Eurosurveillance
Europe's journal on infectious disease epidemiology, prevention and control

Vol. 16 | Weekly issue 46 | 17 November 2011

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Syndromic surveillance of epidemic-prone diseases in response to an influx of migrants from North Africa to Italy, May to October 2011

F Riccardo[1], C Napoli[1,2], A Bella[1], C Rizzo[1], M C Rota[1], M G Dente[1], S De Santis[1], S Declich (silvia.declich@iss.it)[1]
1. National Institute of Health (Istituto Superiore di Sanità), Centre for Epidemiology, Surveillance and Health Promotion, Rome, Italy
2. University of Bari, Department of Biomedical Sciences and Human Oncology, Bari, Italy

Citation style for this article:
Riccardo F, Napoli C, Bella A, Rizzo C, Rota MC, Dente MG, De Santis S, Declich S. Syndromic surveillance of epidemic-prone diseases in response to an influx of migrants from North Africa to Italy, May to October 2011.
Euro Surveill. 2011;16(46):pii=20016. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20016

Article published on 17 November 2011

Following civil unrest in North Africa early in 2011, there was a large influx of migrants in Italy. A syndromic surveillance system was set up in April to monitor the health of this migrant population and respond rapidly to any health emergency. In the first six months, the system produced 67 alerts across all syndromes monitored and four alarms. There were no health emergencies, however, indicating that this migration flow was not associated with an increased risk of communicable disease transmission in Italy.

Managing influx of migrants

Following civil unrest in North Africa (Egypt, Tunisia and Libya) in the first months of 2011, Europe witnessed an important increase in migration flow [1,2]. Official comprehensive estimates of the total number of people who arrived in Italy from the southern shores of the Mediterranean are not currently available, but the International Organization for Migration estimates that more than 25,000 people arrived from Libya alone [3]. The total number was certainly higher, as it does not include people who arrived from the other affected countries.

Italy declared a state of humanitarian emergency on 12 February 2011 and the Italian Civil Protection was charged of coordinating the reception of migrants with all regional and local authorities [4] according to a plan published in April [5] and currently in place. Ports of entry equipped with reception centres ensure registration and medical examinations on entry. If fit for travel, family units are then transferred to migration centres across Italy [6,7], where they stay until their migration status is cleared.

Migration centres are managed by diverse private and public organisations contracted by the Ministry of Interior and are equipped with internal, self-managed, outpatient services [8]. The fragmented distribution of the 2011 North Africa migrants across Italy and the migration centres' independent healthcare provision increased the need to ensure uniform and timely epidemiological surveillance.

We describe here the syndromic surveillance system set up in Italy in April 2011 to detect early signals of potential health emergencies among the migrants. Preliminary results obtained in the first six months of surveillance are also presented.

Setting up a syndromic surveillance system

On 11 April, syndromic surveillance was implemented in migration centres. This syndromic surveillance system complements, but does not substitute for, the existing mandatory infectious disease notification system. The Ministry of Health in collaboration with National Centre for Epidemiology, Surveillance and Health Promotion of the National Institute of Health (CNESPS-ISS) published an official guidance document [9], which was distributed to the 21 Italian regions and autonomous provinces, who then forwarded it to the migration centres in their territories.

The surveillance protocol used was based on the one used in a previously successful integrated surveillance system implemented during the 2006 Winter Olympic and Paralympic Games in Italy [10]. A total of 13 syndromes (Table) were defined as potentially indicative of infectious diseases and/or unusual adverse health events.

Migration centres or local /regional health authorities notified cases fitting the case definitions daily and also provided details of the population residing in each centre, stratified by age group. Notification forms were received via email or fax by the CNESPS-ISS, who entered and analysed the data.

Alert thresholds were calculated to detect statistically significant differences between the observed and

expected incidence of each syndrome. The expected incidence for each day was based on the moving average of the previous seven days. The threshold was calculated on the observed incidence using a Poisson distribution (99% confidence interval (CI) of the observed incidence). When the expected incidence was below the threshold (99% CI of the observed incidence), an alert was automatically issued. Whenever alerts were issued on at least two consecutive days, an alarm was defined.

Whenever an alarm is detected by the system, an analysis, stratified by reporting migration centre, is carried out. If an alarm arises from notifications from a single migration centre, the CNESPS-ISS contacts the reporting health officer of the centre and gives them a report of the analysis. A health emergency occurs when an alarm is epidemiologically confirmed (validated) as an outbreak by the immigration centre concerned, which then sets up appropriate control measures.

