin-pointing the source, even when the most advanced epidemiological techniques are being used. It is therefore relevant that Schmid *et al.* [3] bring the general issue of food safety legislation into this context and discuss potentials for improvement in this area based on current EU regulations.

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Outbreak of *Salmonella* enterica serovar Typhimurium in Switzerland, May – June 2008, implications for production and control of meat preparations

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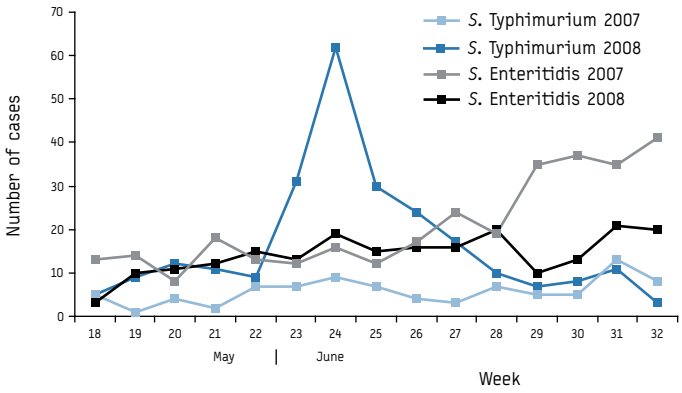
An increased number of *Salmonella* Typhimurium cases were reported in Switzerland between May and June 2008. Investigations involved 72 cases. Results of PFGE typing identified several outbreak strains, the dominating one present in 43 of the 72 isolates. Strains affecting one third of the cases were also found in animal samples, in particular pork. However, no specific food source could be identified. Outbreaks described in this paper highlight the importance of food safety regulations such as those on minced meat and meat preparations issued by the European Commission and adopted by Switzerland into the national law.

Introduction

A sharp and countrywide increase of the number of reported *Salmonella* Typhimurium isolates was observed in May 2008 starting in week 19 and peaking in week 24 (Figure 1). Between early May to late June (weeks 19 – 27), 205 cases (2.70 cases / 100,000 inhabitants) were recorded compared to 44 (0.58 / 100,000 inhabitants) in the same period of the preceding year. In week 28, the number of cases returned to the level of 2007.

Figure 1

Number of reported *Salmonella* Typhimurium and *Salmonella* Enteritidis cases by week of reception of the stool sample in the laboratory, Switzerland, weeks 18 – 32, 2007 and 2008



Methods

A total of 72 patient isolates with dates of isolation extending from week 17 to 27 were subjected to molecular analysis using Pulsed Field Gel Electrophoresis (PFGE) [1] by the National Centre of Enteropathogenic Bacteria (NENT) and the Institute for Food Safety, University of Zurich. Minimal inhibitory concentrations for antimicrobial susceptibility testing of representative strains were determined on Mueller-Hinton agar (Becton Dickinson, Sparks, USA) using E test strips (AB Biodisk, Solna, Sweden).

When a private food quality assurance laboratory reported the isolation of *S.* Typhimurium in pork samples, the cantonal authorities of official food control were asked to intensify the sampling and testing activity of meat products and to submit all *Salmonella* isolates from food analyses to the NENT. Subsequently, four official laboratories of food control (Zurich, Vaud, Fribourg, Liechtenstein) analysed 38 samples of raw meat and meat preparations from pork and 15 samples of raw meat and meat preparations from poultry for the presence of *Salmonella*. Furthermore, 55 samples of ready-to-eat raw meat sausages were tested.

Moreover, 24 patients were interviewed by phone between June 25 and July 7, 2008, using a standardised questionnaire. They were asked about food consumed three days before the onset of illness and travel history during the week before the onset of illness.

Results

Epidemiological data

The cases were located in 22 of the 26 Swiss cantons (203 cases) and in the Principality of Liechtenstein (two cases) (Table 1). The distribution of the cases by age (Table 2) in weeks 19 – 27 showed a shift towards the teenage group (23.4% of cases aged 10-19 years) when compared with the period 2000 - 2007 (13.5%). At the same time, children below the age of five years were much less represented during the outbreak (12.7%) than in the preceding eight-year period (28.0%). The sex ratio male / female seemed to be more even during the outbreak (50.2% / 46.8%) compared to the period 2000 - 2007 (54.0% [range: 49.1-56.9%] / 42.5% [range: 40.0-44.6%]).

Table 1

Number of cases of *Salmonella* Typhimurium and incidences per 100,000 inhabitants in the cantons of residence of the patients, Switzerland, weeks 19 – 27, 2008

Canton	Number of cases	Population	Incidence
Nidwalden	4	40,287	9.9
Grisons	11	188,762	5.8
Uri	2	34,989	5.7
Appenzell Ausser Rhoden	3	52,654	5.7
Lucerne	19	363,475	5.2
Basel-Stadt	8	185,227	4.3
Bern	39	962,982	4.0
Schaffhausen	3	74,527	4.0
Zug	3	109,141	2.7
Basel-Land	7	269,145	2.6
Zurich	31	1,307,567	2.4
Solothurn	6	250,240	2.4
Neuchatel	4	169,782	2.4
Fribourg	6	263,241	2.3
Aargau	13	581,562	2.2
Geneva	9	438,177	2.1
St. Gallen	10	465,937	2.1
Thurgau	4	238,316	1.7
Valais	5	298,580	1.7
Vaud	11	672,039	1.6
Jura	1	69,555	1.4
Ticino	4	328,580	1.2
Total	203	7,593,494	2.7

Note: The Principality of Liechtenstein regularily reports to the Federal Office of Public Health on a voluntary basis. Regarding the outbreak presented here, Liechtenstein reported 2 additional cases, reflecting an incidence of 5.7 cases / 100,000 inhabitants.

Table 2

Age distribution of cases of *Salmonella* Typhimurium in the outbreak in weeks 19 – 27 of 2008, and of all cases of *S.* Typhimurium reported in 2000 – 2007

Age group (years)	Percentage of cases in the outbreak weeks 19-27, 2008	Percentage of all cases reported in 2000-2007
0-4	12.7	28.0
5-9	9.8	14.6
10-19	23.4	13.5
20-29	14.6	9.2
30-39	6.3	8.5
40-49	7.8	6.8
50-59	6.3	7.1
60-69	5.4	5.3
70+	13.7	5.9

Laboratory investigations

The PFGE typing identified several outbreak strains (Figure 2).

The dominating type, designated "strain 2", was found in 43 of the 72 isolates. It appeared for the first time in week 23 and was obviously responsible for the main phase of the outbreak (Figure 3). However, no matching strains from food isolates have been found. None of the 108 samples of raw meat and meat preparations and ready-to-eat raw meat products analysed by four official laboratories of food control revealed *Salmonella* isolates. Other control laboratories reported no *Salmonella* isolations from foods prior and during the outbreak period within their routine testing programs.

"Strain 1" (11 isolates) was present at the beginning of the outbreak and remained up to week 24. "Strain 3" (six isolates) appeared only in weeks 25 and 26. Both strains matched with isolates from pork samples taken from a meat producer/distributor.

Two further pork-related strains were found in some patients. A strain identified in a spare rib sample from Germany (strain pm - processed meat), was found in three patients with an indistinguishable pattern. A strain identified in a sample taken from a pig at a slaughterhouse (strain sl) was isolated from two patients. Strain sl showed a PFGE profile very similar to that of the outbreak strain 3. In fact, one large band appeared to have been split in two smaller ones by a single genetic difference (Figure 2). Strains 3 and sl might therefore be considered two variants of a single clone.

Finally, seven patient isolates yielded PFGE patterns that were different from each other and from all other strains (although one in week 20 resembled strain 1), and can therefore be regarded as sporadic cases. In total, the pork-related strains 1, 3, sl and pm represented 34% (22/65) of the human cases which were not considered sporadic.

The most prevalent PFGE profiles, yielded by strains 1 to 3, were compared to international databases of Enter-Net, Salm-gene/Pulse-Net [2]. All three types matched profiles in the databases (Table 3). For example, strain 1, indistinguishable from JPXX01.0038, was found in seven patients and three non-human specimens (beef and turtle) in 2008 in the United States [personal communication by P. Gerner-Smidt, Centers for Disease Control and Prevention, US]. In Europe, a very similar profile, but with an extra band at 150 kb, was represented by 34 Pulse-Net entries. Strain 2, the dominant Swiss outbreak clone, was found among European data only once. This single entry in the Salm-gene database was submitted as a human isolate of page type DT 193 by German authorities in 2002. Strain 3 was represented three times in the Pulse-net database [personal communication by J. Threlfall and M. Hampton, Health Protection Agency, United Kingdom]. Interestingly, none of the Swiss outbreak strains corresponded to *S.* Typhimurium U292 which is responsible for a large current outbreak in Denmark.

The outbreak strains 1 to 3, as well as strains sl and pm were fully susceptible to the used panel of antimicrobials (ampicillin, ceftazidime, chloramphenicol, nalidixic acid, streptomycin, tetracycline, and trimethoprime/sulfamethoxazole). In contrast, one randomly chosen isolate from a sporadic case (18/022351) was resistant to ampicillin, chloramphenicol and tetracycline (data not shown).

Interview results

Eight of the 24 interviewed patients were found to be infected with pork-related strains 1, 3 or sl. Six of these patients confirmed having eaten pork, one denied it and one was uncertain. The latter two, however, reported that they had eaten chicken and had taken part in a barbecue event where different sorts of meat were grilled, whereby the possibility of cross contamination should be taken into consideration. In further 15 patients among those interviewed the main outbreak strain 2 was found. Eleven of these reported having eaten pork, nine had consumed beef, six had eaten chicken and seven other kinds of meat (lamb, horse), and four participated in a barbecue. Only one patient reported having travelled (to Germany) in the seven days before onset of illness and having fallen ill while travelling, but this patient was among the sporadic cases.

Interviews were not suggestive of any food item other than those mentioned as a possible common source of infection. The variety of mentioned food items and the variety of identified strains favour the possibility that several outbreaks occurred simultaneously.

Discussion

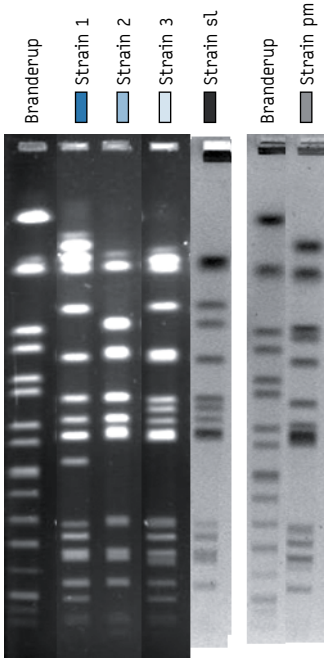
The steep rise in cases of *S.* Typhimurium infections in May 2008 was detected by the mandatory reporting system of the Federal Office of Public Health (FOPH) in the context of infectious diseases surveillance in Switzerland. Within a period of nine weeks, the number of registered cases exceeded almost fivefold those of the preceding year. The investigations in collaboration with the National Centre for Enteropathogenic Bacteria (NENT) and the Institute for Food Safety of the University of Zurich confirmed the ongoing of a countrywide outbreak or – more likely – several simultaneous outbreaks caused by different strains of *S.* Typhimurium. On the other hand, microevolution seems to have already gone on, since strains 3 and sl were differentiated by only one or two bands (Figure 3). Therefore, these two strains could be considered two variants of a single clone.

The findings gathered through the patient interviews showed that there was a median delay of six days between onset of disease and date of reception of the stool sample at the laboratory. In addition, a median delay of 10 days was brought about by the elapsed time between reception of the stool sample at the primary diagnostic laboratory and reception of the notification at the FOPH. In total, two to three weeks could have elapsed between the onset of disease and the registration of the infection. This shows that reducing the statutory notification period (currently one week) to 24 hours would improve the timeliness of patient interviews and of potential public health interventions.

About 34% of the human cases were infected with strains which were also demonstrated in quality control samples of pork from a particular company, on a pig carcass from a slaughterhouse and in an imported (from Germany) spare rib sample. Therefore, the evidence by PFGE analysis of human and food isolates, partly

Figure 2

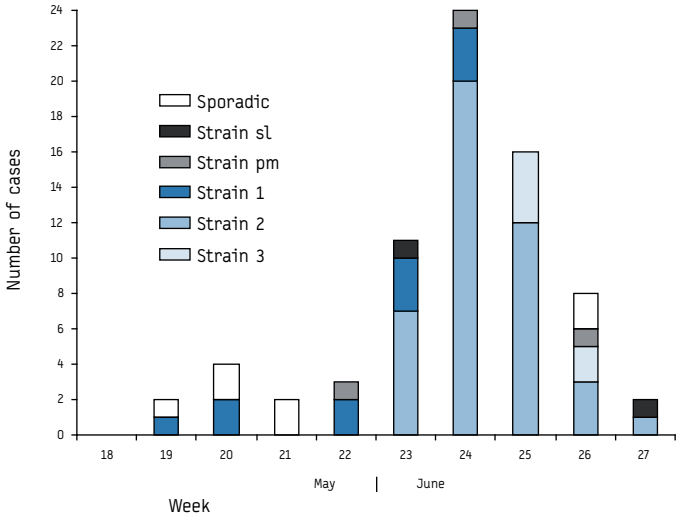
PFGE profiles of the relevant *Salmonella* strains, Switzerland, 2008



Strain 1 (patient 18/027428); Strain 2 (patient 18/027416); Strain 3 (patient 18/027772); Strain sl (slaughter house); Strain pm (processed meat); Braenderup (S. Braenderup (H9812) DNA, restricted with XbaI, and used as a size marker [1])

Figure 3

Number of *Salmonella* Typhimurium isolates belonging to different PFGE types, Switzerland, weeks 18 – 27, 2008 (n=72)



Strains 1, 2, 3 are different outbreak strains; Strain sl (slaughter house) was identified in a pig; Strain pm (processed meat) was found in a meat sample

Table 3

Relatedness of outbreak strains 1 to 3 identified in Switzerland and other *Salmonella* Typhimurium strains deployed in international PFGE databases [2]

Swiss strain	USA[a]	SalmGene / PulseNet Europe[b]	Denmark[c]
Strain 1	JPXX01.0038	STYMXB.0103	JPXX01.0178.DK
Strain 2	no match	STYMXB.0134	JPXX01.0020.DK
Strain 3	no match	STYMXB.0214	JPXX01.0022.DK

a) Courtesy: P. Gerner-Smidt; b) Courtesy: J. Threlfall, M. Hampton; c) Courtesy: S. Ethelberg and R.F. Petersen

supported by patient interviews, allowed the conclusion that about one third of the observed outbreak cases was caused by contaminated pork.

However, in 108 market samples of raw pork and poultry meat, meat preparations and sausages, no *Salmonella* could be isolated. These findings indicated that contamination levels of market products with *Salmonella* must have been low or that the contaminated products were no longer present in the market.

Strain 2 was dominant in the weeks with the majority of cases (43 of 72 cases analysed by PFGE, that may be extrapolated to some 120 of the total 205 cases), but could not be linked to a specific food item. This same profile matched a contemporary cluster of 13 human isolates obtained in Denmark, but was clearly different from strains identified in the large ongoing Danish *S.* Typhimurium U292 outbreak [personal communication by *S.* Ethelberg and R. F. Petersen, Statens Serum Institute, Denmark]. It also matched at least 18 human isolates in France [personal communication by J. de Valk, Institut de veille sanitaire, France]. In France as well as in Switzerland, this strain was found to be fully susceptible to all tested antimicrobials [3].

The pork-related strains 1 and 3 also found their matches in Denmark where strain 3 represented "a rather common profile". Infection through contaminated pork products is also the main hypothesis for the U292 and other *S.* Typhimurium outbreaks that occurred this year in Denmark [4].

Conclusions in the context of food safety legislation

In outbreaks where a large spectrum of foods, such as meat and meat preparations are potential sources of infection, it is more or less accidental to trace a targeted pathogen successfully with a reasonable number of samples. In the present case, market samples were analysed at the end of the outbreak which possibly was too late. The company which found *S.* Typhimurium in several samples of pork in the context of quality control actions launched a large environmental screening for *Salmonella* in their facilities. These investigations clearly revealed that the strain isolated from pork samples was not persistent in the factory but was introduced by pork imported from other European countries. The contaminated meat was processed into products used for barbecue such as pork sausages. The hypothesis that such products contributed to the outbreak is supported by the fact that younger people were overrepresented among the infected persons. In this age group barbecue parties during the summer months are very popular and frequently practiced. Considering this particular risk, FOPH published a fact sheet on hygienic rules to be applied in barbecue events on its website [5].

To prevent outbreaks such as described in this paper, measures have to be taken at the meat production level as well. The faecal carriage of foodborne pathogens among livestock animals at slaughter is strongly correlated with the hazard of carcass contamination. In order to reduce the risk represented by *Salmonella*, the maintenance of slaughter hygiene is consequently of central importance in meat production. *Salmonella* sampling on carcasses is regulated in view of slaughter hygiene monitoring in the European Commission Regulation (EC) No 2073/2005 [6]. In the same regulation, microbiological criteria are decreed for *Salmonella* in minced meat and meat preparations from poultry meat intended to be eaten cooked and minced meat and meat preparations from other species than poultry intended to be eaten cooked (absence in 10 g; n=5; c=0) [6]. This regulation was adopted by Switzerland into the national law [7]. For companies, there remains in fact only one option to deal with the new requirements, namely the use of *Salmonella*-free raw materials for certain final products. There are two ways to reach that target. Either only meat that comes from *Salmonella*-free herds is processed or raw meat is analysed with rapid test for the presence of *Salmonella* prior to further processing. If imported meat is used, the producer has to make it clear to the importing company that only *Salmonella*-free meat is accepted. In this way, a certain pressure will build up on farmers and it is there that the problem has to be addressed. For decades, raw meat has been considered unsafe for consumption since it could contain pathogenic bacteria. With the new EU-regulation which demands the absence of *Salmonella* in minced meat or in meat preparations a change of paradigm occurred. There is no doubt that the practical implementation of this regulation will be a costly and long lasting challenge for all involved stakeholders, in particular the livestock keepers who must make efforts to reduce *Salmonella* prevalence.

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Excess of infections due to a multi-drug sensitive *Salmonella* enterica serotype Typhimurium in France in June 2008

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7. Cellule Interrégionale d'Epidémiologie Nord, Lille, France
8. Cellule Interrégionale d'Epidémiologie Centre, Orléans, France
9. Cellule Interrégionale d'Epidémiologie Ile-de-France, Paris, France
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11. Directions Départementales des Affaires Sanitaires et Sociales, Aude, France
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An unusually high number of cases of *Salmonella* Typhimurium was reported in France in June 2008. In the course of epidemiological investigations 112 cases were ascertained, of whom 75 were interviewed. Subtyping by PFGE and MLVA identified a strain named "majority profile". Subtyping results were available for 45 interviewed cases, 30 of whom (majority below 15 years of age) were found to be infected with the majority profile strain. Evidence suggested the occurrence of an outbreak due to a monoclonal *S.* Typhimurium strain with the single PFGE profile XTYM-50. Cases with identical PFGE profile were also detected in Switzerland but no link with outbreaks occurring in the same period in Denmark and in the Netherlands was found. Contamination of a product distributed nationally was suggested as the cause of the outbreak but investigations did not reveal any specific food source.