A national surveillance report is published each week with an updated public health risk assessment on the website of the CNESPS-ISS [11] and distributed to reporting health officers, Ministry of Health, regional health authorities and the Italian Civil Protection.

Table

Syndromes under surveillance and case definitions, migration centres, Italy, 2011

Syndrome	Case definition
Respiratory tract disease	Fever (>38 °C) and at least one of the following: – cough – sore throat – pharyngitis – bronchitis – pneumonia – bronchiolitis – chest rales – breathing difficulties – bloody sputum – lung infiltrates on X-ray
Tuberculosis (suspected)	– Productive cough lasting more than 3 weeks – Low-grade evening fever[a] – Night sweats[a] – Weakness, AND – Weight loss in the last 3 months
Bloody diarrhoea	Blood in stool[b] and at least one of the following: – frequent diarrhoea (at least 3 loose stools a day) – mucus or purulent material in the stool – abdominal pain – gastroenteritis with vomiting
Watery diarrhoea	At least one of the following: – frequent watery diarrhoea (at least 3 loose stools a day) – abdominal pain – gastroenteritis – vomiting
Fever and rash	Rash and fever (>38 °C) OR Clinical diagnosis of measles, rubella, varicella, erythema infectiosum (fifth disease) or exanthema subitum (sixth disease, roseola Infantum)
Meningitis/ encephalitis or encephalopathy/ delirium	Fever (>38 °C) and at least one of the following: – meningitis – encephalitis OR one of the following: – encephalopathy – confusion – delirium – altered consciousness
Lymphadenitis with fever	Fever (>38 °C) and at least one of the following: – enlarged lymph nodes – lymphadenopathy – lymphadenitis
Botulism-like illness	Absence of known chronic conditions causing the syndrome (e.g. myasthenia gravis, multiple sclerosis) and at least one of the following: - paralysis or paresis of cranial nerves - ptosis - blurred vision - double vision (diplopia) - speech impediments (dysphonia, dysarthria, dysphagia) - descending paralysis OR – diagnosed or suspected botulism
Sepsis (with or without shock) or unexplained shock	At least one of the following: - sepsis - septic shock - severe hypotension unresponsive to medical treatment AND absence of the following conditions: congestive heart failure, acute myocardial infarction or traumas causing the syndrome
Haemorrhagic illness	Fever (>38 °C) and at least one of the following[c]: – haemorrhagic rash – haemorrhagic enanthema
Acute jaundice	– Jaundice – Fever (>38 °C) – Headache – Malaise – Myalgia – Enlarged liver (hepatomegaly) with or without rash, AND – Exclusion of chronic or alcoholic liver disease
Parasitic skin infection	– Skin lesions caused by scratching – Papules, vesicles or small linear burrow tracks, AND – Presence of parasites
Unexplained death	Death of unknown cause

[a] Lasting for more than 3 weeks but less than one month.

[b] Cases presenting with primary gastrointestinal bleeding, for example due to an ulcer, should be excluded.

[c] Cases of acute leukaemia should be excluded.

Alerts and alarms issued

The surveillance system started operating on 11 April 2011. The first few weeks were dedicated to the recruitment of migration centres and familiarising them with the reporting requirements. For this reason, the data in this paper, are from 1 May.

From 1 May to 31 October 2011, 4,103 notifications were received from 97 migration centres in 11 regions (Figure 1). Throughout the six-month period, on average 5,261 people were under surveillance every day (median 5,322; range: 1,726–8,443). Until 23 May, 92% (2,680/2,905) of the population under surveillance every day were adolescents and young adults aged between 15 and 44 years. If the entire period is considered, however, this proportion decreases to 76% (3,143/4,120) due to the arrival of larger numbers of both younger and older migrants. Of all the reported syndromes under surveillance (n=3,401), the most common were respiratory tract disease (2,156 cases, 63%) and watery diarrhoea (970 cases, 29%).

Figure 1

Migration centres reporting through the syndromic surveillance system, per region, Italy, 1 May–31 October 2011

The numbers shown are the numbers of migration centres (n=97) reporting through the syndromic surveillance system, per region.