Introduction

In the middle of June 2008, several community-based medical laboratories reported an unusually high number of *Salmonella* Typhimurium infections to the French Institute for Public Health Surveillance (Institut de Veille Sanitaire). The laboratories were scattered throughout France and most cases were not linked to each other by a common meal. At that time, national and regional outbreak detection thresholds were not exceeded. Initial sub-typing at the French National Reference Centre for *Salmonella* (Centre National de Référence *Salmonella*, CNR *Salmonella*) revealed that several isolates recently received were susceptible to all antibiotics and exhibited an identical Pulsed Field Gel Electrophoresis (PFGE) and Multiple Loci Variable Number of Tandem Repeats Analysis (MLVA) profile. During the investigation, this profile was then named "majority profile". In the same period, *S.* Typhimurium outbreaks were reported in Denmark [1,2], Switzerland [3] and the Netherlands [4].

We carried out an epidemiological and microbiological investigation in order to confirm the occurrence of an outbreak and, if so, to assess its extent, and to identify a potential link between cases in terms of food or other exposure. We also investigated possible links between notified French cases and the Danish and Swiss outbreaks.

Methods

A case was defined as a person from whom *S.* Typhimurium was isolated in June or July 2008. Cases were identified by contacting all major laboratories in districts where an increase of cases was reported. Patients were interviewed via telephone using a standardised trawling questionnaire on possible exposures including questions on food consumption (dairy, meat, fish, vegetable, pastry and chocolate products), occurrence of other cases in the family, meals in restaurants or other facilities, and animal contacts in the three days preceding the onset of symptoms. Medical laboratories were asked to send their isolates to the CNR *Salmonella* for PFGE [5] or MLVA sub-typing [6].

The French Food Safety Agency (Agence Française de Sécurité Sanitaire, AFSSA) sub-typed by PFGE the *S.* Typhimurium food isolates that were fully susceptible to all antibiotics and had been received through routine collection since January 2008.

We reviewed point-source food-borne outbreaks due to *S.* Typhimurium that were reported through the mandatory notification system during the period investigated.

We carried out a case-case comparison study among individuals who were interviewed and for whom the strain subtype was available. Cases were individuals infected with the *S.* Typhimurium majority profile strain. Controls were selected among individuals who, during the same period as the cases, were infected with a strain of *S.* Typhimurium with a non-majority profile. One individual for each non-majority profile strain was selected, in order to ensure the highest possible heterogeneity of strain profiles among controls [7]. Selected controls were therefore individuals infected with strains presenting different non-majority profiles.

Data were analysed using Stata 9.2 (College Station, Texas). We calculated univariate odds ratios and their exact 95% confidence intervals to examine the risk associated with each exposure. Differences in categorical variables were compared using the $\chi 2$ Fischer exact test.

Results

The number of *S.* Typhimurium isolates received by the CNR *Salmonella* in June 2008 was twice the mean number of those received in June of the previous four years (312 isolates versus 115 mean isolates in 2004-2007). With reference to the date of first laboratory diagnosis, the number of cases started increasing in the first week of June 2008, peaked (95 isolates) in the following week, and gradually returned to the expected seasonal values in the second week of July (Figure 1).

A total of 112 cases were ascertained in districts reporting an excess of cases between June and July 2008. Seventy-five were interviewed.

The CNR *Salmonella* sub-typed 90 isolates received between April and July 2008. Fifty-two isolates presented the MLVA "majority profile": 42 isolates with profile STTR3, number of repeats 11 (500 bp), STTR5, number of repeats 17 (282 bp), STTR6, number of repeats 9 (317 bp), STTR9, number of repeats 4 (171 bp), STTR10, no amplification, and 10 isolates with a single difference either in the locus STTR5 or in the locus STTR6. Isolates with the "majority profile" were fully susceptible to the most commonly used antibiotics [5], showed a Xba-I PFGE profile XTYM-50 and had a different PFGE profile than the DT104 *S.* Typhimurium profile. The remaining 38 isolates presented 31 different MLVA profiles.

The isolated strain was sub-typed for 45 interviewed cases. Thirty cases were infected with the majority profile strain and diagnosed between 3 and 22 June 2008; 15 cases were infected with 13 different MLVA profile strains ("control cases") and diagnosed between 13 May and 21 June 2008.

Among the 30 majority profile strain cases, 24 (80%) were below 15 years of age, all, except one child of 1 month of age, were between 1 and 14 years. Age distribution below 15 years was higher in majority profile strain cases, when compared with *S.* Typhimurium cases recorded at the CNR *Salmonella* in the years 2004-2007 (62%), a difference that was very close to statistical significance (p = 0.057). Male/female ratio among the majority profile strain cases was 1.1. Twelve majority profile strain cases (34%) were residents in one district of region Centre. Two further cases were resident in another district of the same region, and eight cases were living in three neighbouring districts of regions Ile-de-France and Haute-Normandie. The other eight majority profile strain cases were scattered in fours different districts of France (Figure 2).

The French majority profile strain corresponded to the dominant Swiss outbreak strain [3], but did not correspond to the Dutch outbreak strain in August 2008 [4]. Neither the majority profile strain nor any other non-majority profile strain sub-typed during this investigation matched with the Danish outbreak profile [1,2].

Figure 1

Comparison of weekly number of *Salmonella* Typhimurium isolates received in 2008 with mean number for the years 2004-2007, by date of first isolation of the strain, CNR Salmonella, Pasteur Institute, Paris, France

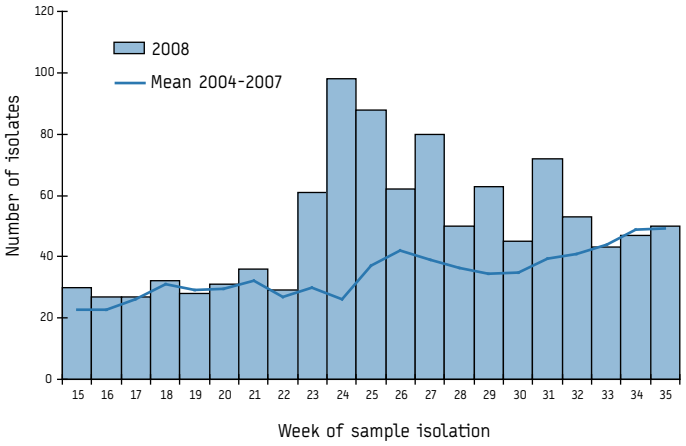
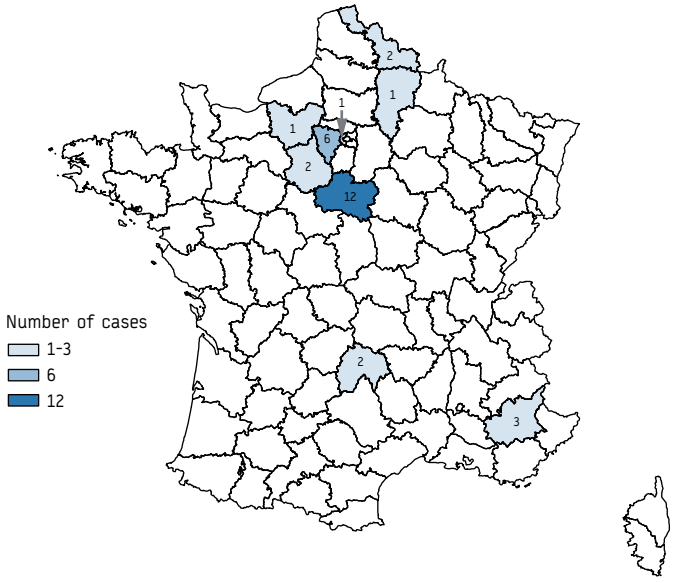


Figure 2

Cases infected with the *Salmonella* Typhimurium majority profile strain PFGE profile XTYM-50, by district of residence, France, June 2008 (n =30)



We identified one notified point source food-borne outbreak due to the *S.* Typhimurium majority profile strain involving two cousins. However, assessments of family food consumption did not permit identification of any exposure that could be incriminated as source of contamination.

The case-case comparison study was carried out on the 30 majority profile strain cases and 13 controls. Cases and controls did not significantly differ in age, symptoms and hospitalisation rate. No food product or other exposure was significantly associated with the majority profile strain infection.

AFSSA sub-typed 22 *S.* Typhimurium food isolates received through routine collection since January 2008. None of these corresponded to the PFGE profile XTYM-50 (majority profile strain) or to the Danish outbreak profile [1,2].

Discussion

Available information strongly suggested the occurrence of an outbreak due to a monoclonal *S.* Typhimurium strain with the single PFGE profile XTYM-50 in France in June 2008. This strain may have affected a younger than usual population. Although the majority of cases infected by this strain were concentrated in three regions, other cases were scattered in other French regions, suggesting the contamination of a product distributed nationally. Cases with identical PFGE profile were also found in Switzerland [3], but microbiological assays indicated no link with the outbreaks occurring in the same period in Denmark [1,2] and in the Netherlands [4].

Despite extensive epidemiological and microbiological investigations, we were not able to identify any specific food or other exposure as possible vehicle or way of contamination which could explain the occurrence of this outbreak. Hence no specific control measures could be proposed following this investigation. In July the number of human *S.* Typhimurium isolates reported at the CNR *Salmonella* returned within the expected values for the season.

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Large outbreaks of *Salmonella* Typhimurium infection in Denmark in 2008

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An outbreak of *Salmonella* Typhimurium phage type U292 has been ongoing in Denmark since 1 April, with 1,054 cases registered until 23 October 2008. Extensive investigations including hypothesis-generating interviews, matched case-control studies, cohort studies in embedded outbreaks, shopping list analyses, analyses of food samples from patient's homes, trace-back analyses and extensive microbiological analysis of products have not provided clear indications of a specific source of infection but the main hypothesis is that the vehicle of the outbreak are different pork products. In addition to the large U292 outbreak, at least four other *S.* Typhimurium outbreaks (caused by phage types U288, DT120, DT3 and DT135) have been investigated in Denmark in 2008.