The system produced 67 alerts across all syndromes. These alerts led to four alarms being issued (Figure 2), which were triggered by respiratory tract disease (one alarm), parasite skin infection (one alarm) and watery diarrhoea (two alarms). None of these events qualified as a health emergency, based on the feedback of the migration centres involved. All alarms subsided within 24–72 hours as the number of cases decreased spontaneously. No outbreak response was required.

Value of syndromic surveillance

The high-profile situation triggered in early 2011 by the arrival of large numbers of people who had experienced very harsh travelling conditions challenged Italian authorities to set up appropriate emergency responses. Through early interaction with North African country partners of the CNESPS ISS-led EpiSouth Plus project [12], it became clear that the people arriving in Italy would be, for the most part, young adults in good health. The syndromic surveillance system was therefore a tool set up to detect potential outbreaks occurring after migrants had settled within the migration centres. This system became a primary source of timely health data for this population at a national level.

The usefulness of implementing a syndromic surveillance system to monitor situations of potential public health impact, when timely health data are needed, has been widely documented during uncertain and high-profile events – for example, during the 2009 influenza A(H1N1) pandemic [13], the Icelandic volcanic ash plume [14], waterborne outbreaks [15], heat waves [16] and mass gatherings [17,10]. Syndromic surveillance provides information at an earlier stage than laboratory confirmation [14] and therefore has the potential to inform timely actions that might reduce the impact of disease in a community.

The syndromic surveillance system set up in Italy has several limitations, such as uncertainty about the total number of migrants residing within migration centres at any given time, the fact that only some regions adhered to the protocol and the lack of zero reporting from some centres. Entry data are collected by the Italian Civil Protection and the police, so the data are complete and constantly updated. Once migrants are transferred to centres within the country, however, data collection is managed at the local level, making it difficult to update and verify the collation of national figures. The CNESPS-ISS is currently strengthening collaboration with the Italian Civil Protection in order to acquire a better understanding of this population and consequently of the representativeness of the surveillance system.

The experience of the first six months of this system in Italy, in addition to providing a timely description of the population migrating in 2011 through Italy into other parts of Europe, demonstrated the benefit of using syndromic surveillance to monitor this particularly vulnerable subpopulation group. It also filled a

potential reporting gap between migration centres and the National Health System and created an environment conducive to collaboration among the different stakeholders involved in this humanitarian emergency.

The continued availability of updated risk assessments was of great value during this emergency to avoid undue concerns triggered by anecdotal evidence disseminated by media. The absence of outbreaks during the first six months of surveillance provides strong evidence that this migration flow was not associated with an increased risk of communicable disease transmission in Italy. This approach has proved beneficial: other countries may choose to replicate it in similar situations.

Acknowledgments

We would like to thank all health professionals from regions, local health departments and migration centres that provide daily data.

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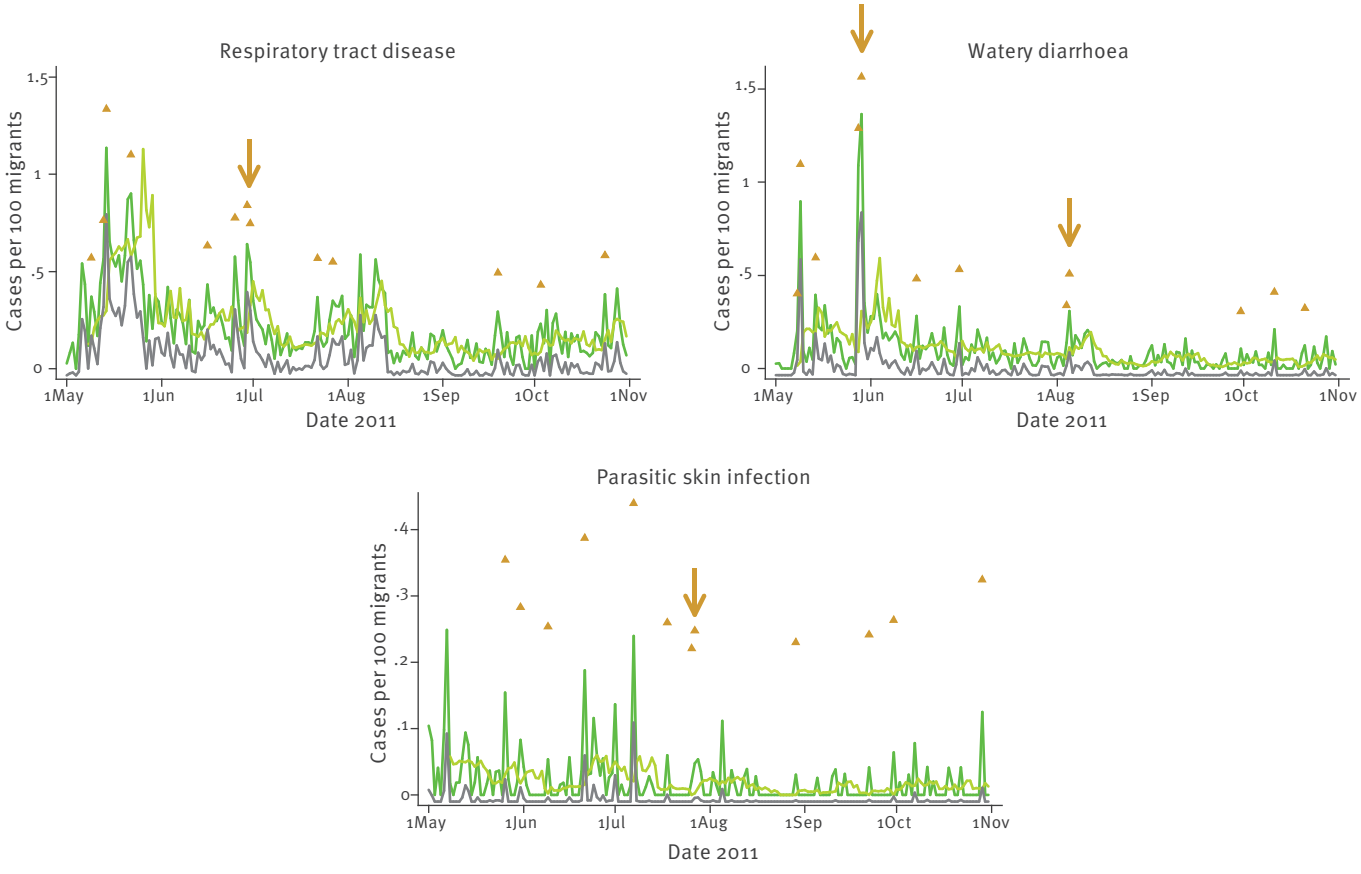
Figure 2

Alerts and alarms issued by the syndromic surveillance system triggered by notification of respiratory tract disease, watery diarrhoea and parasitic skin infection, migration centres, Italy, 1 May–31 October 2011



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Recruiting individuals into the HTLV cohort study in the United Kingdom: clinical findings and challenges in the first six years, 2003 to 2009

L J Brant[1,2], C Cawley[1,2], K L Davison (Katy.Davison@HPA.org.uk)[1,2], G P Taylor[3], the HTLV National Register Steering Group[4]
1. Health Protection Agency Centre for Infections, Immunisation Hepatitis and Blood Safety Department, London, United Kingdom
2. National Health Service Blood and Transplant, London, United Kingdom
3. Imperial College, Communicable Diseases, London, United Kingdom
4. The members of the group are listed at the end of the article

Citation style for this article:
Brant LJ, Cawley C, Davison KL, Taylor GP, the HTLV National Register Steering Group. Recruiting individuals into the HTLV cohort study in the United Kingdom: clinical findings and challenges in the first six years, 2003 to 2009.
Euro Surveill. 2011;16(46):pii=20017. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20017

Article published on 17 November 2011

Human T-lymphotropic virus (HTLV) infection is rare in the United Kingdom (UK) and few studies are available worldwide. Following introduction of blood donation testing in 2002, a cohort of individuals could be identified and prospectively recruited to describe progression and onset of disease. Here we describe baseline characteristics of participants, and evaluate recruitment into the UK HTLV National Register over the first six years, from July 2003 to June 2009. A multicentre cohort study recruited participants from the UK blood services (recipients and donors) and specialist HTLV clinics. Almost half of the 148 participants recruited were blood donors, nine were blood transfusion recipients, 40 contacts and 29 clinic attendees (nine asymptomatic and 20 symptomatic). Most participants were HTLV-1 positive (n=115); 11 had HTLV-2 and 22 were HTLV-negative. Baseline self-completion questionnaires were received for 83%. The most commonly reported condition was a past operation/serious illness (69%). Twenty-six participants reported four or more possible signs/symptoms of HTLV-1-associated myelopathy/tropical spastic paraparesis. Recruitment into a study of a rare, long-term infection is challenging. This cohort will enable descriptions of HTLV-associated disease progression amongst people recruited from varying sources; it is the first prospective study of its kind in Europe.