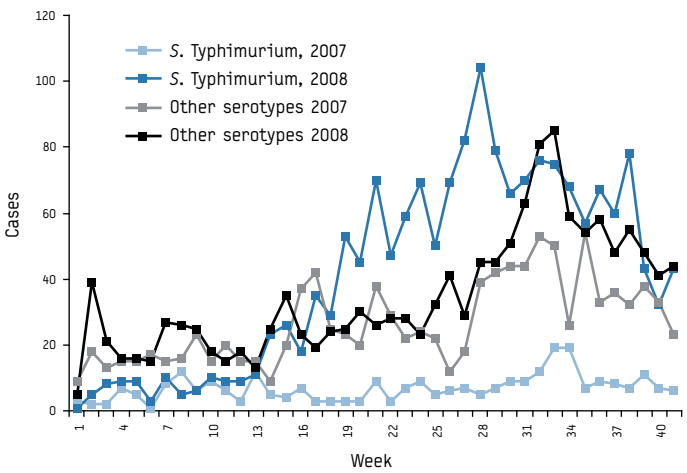
Introduction

The outbreak caused by *Salmonella* enterica serotype Typhimurium phage type U292 which was detected in April 2008 [1] is still ongoing and the source has not been found. The outbreak includes 1,054 patients as of 23 October 2008, thus being the largest outbreak of salmonellosis in Denmark recorded since 1980 when the present surveillance system became active.

The total number of laboratory-confirmed infections with *S.* Typhimurium (phage type U292 and other phage types) was 1,652 as of 12 October 2008; at the same time in 2007 the cumulative annual number of *S.* Typhimurium infections was 285 (Figure 1). In comparison, the number of *Salmonella* Enteritidis infections registered up to this time of the year (i.e. end of week 41) was 557 in 2008, 473 in 2007 and 497 in 2006 [2].The high number of *S.* Typhimurium infections in 2008 include several distinct outbreaks in addition to the U292 outbreak. This report gives a brief account of the present status of the investigations of the U292 outbreak and presents basic epidemiological facts of the other recent *S.* Typhimurium outbreaks.

Figure 1

Number of cases of *Salmonella* Typhimurium and other *Salmonella* serotypes registered by Statens Serum Institut in Denmark for 2007 and 2008, by week of submission of stool sample to the laboratory (weeks 1-41)



Methods

In Denmark clinical microbiology laboratories are required, within one week, to notify Statens Serum Institut (SSI) of findings of salmonella from patient samples. In addition strains are sent to the SSI and further characterised. Currently, all strains of serotype Typhimurium are subtyped using Multiple Loci Variable Number of Tandem Repeats Analysis (MLVA) as a means of detecting outbreaks [3]; furthermore *S.* Typhimurium strains are phage typed and tested for resistance, and selected strains are typed by Pulsed Field Gel Electrophoresis (PFGE). Clusters of patient-isolates with identical MLVA types are investigated as potential outbreaks. The case definition in the outbreaks described here is by MLVA type.

Investigation of the U292 outbreak has been performed using a number of different methods which include the following: 1) Patient interviews performed using telephone-administered trawling questionnaires, focus group interview and home visits, the latter including recently conducted interviews of cases occurring at the Faroe Islands (which are part of the Danish kingdom). 2) Three separate matched case-control investigations with 29/83, 21/41 and 30/35 case/control sets respectively. 3) Investigations into point source sub outbreaks occurring among groups of people in closed settings, including two outbreaks where it was possible to perform cohort studies with 15/8 and 46/24 ill/healthy respondents respectively. 4) Two rounds of comparative analyses of patients'

shopping lists obtained from supermarket computers with 126 cases invited out of whom data were collected for 41 cases. 5) Case-case analyses of interviewed *S.* Typhimurium cases of different phage types. 6) Early visits to homes of suspected *S.* Typhimurium patients in order to collect and analyse samples of food items which might have been eaten prior to onset of symptoms. 7) A large number of trace-back analyses of suspect food products, trade patterns and connections between herds in addition to geographical analyses. 8) Comparative molecular subtyping of patient-isolates with isolates obtained from food, animals and slaughterhouses in Denmark. 9) And finally, investigations, including sampling and microbiological analyses, into many domestic food production facilities and slaughterhouses of which some were selected based on epidemiological leads and some following a structured risk ranging approach.

Results

Outbreak of *S.* Typhimurium phage type U292

The first cases of the U292 outbreak reported onset of illness in February. Over the following three months the weekly number of cases increased and since May has stayed at the level of 30-60 cases per week (Figure 2). The age distribution is skewed towards younger age groups; the median age is 15 years. For comparison 70% of *S.* Typhimurium cases registered in previous years had been older than 15 years of age. The gender distribution is almost even, with 53% female cases. Cases have occurred in almost all parts of the country, but are not evenly distributed among the regions. Nine persons infected with the outbreak strain are known to have died; however, these patients had severe underlying illnesses. The strain is fully susceptible to all antibiotics in the test panel and does not appear to cause severe symptoms; the hospitalisation rate is between 15 and 20%.

Close to 500 cases have been interviewed as part of the different investigations. No vegetarians or persons specifically reporting never to eat pork have been identified in the course of these interviews. Judging by the names of patients, among those who have not been interviewed we have not been able to identify any persons originating from countries where people are predominantly Muslim. The outbreak appears to be confined to Denmark; U292 is a rare phage type and clusters of cases have not been reported from other countries. Less than 10 cases (not counting 14 cases from the Faroe Islands) from outside of Denmark have been detected; they originated from Norway, Sweden and Canada and all, except one, had become infected while staying in Denmark for more than one week.

The analytical epidemiological investigations have largely been inconclusive and not been able to provide a clear indication of the source. Restaurant outbreaks or cases associated with canteens or similar facilities have not been detected, but four distinct embedded outbreaks are known and there are several occurrences of multiple cases within families. The outbreak strain has been found in pork from a major Danish slaughterhouse, in clinically ill calves or cows at three separate farms and at a broiler farm, in addition to food products of pork origin obtained from the home of a case family, but under circumstances that did not allow for epidemiological conclusions to be drawn. *S.* Typhimurium U292 with the same resistance pattern (fully susceptible) and same PFGE pattern (using XbaI), but with a MLVA type differing in two loci, has been found in a number of Danish pig herds within recent months.

Outbreaks of other *S.* Typhimurium phage types

In addition to the large U292 outbreak, at least four other *S.* Typhimurium outbreaks have been investigated in Denmark in 2008 (Figure 3). Outbreak 1 was caused by a strain of phage type U288. It comprised 37 cases and occurred from March to May. Cases were predominantly living near Denmark's second largest town, Århus, and epidemiological investigations showed a clear link to a group of kebab restaurants located in Århus. The precise mechanism of transmission of the infections was not found. U288 is a rare phage type in humans in Denmark, but is known to have been present for many years among pig herds in Denmark.

The three other outbreaks were not geographically restricted. Outbreak 2 was caused by a strain of phage type DT120. There

FIGURE 2

Cases of *Salmonella* Typhimurium U292, with the outbreak MLVA type, by week of submission of stool sample to the laboratory, Denmark 2008, (n=1,054 as of 23 October)

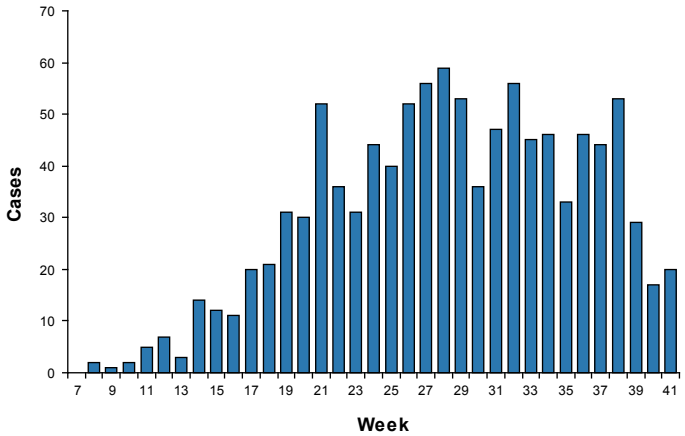
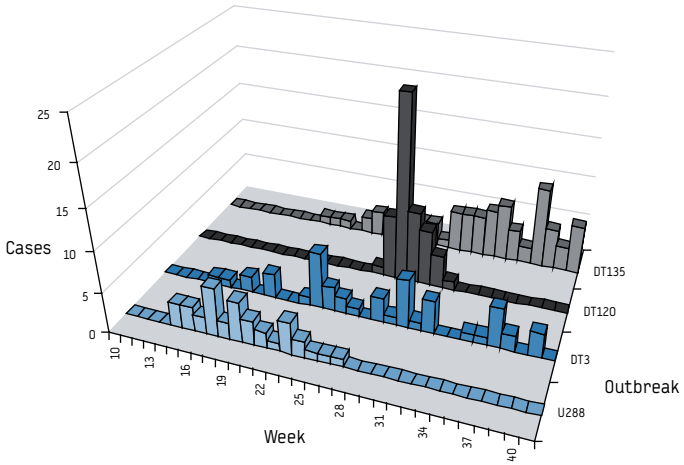


FIGURE 3

Registered cases of *Salmonella* Typhimurium associated with four different outbreaks (U288, DT120, DT3 and DT135), by week of submission of stool sample to the laboratory, Denmark 2008 (n=214, as of 12 October)



were 55 cases predominantly in June and July. As a side-result of investigations into the U292 outbreak, a Danish-produced smoked ham collected from the refrigerator of a case was found positive for this outbreak strain and hence it is believed that this outbreak was caused by consumption of products of the same brand.

Outbreak 3 is caused by a strain of which the majority of isolates have been found to be of phage type 3. Low numbers of cases have been detected since the beginning of the year and are still occurring; currently a total of 50 cases have been registered. A clear hypothesis as to the source of this outbreak does not exist.

Outbreak 4 caused by a strain of phage type DT135 is ongoing. Up to now 77 cases have been registered, predominantly since June. This outbreak shares a number of the epidemiological characteristics of the U292 outbreak. Investigations into this outbreak are ongoing.

Conclusions

The results of the investigations into the U292 outbreak indicate that the outbreak is not caused by a single type of food vehicle. The main working hypothesis continues to be that the outbreak originates from pigs, but it should be stressed that an association with pork or pork products has not been proved and that other hypotheses are also being actively investigated.