Introduction

Human T-lymphotropic viruses (HTLV) are enveloped, double-stranded RNA viruses. Type 1 (HTLV-1) was first described in 1980 [1] and type 2 (HTLV-2) in 1982 [2]. Most people infected with HTLV have a low (<5%) risk of developing disease; however, there are relatively few studies on the natural history of HTLV infection worldwide and few prospective studies of HTLV-1-associated disease have taken place in Europe. Although evidence from epidemiological studies confirms the role of HTLV-1 in adult T-cell leukaemia/lymphoma (ATLL), HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and uveitis [3], more studies are needed to investigate the role of the virus in other disease outcomes, particularly other inflammatory disorders such as arthritis, urinary tract disorders and susceptibility to infectious diseases [4]. Long term follow-up studies could describe the timing and progression of disease from the asymptomatic carrier state to the known disease outcomes and investigate previously unsuspected disease associations.

HTLV-1 is endemic in southern Japan, the Caribbean, parts of Africa, the Middle East, South America and the Melanesian Islands of the south-west Pacific [3]. HTLV-2 is more commonly found among indigenous American populations and injecting drug users (IDU) [5]. Modes of transmission include transfusion of unscreened blood, mother-to-child contact (including breastfeeding), sex and injecting drug use [3]. HTLV is rare in the United Kingdom (UK); seroprevalence among blood donors and pregnant women is low (6 per million donations [6] and 340 per million women [7], respectively). In the 1980s and 1990s a large proportion of infections reported to UK HTLV national surveillance were among minority ethnic populations originating from HTLV-endemic areas and consisted mainly of patients with HTLV-associated disease [8].

In Summer 2002, the UK blood services introduced blood donor testing for HTLV antibodies (anti-HTLV) [9]. It was recognised that some HTLV-positive donors may have made previous donation(s) before testing was introduced, so the blood services began a 'lookback' programme to trace the outcome and/or recipients of blood components derived from these donations, as they did when anti-HCV testing was introduced in the early 1990s [10]. These actions provided a rare opportunity to identify and prospectively recruit a cohort of individuals for long-term follow-up to investigate and

describe clinical progression and onset of disease. All positive blood donors and recipients of their blood were offered the option to attend a specialist HTLV clinic. Their contacts, patients with symptomatic disease, and other people with HTLV were also seen at these clinics.

The HTLV National Register cohort study was established as a collaboration between National Health Service (NHS) Blood and Transplant (NHSBT), the Health Protection Agency (HPA) and Imperial College, London. The objectives were to describe the clinical state at diagnosis, determine the long-term outcome in HTLV-infected individuals and to investigate factors associated with transmission, disease and survival. Here we assess recruitment into the register in the first six years (July 2003 to June 2009) and describe the baseline health characteristics of the cohort.

Methods

Participant consent, recruitment and registration

Consent and recruitment began in July 2003. All participants were asked to provide signed consent for up to four options: (i) processing and disclosure of personal data contained in medical records to the register co-ordinator, (ii) flagging the participant's NHS number in the NHS Health and Social Care Information Centre (NHSIC) (described below), (iii) approaching the participant's general practitioner (GP) for additional information if required and (iv) follow-up in order to be contacted for further information at a later date (including follow-up questionnaires). Consent to approach GPs was not included in the initial consent request to participants but introduced from September 2005 to maximise possibilities for follow-up of information about participants)

Participants were recruited prospectively and classified according to the source where they were first identified:

- Group A: HTLV-positive blood donors tested by the UK blood services,
- Group B: blood transfusion recipients identified through the UK blood services 'lookback' programme (HTLV-positive and -negative);
- Group C: contacts of HTLV-positive and -negative blood donors and recipients or symptomatic patients recruited through HTLV clinics (HTLV-negative contacts recruited from 2004);
- Group D: HTLV-positive symptomatic patients diagnosed with an HTLV-associated disease (from 2004);
- Group E: HTLV-positive asymptomatic clinic attendees who were not blood donors or linked to another study participant.