Circumstantial evidence pointing towards pork as the source of the U292 outbreak include: Very high exposure to pork among interviewed cases, apparent absence of cases that would refrain from eating pork out of religious beliefs or vegetarianism, findings of the outbreak strain in pork and of closely related strains in domestic pig herds and the lack of strong competing hypotheses. A number of large salmonella outbreaks in Denmark have previously been associated with pork [4-8], however, except for one instance, case-control studies have failed to provide evidence for these links [6].

Among the non-U292 outbreaks, the one caused by *S.* Typhimurium DT120 was likely to be associated with Danish produced salted, smoked and cooked ham. It is possible that some of the increased numbers of infections with *S.* Typhimurium observed in Denmark, including the currently ongoing outbreak of *S.* Typhimurium DT135, are also associated with consumption of pork or pork products, which would point to the same general food safety problem. However, due to lack of clear evidence more definite conclusions leading to possible control measures are not possible at this stage of the investigations.

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A large number of persons have been involved in these outbreak investigations, including regional food control officers, medical officers, staff from the clinical, typing, food and veterinary laboratories and other members of the National Food Institute, Statens Serum Institut, Veterinary and Food Administration, National board of Health and Regional Veterinary and Food Control Authorities.

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Salmonella Typhimurium outbreaks in the Netherlands in 2008

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A large, countrywide outbreak due to multi-resistant *Salmonella* Typhimurium phage type DT104 is ongoing in the Netherlands, with 152 cases as of 20 October. Pilot interviews did not suggest any specific source of infection but a hypothesis pointing to pork products has been formulated and a large case-control study is under way. Earlier this year two other oubtreaks due to *S.* Typhimurium were detected and investigated, the first (DT15A) linked to a particular brand of cream cheese, the other (Dutch phage type ft507) to a local butcher.

Introduction

In August 2008, a marked increase in the number of reported infections with multi-resistant *Salmonella* enterica serotype Typhimurium phage type DT104 was observed in the Netherlands. The outbreak is still ongoing, with 152 patients included as of 20 October 2008. The outbreak strain is resistant to ampicillin, tetracycline, co-trimoxazol, streptomycin and chloramphenicol and is also less susceptible to ciprofloxacin (minimum inhibitory concentration – MIC 0.25) and nalidixic acid (MIC > 64). Of the patients, more than 20% were hospitalised. Cases are distributed countrywide and no travel-related cases have been reported. The age distribution is similar to that of sporadic *S.* Typhimurium cases and the sex ratio male / female is 1.0. A case-control study is currently being performed. In this report we shortly review the present status of the investigation of the DT104 outbreak and we describe the investigations of two other recent *S.* Typhimurium outbreaks.

Methods

This outbreak investigation used the Dutch laboratory-based salmonella surveillance at the National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu – RIVM) as a source of laboratory data on *S.* Typhimurium DT104 cases and descriptive statistics with regard to age, gender and place of residence of the patients [1]. All strains were subtyped using Multiple Loci Variable Number of Tandem Repeats Analysis (MLVA) and Pulsed Field Gel Electrophoresis (PFGE).

Between 10 and 17 September, trawling interviews with eight recent DT104 cases were performed by telephone using a standardised questionnaire. These interviews covered consumption of different meats, fish, dairy products, vegetables and fruits, establishments where food was purchased and contact with animals in the seven days before onset of illness.

A case control study was started on 22 September. In the case-control study a case was defined as a person in whom *S.* Typhimurium DT104 was isolated after 25 August 2008. Local public health services were asked to contact the cases (after approval of the laboratories and treating physician) to collect their e-mail addresses or, if not available, their home address. Questionnaires were sent to the cases by e-mail using Questback or by post. 240 frequency-matched controls (matched for age, gender and degree of urbanisation) were selected from the Dutch population register and were sent a postal questionnaire. In addition, cases were asked to nominate two controls of the same age (less than 5 years difference) and not living in the same household.

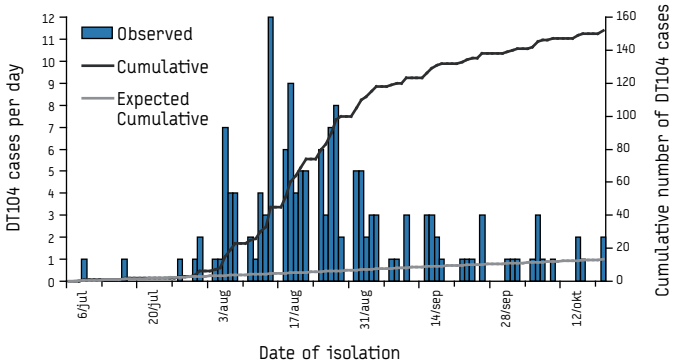
Results

Outbreak 1: *Salmonella* Typhimurium DT104

The first cases of the DT104 outbreak were reported in the beginning of August 2008. The number of cases clearly exceeded the expected cumulative number of cases based on a 5-year time series analysis (Figure 1). By September, the weekly number of cases declined, but the outbreak is still ongoing with 5 to 10 cases reported each week. The age distribution is similar to that observed in sporadic cases of *S.* Typhimurium DT104 in the Netherlands and the gender distribution is even (Figure 2). No regional clustering of cases was observed.

Figure 1

Number of *Salmonella* Typhimurium DT104 isolates by date of isolation, the Netherlands 2008 (n=152)



MLVA typing of 117 strains showed several MLVA types of which type 02-07-12-10-03 dominated: 62 strains had this MLVA type and 36 strains differed only on one locus, of which 20 strains had MLVA type 02-07-12-10-00. These in total 98 strains were considered as related. This MLVA type had not been found in the Netherlands before. All isolates shared the same PFGE profile.

The PFGE profile and the dominant MLVA type were compared to those in databases in other countries. The dominant MLVA type was also found in one patient from Denmark who became ill on the first of August after consumption of sliced ham from a well-known Dutch exporting butcher. Furthermore, in an outbreak in West London in the beginning of August an MLVA type was found that differed on one locus from the dominant MLVA type, but the source of the outbreak was unknown [personal communication with Chris Lane and Tansy Peters, Health Protection Agency, United Kingdom].

The trawling interviews with eight cases did not lead to a clear hypothesis about the possible source of infection, but it appeared that fish and dairy products and contact with animals were unlikely as sources of infection. Subsequently, a case-control study was started to further explore possible sources and to ask detailed questions on food items mentioned frequently in the trawling interviews. In the case-control questionnaire, we reduced the number of questions about consumption of fish and dairy products and contact with animals and we added more detailed questions about other food items, including consumption of sliced ham. In total, 75 cases matched the case definition for the case-control study. So far, 36 cases (48%) have completed the questionnaire and another nine cases have been invited by e-mail. Ten of the 36 cases (28%) had been hospitalised. Of the 240 community controls, 60 (25%) have completed the questionnaire to date. Cases nominated only eight controls and six of them completed the questionnaire. We are awaiting the results of the analysis of the case-control study, which will be done in the following weeks. So far, no clear conclusion could be drawn from the case questionnaires.

In addition to the DT104 outbreak, two other *S.* Typhimurium outbreaks have been investigated in the Netherlands in 2008.

Outbreak 2: *Salmonella* Typhimurium DT15A

In March 2008, a countrywide outbreak of *S.* Typhimurium DT15A was detected: 27 cases were identified, whereas only four cases of this phagetype occurred in the past five years. 63% of the cases were below six years of age. Of the cases older than 15 years, 83% were women. Of the 19 interviewed cases, 16 (84%) reported consumption of cream cheese of a brand that is very popular among young children. Instead of comparing with controls in a case-control study, we compared the information of the cases with results from the Food Consumption Survey performed in 2005 and 2006 among 1700 children aged 2-6 years. This supported the hypothesis that cream cheese of a specific brand was the likely source of infection. The Dutch Food and Consumer Product Safety Authority did not find any abnormalities when visiting the producer. The exact methodology of this investigation will be published in more detail in a forthcoming short report.

Outbreak 3: *Salmonella* Typhimurium (Dutch phagetype ft507)

In the middle of June 2008, a local outbreak of *S.* Typhimurium (Dutch phagetype ft507) in the south-west of the Netherlands was detected. Patient interviews showed a clear link to a local butcher. The exact vehicle of transmission of the infections remained unknown. The Dutch Food and Consumer Product Safety Authority tested several meat products and environmental swabs for the presence of *Salmonella*, but all were negative. In total, 18 laboratory-confirmed cases were identified between 30 May and 14 June.

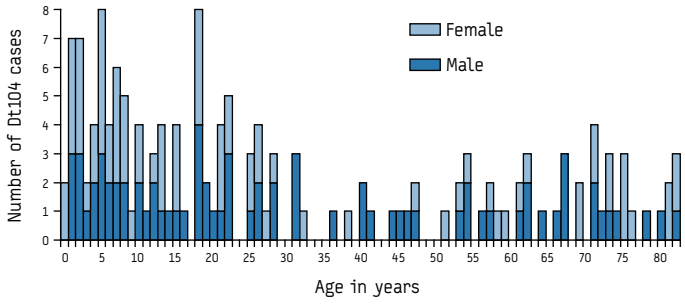
Conclusion

A large, countrywide *S.* Typhimurium DT104 outbreak is still ongoing in the Netherlands. As the outbreak strain is multi-resistant and has reduced susceptibility to ciprofloxacin, it causes severe symptoms and the hospitalisation rate is high. The outbreak is currently under investigation. Pilot interviews did not lead to a clear hypothesis. However, fish, dairy products and contact with animals were less likely sources of infection. One hypothesis comes from a matching MLVA-type from a patient in Denmark who consumed ham from a Dutch exporting butcher. So far, this is the only lead to a possible source of infection. The case-control study should reveal whether ham is a likely source.