All HTLV-positive blood donors identified before July 2003 were invited to participate in writing in late 2003 by blood service clinicians and again when they attended a specialist HTLV clinic.

Recruitment of blood recipients identified through the HTLV 'lookback' was to enable the investigation of factors associated with onset of HTLV-related disease by providing a source of cases (infected recipients) and controls (uninfected recipients). Extrapolating from findings from the hepatitis C 'lookback' [11] indicated that for every 100 infected blood donors, 29 infected and 55 non-infected recipients would be identified. It was estimated that the first two years of testing would identify 120 infected blood donors, therefore 34 and 66 infected and non-infected recipients, respectively, might be identified. This would enable a formal statistical analysis at 80% power and 5% significance. However, by June 2009 the HTLV 'lookback' programme was almost complete and it was clear that the sample size would not be reached: the majority of transfusion recipients were not infected with HTLV [12] and few agreed to participate. Therefore recruitment of HTLV-negative individuals was halted by the steering group on ethical grounds.

At registration we collected details of name, address, date of birth, sex, General Practitioner (GP), the responsible clinician, recruitment source, date and result of HTLV test, HTLV type, risk exposure(s) and summary signs and symptoms of disease (if any). Age was calculated at date of consent.

At the time of publishing of this report, enrolment in the cohort is not complete and follow-up is currently open-ended.

Baseline health status

All participants were requested to complete a baseline self-completion health questionnaire (SCQ) in four parts. Section A collected the participant's demographic details (age, sex, marital status, number of children). Section B explored possible risk exposures, which were assigned, according to a hierarchy, as the participants' probable source of infection. The probable risk exposures, used by the HPA and NHSBT surveillance, were based upon published information about the epidemiology of HTLV and the opinion of HTLV experts. Information on general health and signs and symptoms of disease were gathered in sections C (health in the past) and D (current health).

Maintaining contact and assessing mortality outcomes

Every patient registered with the NHS in the UK is identified by a unique NHS number. Researchers in the UK, whose studies have been granted ethical approval, can put a flag against a participant's NHS number, thereby identifying that person as a member of a particular study. For each flagged participant, the NHSIC notifies the register coordinator of movement between health authorities, cancer registration and/or death (including death certificate details). To maintain contact and

participation, an annual newsletter was distributed to the participants, incorporating an address change form.

Recruitment uptake

Recruitment uptake was assessed for each recruitment group. Data on the number of transfusion recipients and HTLV-positive blood donors were obtained from NHSBT. Differences in characteristics of consenting and non-consenting blood donors were investigated using chi-squared test. Data on the number of HTLV-positive patients identified between July 2003 and June 2009 was obtained from the HPA [13]; information on symptoms (excluding blood donors, for whom uptake was known) were used to assess uptake in symptomatic and asymptomatic clinic attendees respectively; patients with unknown symptomatic/asymptomatic status were excluded (n=152). Data on the number of contacts (HTLV-positive or negative) invited to participate at the specialist clinics were not available.

Analysis of clinical data

Data from Sections C and D of the baseline SCQ were tabulated using Stata version 10. Reported symptoms and health outcomes were reviewed by recruitment group. The following questions were considered to identify possible signs/symptoms of HAM/TSP: (i) can you walk unaided, (ii) do your legs feel weak, clumsy, jumpy or stiff, (iii) do you have pain in your lumbar spine/lower back, (iv) during the day, how often do you normally pass urine, (v) do you have to hurry to the toilet when you feel the need to pass urine, (vi) are you constipated? Two questions were considered together to possibly indicate Sjogren's syndrome: (i) are your eyes dry or itchy, and (ii) do you have a dry mouth?

Ethical approval and data entry

Ethical approval was obtained from the Northern and Yorkshire Multi-Centre Research Ethics Committee (03/03/021), with the HPA as the sponsoring body. Data were entered in duplicate into a secure MS Access database, and entries were validated before entry into the master database.

Results

Between July 2003 and June 2009, 148 people consented to participate in the study (Table 1). Most participants recruited in the first six months were blood donors (Figure) and most provided full consent as it was offered to them, although some declined consent for 'flagging', further follow-up and/or for GP contact (Table 1).