Earlier in 2008, we experienced two other *S.* Typhimurium outbreaks in the Netherlands. A regional outbreak in June was related to a local butcher, but the exact vehicle of infection was not identified. Another nationwide outbreak in March was likely associated with cream cheese of a specific brand. Several other European countries have experienced *S.* Typhimurium outbreaks of various subtypes this year. Denmark faced four outbreaks and is currently experiencing a large-scale nationwide outbreak of *S.* Typhimurium U292. In spite of extensive investigations, the source or sources of infection have not yet been identified, but the main hypothesis is that the source is one or more pork products [2,3]. In February, *S.* Typhimurium U292 was found in a pig in the Netherlands, but no further link with the Danish outbreak was found. Outbreaks in Switzerland and France in May to July shared the same strain [4,5]. The Swiss investigation revealed that pork was the probable source. Microbiological data indicated that the Dutch outbreaks were not related to any of the outbreaks occurring in Switzerland, France and Denmark in the same period.

FIGURE 2

Age and gender distribution of registered cases in the *Salmonella* Typhimurium DT104 outbreak, the Netherlands, 2008 (n=152)



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Import of norovirus infections in the Netherlands and Ireland following pilgrimages to Lourdes, 2008 – preliminary report

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Between mid-September and 19 October 2008, nine clusters of norovirus infection involving around 90 primary cases and over a hundred secondary cases were identified in patients from the Netherlands, Ireland, Italy and France, linked to pilgrimage to Lourdes, France.

Introduction

Norovirus is a highly infectious causative agent of acute gastroenteritis (AGE). Transmission can easily occur through contact with people shedding the virus, through consumption of contaminated food or water , through contaminated aerosols resulting from vomiting, and through environmental contamination [1]. Once the virus is introduced in settings with a high concentration of people, person-to-person transmission is likely to occur [2]. Attack rates are high among all groups of people, however, the impact of the disease is more serious among the elderly [3]. Within Europe, norovirus outbreaks are monitored by the *Food-borne Viruses in Europe* (FBVE) network, which has been collecting molecular and epidemiological data since 1999 [4].

Lourdes, France, is a major destination for Christian pilgrimage following claims of apparitions in 1858. A yearly number of five million people, including many with underlying diseases, visit Lourdes and often collect spring water for consumption, which is believed to possess healing properties. With 2008 being the 150th anniversary of the apparitions, the number of visitors has increased to eight million this year, with a peak in visitor numbers around the time of the Pope's visit. Norovirus outbreaks have previously been linked to pilgrimage to Lourdes in 2002 [5, FBVE unpublished data].

Outbreak report

On 20 October 2008, the FBVE network was notified of an outbreak due to norovirus in a mental health care institution for the elderly in the Netherlands, that had serious consequences. Norovirus was confirmed in two patients.

A group of 10 patients and 14 health workers at the institution had visited Lourdes between 26 September and 1 October as part of a group of 1,025 Dutch pilgrims. On 29 September, one of the health workers started showing symptoms of AGE that lasted 24 hours and made it necessary that she stayed in the hotel room. During the return trip by train on 1 October, one of the patients in the group became symptomatic and required medical assistance. After the group had returned to the Netherlands, the virus spread within the institution.

A total of 119 of the 550 institutionalised patients and health care workers (22%) showed AGE symptoms. At the time of publication of this report, the outbreak was still ongoing due to difficulties in compliance with the control measures in this particular group of patients. Four people (3%) died during this outbreak, with norovirus reported as a contributing factor. One patient is still hospitalised and in critical condition.

Norovirus infection is not a notifiable disease in the Netherlands unless outbreaks occur in institutions. As information form the Dutch organisation that facilitated the trip indicated that more pilgrims were returning from Lourdes with symptoms of AGE, the Center of Infectious Disease Control (RIVM/CIb) requested the Municipal Health Services and microbiologists to report norovirus infections related to Lourdes. This resulted in three more AGE notifications: two clusters of Dutch pilgrims who had visited Lourdes between 16 and 23 September, one of which led to secondary cases in the patient's family, and an elderly pilgrim with confirmed norovirus infection who required hospitalisation 32 hours after returning from Lourdes on 18 October. RT-PCR and subsequent sequencing of parts of the polymerase (region A) and VP1 capsid (region D) genes identified this strain as the widely detected genotype II.4 2006b variant.

Other cases related to this outbreak

An alert within the FBVE-network revealed that other outbreaks of AGE with a link to Lourdes had been reported. Ireland noted three clusters of norovirus infections:

- one involving 40 patients infected in Lourdes in late September,
- one involving 20 cases infected in Lourdes between 1 and 15 October,
- and one cluster involving two cases infected in Lourdes between 1 and 15 October, one of whom required hospitalisation and caused 11 secondary cases in the hospital.

Epidemiological investigation

Local investigation by the French Institute for Public Health Surveillance (InVS) pointed out that at least six hotels with Dutch, French and Italian visitors were coping with AGE patients, who may include two Dutch clusters and one Irish cluster, in the period between 28 September and 16 October. Laboratory tests were done in France and norovirus was confirmed in three people, housed in three different hotels that experienced outbreaks: two samples from Dutch patients and one sample from a French patient. All three samples were found to be positive for the genotype II.4 2006b variant, with the sequence of region A and parts of the capsid gene identical to the one detected in the Dutch cases described above, but also to isolates found in outbreaks not linked to Lourdes.

To summarise, around 90 primary cases of AGE were reported in Lourdes, belonging to seven different pilgrim groups from the Netherlands, Ireland, Italy and France, resulting in more than a hundred secondary cases. These groups were housed in six hotels in Lourdes between mid-September and 16 October. Physicians and pharmacists in Lourdes reported a small peak in diarrhoea consultations between 22 and 26 September, coinciding with the peak in the number of pilgrims related to the Pope's visit.

The French district health office regularly checks the bacteriological quality of the tap and spring water in Lourdes, which were both in accordance with the required standards.

Discussion

In this rapid communication we report one single case in the Netherlands and at least nine clusters of AGE that occurred between mid-September and 19 October 2008 following pilgrimage to Lourdes: three clusters in the Netherlands, three in Ireland, and six in France, of which three are possibly overlapping. One case/cluster and four clusters were tested by RT-PCR, and noroviruses of a commonly detected genotype were found in all of these patients. One of the confirmed clusters led to a large outbreak in a mental health institution that is still ongoing. The substantial attack rate and case fatality rate in this institution reflects the vulnerability of the patient group in which the virus was introduced.

Although detailed information on the source of exposure is not (yet) available, person-to-person spread is likely to be the most important route of transmission in this outbreak, given the large numbers of people visiting Lourdes and the health condition of the exposed population, since it is mainly people with delicate health who visit the site for its healing properties In 2002, a comparable situation was reported from Switzerland [5]. Once norovirus is introduced in settings with high concentrations of people, environmental contamination is likely to occur, for example due to projectile vomiting, which is an effective transmission route [6]. Furthermore, introduction of the virus through food or water cannot be ruled out. The spring water that is drunk by the pilgrims was approved according to bacteriological quality standards, but this does not exclude the presence of viruses [7,8]. Information on locations visited by the cases in the days before their illness will be collected to support France in the outbreak investigation.

It is of interest to know whether norovirus continues to circulate among pilgrims in Lourdes. If so, travel agencies and visitors should be informed to be able to take preventive measures around any visitor showing symptoms of AGE during their stay in or returning from Lourdes. The latter is particularly important if the traveller lives among fragile people, for instance in a nursing home or hospital. Hotels housing vulnerable people should be alert when visitors show symptoms of AGE.

To determine whether the outbreak is still ongoing in Lourdes, and to determine the consequences of this outbreak, the FBVE network is interested in laboratory specimens of related cases. If you have any additional information on confirmed cases linked to Lourdes, please contact fbve@rivm.nl.

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Mapping the future dynamics of disease transmission: risk analysis in the United Kingdom Foresight Programme on the detection and identification of infectious diseases

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This paper reflects on the qualitative risk analysis framework developed for a Foresight study on the Detection and Identification of Infectious Diseases, which was coordinated in 2005 by the United Kingdom (UK) under what is now the Government Office for Science, Department for Innovation, Universities and Skills. The risk assessment covered human, plant and animal diseases in the UK and Africa in the years 2015 and 2030. Through engaging a diverse pool of experts, we developed a model conceptualising disease spread as the outcome of interactions among sources, pathways and drivers. We then used this model to conduct a Delphi survey of experts. The factors perceived most likely to contribute to infectious disease spread in 2015 and 2030 included geographic extension of existing pathogens (partially due to climate change), over-use of antibiotics/antivirals/pesticides leading to drug resistance, and zoonoses. Our methodology provides a framework for those who need to integrate a wide range of perspectives and factors into their planning and analyses.

Table 1

Main categories of drivers associated with emergence and reemergence of human pathogens (reproduced from Woolhouse *et al.* (2005) [5])

Rank*	Driver
1	Changes in land use or agricultural practices
2	Changes in human demographics and society
3	Poor population health (e.g., HIV, malnutrition)
4	Hospitals and medical procedures
5	Pathogen evolution (e.g., antimicrobial drug resistance, increased virulence)
6	Contamination of food sources or water supplies
7	International travel
8	Failure of public health programs
9	International trade
10	Climate change

* Ranked by the number of pathogen species associated with them (most to least).

Introduction

It is by now well documented that a wide range of factors, including changes in land use and agricultural practices, changes in human demography, pathogen evolution, international travel and trade, climate change, and poor public health infrastructures can all trigger or exacerbate the spread of infectious diseases, determining how and where they will emerge in the future and the circumstances under which they could progress to epidemic or even pandemic proportions (Table 1) [1-5].

Less widely documented are methods for analysing these factors in ways that enable a better understanding of how they are interlinked and how to prioritise their importance. One of the key challenges is that relevant information, when available, is not consolidated in a few hands but spread across numerous institutions and disciplines. Anticipating the emergence or altered transmission of any disease is likely to require expertise in biology, epidemiology, animal and human medicine, demographics, economics, and even sociology and anthropology. Although the importance of cross-sectoral collaboration in disease control is increasingly recognised [6-8], there remains the need to develop new ways of ensuring that diverse and sometimes divergent perspectives are accounted for. Doing so is essential for developing multi-sectoral understanding and commitment – increasingly required for the pursuit of pubic health action in a rapidly changing world.