Recruitment

Group A: Blood donors

By June 2009, 146 HTLV-positive blood donors had been identified by NHSBT and other UK blood services. As of January 2010, 48% had consented to participate (Table 1). Of the 76 non-consenting blood donors, 31 (41%) were identified before recruitment started and were only invited to participate when (or if) they attended their clinical referral appointment and by letter. There was no difference between consenting and non-consenting blood donors with respect to sex (chi-squared=1.12, p=0.291), age group (chi-squared=4.46, p=0.486), ethnicity (white or non-white, chi-squared=0.07, p=0.786), or donation year (chi-squared=6.48, p=0.484). The mean number of days between date of HTLV-positive donation and consent was 359.

Group B: Transfusion recipients

Nine of the 109 living transfusion recipients tested as part of the HTLV 'lookback' programme [12] consented to participate, detailed data were not available on the other living transfusion recipients.

Group C: Contacts

The denominator for this group was not estimated.

Group D: Symptomatic patients

Between July 2003 and June 2009, 125 people known to have symptomatic HTLV infection (and who were not blood donors) were reported to the HPA (S. Ribeiro, personal communication, September 2010). Assuming that all were eligible, attended a specialist HTLV clinic and were invited to participate, 16% consented. Recruitment increased from 2.4% in the first year to 25% in the fifth year.

Group E: Asymptomatic clinic attendees

Forty-seven patients, known to be asymptomatic (and not blood donors) were reported to the HPA from July 2005 to June 2009 (S. Ribeiro, personal communication, September 2010). Assuming all were eligible and invited to participate, 19% were recruited.

Demographics and characteristics

The majority of participants were HTLV-1 positive (Table 1); of the HTLV-2 positive participants 82% were blood donors. Information on sex and date of birth was complete; three quarters were female. Blood transfusion recipients were the only group with more male than female participants. Blood donors were the youngest group recruited and symptomatic clinic attendees the eldest. The ethnic background of the groups differed: the majority of symptomatic patients were Black Caribbean whereas the majority of blood transfusion recipients were white.

All 20 symptomatic patients were recruited by clinicians from one single clinic. At registration, three participants had been diagnosed by clinicians with ATLL and eight with HAM/TSP; the remaining nine participants were reported to have gait problems, uveitis, generalised lymphadenopathy, chronic HTLV-1-driven lymphocytosis, neurological symptoms and mononeuritis multiplex.

Heterosexual sex (or heterosexual sex/mother-to-child transmission) was the main risk exposure reported (Table 1). Both the symptomatic and the asymptomatic

clinic attendees that reported blood transfusion (in 1989 and 1985, respectively) as their risk exposure had not been identified during the blood services 'look-back', so transmission had not been confirmed.

Among the contacts, 16 people (seven with HTLV-1, one with HTLV-2, eight HTLV-negative) were current or previous sexual partners of HTLV-infected individuals, 10 (four with HTLV-1, six HTLV-negative) were children of positive parent(s), 10 (five with HTLV-1, one with HTLV-2, four HTLV-negative) were a family member of a positive individual, and two (both HTLV-positive) were mothers of positive individuals. One participant (HTLV-1-positive) was a close friend of a patient with

Table 1

Recruitment, consent and characteristics of participants by recruitment source, HTLV National Register, United Kingdom, July 2003–June 2009 (n=148)

	Asymptomatic clinic attendee (Group E)	Blood donor (Group A)	Blood recipient (Group B)	Contact (Group C)	Symptomatic patient (Group D)	**Total**
Number eligible	47	146	109	n/a	123	425
Number recruited (%)	9 (19)	70 (48)	9 (8)	40 (n/a)	20 (16)	148 (35)[a]
Proportion of cohort in %	6.1	47.3	6.1	27.0	13.5	100
Consent						
Full[b] - three options	1	42	8	20	7	**78**
Full[b] - four options	7	16	0	13	10	**46**
Partial	1	12	1	7	3	**24**
Declined flagging[c,d]	0	7	1	2	2	**12**
Declined further contact[d]	0	4	0	1	2	**7**
Refused GP consent[d,e]	1	4	0	4	0	**9**
Baseline SCQ returned	6	62	8	33	14	**123 (83.1)**
Characteristics						
Number of females[f]	6	58	3	28	16	**111 (75.0)**
Mean age (range)	56.3 (21.8-81.4)	45.3 (17.6-70.5)	56.2 (33.3-76.2)	47.9 (3.6-79.3)	56.8 (34.9-85.5)	**48.9 (3.6-85.5)**
Ethnicity						
White	1	32	8	10	2	**53 (35.8)**
Black Caribbean	7	27	0	24	16	**74 (50.0)**
Other[g]	1	11	1	6	2	**21 (14.2)**
HTLV type						
HTLV-1	9	61	5	20	20	**115 (77.7)**
HTLV-2	0	9	0	2	0	**11 (17.4)**
HTLV-negative	0	0	4	18	0	**22 (14.9)**
Risk exposure(s)						
Heterosexual sex	0	26	0	12	1	**39 (26.4)**
Mother to child	4	9	0	15	5	**33 (22.3)**
Heterosexual sex and mother to child	4	18	0	11	12	**45 (30.4)**
Blood transfusion	1	7	9	0	1	**18 (12.2)**
Blood transfusion and mother to child	0	1	0	0	0	**1 (0.7)**
Not known	0	9	0	2	1	**12 (8.1)**