With a long-term vision in mind, the United Kingdom (UK), under what is now the Government Office for Science, Department for Innovation, Universities and Skills, conducted a Foresight project on Detection and Identification of Infectious Diseases (DIID) with the objective of supporting strategic investment in disease detection, identification and monitoring technologies and systems [9-12]. This paper reflects on the risk analysis component of the DIID project, describing a methodology that could be adapted to subsequent analyses.

Methodology

We analysed expert opinion on infectious disease risks in plants, animals and humans, in sub-Saharan Africa and the UK in 2015 and 2030 (comprehensive details on the methodology, workshop

and survey results are available at the Foresight website [12]). Potential changes in sources, pathways and drivers of disease risks were identified and assessed according to how the magnitude and nature of risks are evolving, as well as the range of plausible future risk patterns. Research questions focused on:

- Factors driving changes in infectious disease risks ('risk drivers') and how they might evolve;
- Future risks for infectious diseases and their importance;
- Uncertainty attached to future risks;
- Comparisons among plant, animal and human disease risks.

To answer these questions a preliminary scoping phase, which included an expert workshop, developed an understanding of important issues and their interactions and formulated the overall approach to the research. A Delphi survey was then carried out in order to assess a broad range of expert opinions on future risks in the UK and Africa.

Scoping phase

The scoping workshop brought together 22 UK infectious disease experts (recommended by the UK Foresight Scientific Advisory Group) to advise on the challenges presented by new and emerging infectious diseases. A disease systems model was developed (Figure 1), as well as an initial list of key factors ("drivers") likely to give rise to changes in disease patterns and emergence of new diseases, such as biological changes and socio-economic factors acting on disease sources and pathways of disease spread. The initial long list of drivers derived at the workshop was refined and clustered under the six main headings listed in Table 2.

Identification and selection of participants for the survey

The experts who took part in the Delphi survey were scientists selected to cover a broad range of expertise in plant, animal and human diseases, from epidemiological modelling, disease identification and disease pathology to disease control, regulation and policy making. They were selected upon the advice of approximately 30 senior advisers who took part in the DIID Foresight project, including members of the UK Foresight Scientific Advisory Group, the UK Foresight High Level Stakeholder Group and UK Health Protection Agency staff, to represent the best available informed judgement across our six areas of interest – the future development of plant, animal and human diseases in the UK and in sub-Saharan Africa.

African respondents from 20 countries in sub-Saharan Africa were invited on the basis of the best available expertise, rather than ensuring geographical equity. Francophone countries were under-represented as we did not have sufficient time within the project to translate questionnaires. This omission may have influenced the findings. There was, however, no evidence of any specific bias among the 55% respondents who completed the questionnaires, with relatively equal representation across the six survey areas (Table 3), and also across relevant areas of expertise (20 areas of expertise were mentioned in the questionnaire responses).

Questionnaire development

A two-stage questionnaire-based survey was sent to 145 experts in infectious diseases from the UK and sub-Saharan Africa. In the second stage of this Delphi-type process [13], respondents were given the results from the first phase and asked to re-assess their own responses. Where their opinions diverged from those of others they were asked to explain their reasons rather than being encouraged to reach a consensus.

The questionnaire was based on the disease systems model (Figure 1, Table 2), but slightly different versions were sent out depending on whether the participants were being asked about human, plant, or animal diseases. Nonetheless, the questionnaires were designed so as to be as comparable as possible. For example, question 3.2.4 in Table 2 was worded as "lack of availability of new vaccines or engineered resistance", broadening the scope of the question from vaccines (mainly relevant for humans and animals) to also include engineered resistance (mainly relevant for plants and animals). As another example, question 2.9 in Table 2 shows a question that was worded differentially depending on whether it was considering animal or human diseases; however, this question was not included in the plant diseases survey.

Each questionnaire asked about future changes in disease sources, pathways and drivers, leading to future disease outcomes. These terms were defined as follows:

- Sources: phenomena or biological events that give rise to potential new diseases, enable existing diseases to become more harmful, enable existing diseases to infect new hosts, or enable existing diseases to spread to new areas;

FIGURE

The disease systems model as a tool for assessing future infectious disease risks

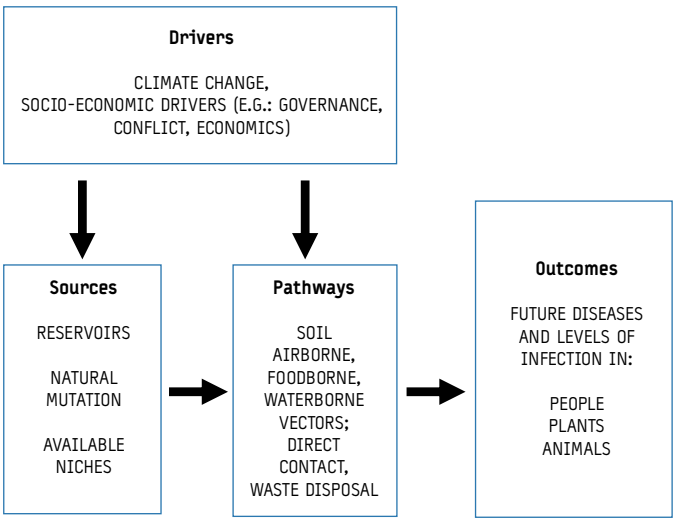

TABLE 3

Sample size, UK Foresight questionnaire, 2005

Questionnaire type	No. distributed	No. of responses (Round 1)	No. of responses (Round 2)
UK animals	20	10	6
UK humans	20	12	5
UK plants	24	13	5
Africa animals	29	18	11
Africa humans	27	13	9
Africa plants	25	14	6
Total	145	80	42

Table 2

Classification of factors influencing the spread of infectious disease, Foresight questionnaire, 2005

	Sources
1.1	New pathogens or new strains of existing pathogens arising through natural genetic change
1.2	Geographical expansion of pathogens
1.3	Emergence of new disease vectors
1.4	Failure of engineered resistance (e.g. vaccines, genetically manipulated animals/crops)
1.5	Increased number of accidental introductions of pathogens
1.6	Increased pathogen resistance (e.g. to microbicides, antivirals, pesticides)
1.7	Decreased immuno-competence of target populations
1.8	Emergence of new diseases from other species reservoirs, including wild species reservoirs
	Pathways
2.1	Increased role of soil-borne route for disease spread
2.2	Increased role of air-borne route for disease spread
2.3	Increased role of water-borne route for disease spread
2.4	Increased populations of disease vectors
2.5	Increased host-to-host transmission due to increased density of host populations
2.6	Increased role of food-borne (or feed-borne) route for disease spread (plant diseases excluded)
2.7	Increased role of food-borne (or feed-borne) route for disease spread (plant diseases excluded)
2.8	Increased spread of disease in veterinary hospitals and/or herding of animal for veterinary interventions (animal diseases) OR Increased spread of disease in hospitals (human diseases) (plant diseases excluded)
2.9	Increased spread of disease through mass veterinary interventions (e.g. campaign vaccinations with shared needles) (animal diseases) OR Increased spread of disease through blood/tissue (e.g. needle sharing, blood transfusions, transplantation) (human diseases) (plant diseases excluded)
2.10	Increased spread of disease due to sexual contact (human diseases only)
	Drivers
3.1	Legislation and government systems
3.1.1	Lack of adequate systems for disease control
3.1.2	Lack of adequate surveillance systems to detect and monitor diseases
3.1.3	Poor implementation of national legislation on disease surveillance and control
3.1.4	Poor implementation of international legislation on disease surveillance and control
3.1.5	Lack of or ineffective biosecurity legislation regarding disease surveillance and control
3.1.6	Low degree of inter-institutional cooperation
3.1.7	Failure of government bodies to accurately or honestly report disease incidences
3.2	Technology and innovation
3.2.1	Lack of innovation in relevant and rapid technologies for detection and identification of existing diseases
3.2.2	Lack of innovation in technologies for detection and identification of new diseases
3.2.3	Lack of innovation in information technology for disease surveillance and communication
3.2.4	Lack of availability of new vaccines or engineered resistance
3.2.5	Development of potential new pathogens for bioterrorism
3.2.6	Drug use leading to the emergence of drug-resistant disease organisms
3.2.7	Lack of new food preservation and decontamination technologies
3.2.8	Lack of new drugs (or pesticides for plants) to control disease
3.3	Conflict and war
3.3.1	Loss of effective detection and identification systems
3.3.2	Increased movement of people (e.g. refugees, armies) spreading disease
3.3.3	Damage to infrastructure (e.g. water, sewage, power supplies)
3.3.4	Increased bioterrorism, exploiting existing diseases
3.3.5	Increased use of wild species as alternative human food source (plant diseases excluded)
3.4	Economic factors
3.4.1	Decreased economic prosperity
3.4.2	Increased disparity between rich and poor
3.4.3	Increase in trade and transport of animals and crops
3.4.4	Decreased average education levels
3.4.5	Reduced quality of sanitation and water supplies
3.4.6	Increased movement of migrant workers, spreading disease
3.4.7	Increased number of disease-susceptible individuals in the population
3.5	Human activity and social pressures
3.5.1	Decrease in public willingness to change behaviour in order to help contain or prevent disease
3.5.2	Decrease in individuals' readiness to report disease incidences
3.5.3	Increase in illegal practices leading to spread of disease
3.5.4	Malnutrition/poor husbandry of animals/crops affecting resistance to disease
3.5.5	Increased travel related to tourism and international business, spreading disease
3.6	Climate change
3.6.1	Increase in mean temperature in the range of 0.5-2.0 °Celsius
3.6.2	Increase in frequency of heavy rainfall events and/or flooding
3.6.3	Increase in frequency of drought in arid and semi-arid areas

- Pathways: mechanisms or routes by which a disease-causing organism can be transferred from one host to another, within or between species;
- Drivers: social, economic, biological or environmental factors that affect disease outcomes, by changing the behaviour of disease sources or pathways;
- Outcomes: plants and animals at the individual, community and ecosystem, or farming system level, and humans at individual and societal levels, that are affected by infectious diseases.

'Drivers' operate in the infectious disease system through 'sources' of disease emergence and/or 'pathways' of disease transmission to determine the 'outcome' in terms of the emergence of future diseases and the levels of infection.

'Risk' was defined as the product of 'the future extent of a hazard' and 'the probability of occurrence of that hazard'. For each factor listed in Table 2, the respondents were asked to rate the extent and probability of different outcomes in the years 2015 and 2030, on a three-point scale. The survey thus provided a systematic method for gathering informed opinions on rankings of the impact of drivers on sources and pathways, as well as on the importance of changes in sources and pathways themselves.

The questionnaires also asked respondents for additional observations, including the phenomena or processes they thought were likely to decrease risk and what they expected to be future risks (for example, which classes of diseases or organisms were likely to represent the greatest risk).

Data analysis

Questionnaires generated qualitative scores for both the perceived extent of the hazard and the perceived probability of its occurrence (1, 2 or 3; low, medium or high). The risk associated with a particular factor for each source, pathway and driver was then calculated as the product of these two scores, giving a range of potential values: 1, 2, 3, 4, 6 or 9. , Thus we compared the perceived importance of sources, pathways and drivers in contributing to future disease outcomes for the six risk questionnaire categories (permutations of host and location: Africa-human (AH), UK-human (UKH), Africa-animal (AA), UK-animal (UKA), Africa-plant (AP), UK-plant (UKP)). We focused on factors that were consistently predicted to be of higher risk through a data filtering process - risk assessments were categorised as low, moderate or high as follows:

- Low risk: an overall score in the range 1-3, i.e. either hazard or probability were scored as low (1);
- Moderate risk: an overall score of 4, i.e. both hazard and probability were scored as moderate (2);
- High risk: an overall score of 6 or 9, i.e. either hazard or probability were scored as high (3) and the other was scored as moderate or high (2 or 3).

The first filter selected the cases for which more than 50% of the responses were in the moderate or high category (scores 4, 6 or 9). The second filter selected cases for which more than 50% of responses were in the high category (scores 6 or 9).

Survey results

Participants

The response rate in the first round of the survey was 55%, and 53% of the first round respondents contributed to the second round (Table 3). The respondents' self-reported areas of expertise were primarily: epidemiology (12%), virology (9%), pest and disease management (8%) and animal health and veterinary science (7%). This participation rate was more than sufficient to conduct the analysis, as breadth of expertise was deemed to have priority over absolute number of respondents. The declining number of respondents from the first and second round partially reflects those participants that did not feel that they needed to alter their responses.

Risk assessments

The complete survey results are available on the UK Foresight website [10]. Table 4 compares the factors which, for 2015 and 2030, passed the first and second filters of 50% or more of respondents.

The highest perceived risks (for 2030) related to:

- new pathogens or new strains of existing pathogens arising through natural genetic change;
- and geographical expansion of pathogens from within or outside the UK and Africa.

In five of the six categories there was a perceived high risk of:

- new diseases from other species reservoirs, including wild species reservoirs;
- drug use leading to the emergence of drug-resistant disease organisms;
- an increase in disease due to a mean temperature increase in the range 0.5-2 °C.

Changes in sources were seen as important in all six categories (plants, animals and humans; UK and Africa), and there was little difference between UK and Africa in perceived overall risks generated by changes in sources.

Changes in pathways were seen as less important generators of disease risks across all categories than were changes in sources, although there were marked differences between UK and Africa. Increased host-to-host transmission due to increased density of host populations was seen as important for animals, plants and humans in Africa, but not at all in the UK. Increased disease vector populations were seen as important for plants and animals in the UK and for plants in Africa.

Many more disease drivers were considered important in Africa than in UK. For Africa, intriguingly, many respondents predicted lower risks arising from 'Legislation and Systems of Government' and 'Conflict and War' in 2030 compared to 2015, which reflects optimism about the future.

Finally, the three elements of climate change that were examined (increased temperature, rainfall and drought) were all seen as important drivers for human disease risks in Africa; yet only drought was highlighted for animals, and only temperature and rainfall was highlighted for plants.

In the UK, drivers seen as generating high levels of risk for human diseases were: drug use leading to the emergence of drug-resistant disease organisms and climate change, specifically rising temperatures. For UK plant diseases, the emergence of pesticide-resistant disease strains and the lack of new pesticides, increased trade and transport of crops and higher ambient temperatures, were seen as important risk drivers. For UK animal diseases, lack of adequate systems for disease control, poor implementation of international systems of disease surveillance and control, increased ability to engineer new diseases or to exploit existing diseases for bio-terrorism, emergence of drug resistance and the lack of new drugs, increased trade in animals, increase in illegal practices

Table 4

Responses for the years 2015 and 2030 that passed the first filter (moderate and high > 50%) and the second filter (high >50%), Foresight questionnaire 2005

	Africa animals		UK animals		Africa plants		UK plants		Africa humans		UK humans	
Year	2015	2030	2015	2030	2015	2030	2015	2030	2015	2030	2015	2030
Source												
1.1												
1.2												
1.3												
1.4												
1.5												
1.6												
1.7												
1.8												
Pathway												
2.1												
2.2												
2.3												
2.4												
2.5												
2.6												
2.7					n/a	n/a	n/a	n/a				
2.8					n/a	n/a	n/a	n/a				
2.9					n/a	n/a	n/a	n/a				
2.10					n/a	n/a	n/a	n/a				
2.11	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a				
Driver: Legislation & government												
3.1.1												
3.1.2												
3.1.3												
3.1.4												
3.1.5												
3.1.6												
3.1.7												
Driver: Technology & innovation												
3.2.1												
3.2.2												
3.2.3												
3.2.4												
3.2.5												
3.2.6												
3.2.7												
3.2.8												
Driver: Conflict & war												
3.3.1												
3.3.2												
3.3.3												
3.3.4												
3.3.5	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a				
Driver: Economic factors												
3.4.1												
3.4.2												
3.4.3												
3.4.4												
3.4.5												
3.4.6												
3.4.7												
Driver: Human activity & social factors												
3.5.1												
3.5.2												
3.5.3												
3.5.4												
3.5.5												
3.5.6	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a				
Driver: Climate change												
3.6.1												
3.6.2												
3.6.3												

The numbers in the first column correspond to the variables listed in Table 2.
Black cells represent 'high risks' (factors passed the first and second filter); grey cells represent 'moderate risks' (factors that passed the first filter but not the second); empty cells represent 'low risks' (factors that passed neither filter).

leading to the spread of diseases and climate change, specifically increased temperatures, were highlighted as important.

High hazard, low probability responses

We also examined high hazard, low probability risks, which would be scored as a 3 (1 for probability multiplied by 3 for hazard) and therefore would not have passed through the data-filtering analysis. However, only 17 out of the total 636 possible responses were of this nature, and in each case only between two and four respondents had categorised the risk in this way.

Discussion: Employing Foresight to understand future disease outcomes

If it is clear that a wide range of factors influence the spread of infectious disease [1-3,14], then there is a need to better understand and prioritise them:

"The rate and scale of global change in agriculture, trade, demographics, species translocations and invasions, microbial adaptation, and other complex factors, have evidently outstripped our ability to understand and respond to EIDs [emerging infectious diseases], and exposed serious limitations of approaches that fail to engage with the wider contexts from which infectious diseases emerge." [15]

For each factor, it is important to: identify and quantify the relevant sources, pathways and drivers, model their relationships and interactions, and identify potential intervention points where synergistic interactions promoting disease emergence can be arrested. Quantitative analyses are ideally suited for this, yet in many instances crucial knowledge gaps exist, creating the need for complementary analyses to help guide decision-making and priority-setting until more hard evidence becomes available. Although some analysts have called for interaction across a very broad range of expertise [15-17], there has been little discussion about how this could be practically done.

Foresight projects, such as the UK DIID project, aim to develop scientific and technological priorities, integrate multi-disciplinary perspectives, co-ordinate research opportunities with economic and social needs, and stimulate communication and partnerships between researchers, research users and research funders [18,19]. Meanwhile, survey methodologies such as Delphi enable a systematic approach to eliciting, aggregating and synthesising expert opinions [20-22]. The approach we describe here begins to develop a framework for identifying, assessing and prioritising infectious disease spread by incorporating a wide range of perspectives and insights into the analysis. Through engaging a wide range of expertise, we identified and developed a preliminary prioritisation of the myriad factors relevant to plant, animal and human disease.

There are, of course, limitations to this approach. One is that in order to cover the broad geographic and disease range mandated by this project, it was inevitable that the disease systems model on which the research was based would be rather general; the predictions should be interpreted with this in mind.

One other limitation of our study, and perhaps of Foresight in general, is that the answers are not 'evidence-based' in the scientific sense of the word. In our study, the respondents' predictions are based on their experience and knowledge, and represent the respondents' expectations of future courses of events. Where little data exist (necessarily the case when mapping the future), or where these data are not easily comparable, we would suggest that demonstrating general agreement – or the lack thereof – on common themes across a broad range of disciplines and institutions can be an important starting point for framing and pursuing multi-agency action.

Finally, we are also aware that our disease systems approach has been unrealistically linear. For any specific disease, dynamic interactions and feedback loops among drivers, sources and pathways will amplify or diminish overall disease risks. However, it was not possible to include this level of sophistication in a general, meta-level model applicable to all the disease categories in this study. Future studies would be well advised to focus on specific classes of disease, or even on specific drivers, pathways or sources of disease.

Ultimately, the challenge is to identify the processes that influence the spread of new and emerging diseases before they become significant problems for national public health systems or public health emergencies of international concern. The approach described here, appropriately applied, could help facilitate this.

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