GP: general practitioner; HTLV: human T-lymphotropic virus; NHSIC: National Health Service Health and Social Care Information Centre; SCQ: self-completion questionnaire.

[a] Excluding contacts, because a denominator was not available.

[b] Full consent is as it was offered to the patient. The fourth option (consent to contact the patient's GP for additional information) was added in September 2005.

[c] Flagging refers to putting a flag against a participant's NHS number. For each flagged participant, the NHSIC notifies the register coordinator of movement between health authorities, cancer registration and/or death (including death certificate details).

[d] Patients can be shown more than once in the declined section as they could have declined one or more options.

[e] A further three patients gave consent but did not explicitly specify which parts they consented to; they are included in the total of 24 but not in the breakdown.

[f] Reporting of sex was 100% complete.

[g] Other ethnicities reported were: asymptomatic (1 Black African), blood donor (2 Black African, 2 Black Other, 1 Indian, 1 Pakistani, 4 Asian other, 1 Other –no further details), Blood recipient (1 Bangladeshi), Contacts (2 Black Other, 1 Asian Other, 3 Other–no further details), Symptomatic (1 Chinese, 1 Other).

ATLL, and for one (HTLV-1-positive) no relationship was stated.

Baseline health status

Baseline SCQs were received for most participants; the response rate was highest among blood transfusion recipients and donors (Table 1). At least 90% of respondents answered each question. The few questions that were more poorly completed required more than one response e.g. do you have any problems with your nails, scalp, skin (tick yes/no to each). Here, 12-33% of respondents left one or more response blank.

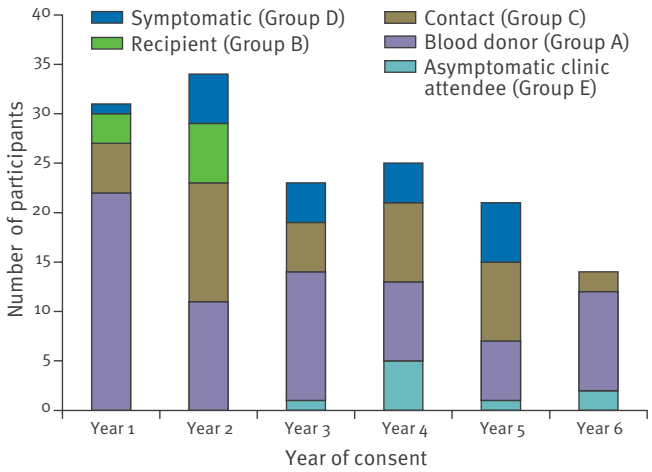
Overall, past surgery or serious illness was the clinical feature most commonly reported by participants, followed by any treatment for back pain (physiotherapy/medication) and cystitis or kidney infection treated with antibiotics (Table 2). Half of the symptomatic patients reported arthritis. Forty-four percent of reports of a past operation or serious illness related to obstetric or gynaecological problems (e.g. hysterectomy, caesarean section, ectopic pregnancy) or routine procedures (e.g. appendectomy, tonsillitis).

A greater proportion of symptomatic patients reported four or more possible signs/symptoms of HAM/TSP than other groups (Table 2). Seven blood donors (11%) reported four or more possible sign/symptoms of HAM/TSP (one had a formal diagnosis of HAM/TSP at registration at the clinic) and more than three-quarters of blood donors reported between one and three symptoms.

Ten participants reported symptoms indicative of Sjogren's syndrome (Table 3). Few of the 123

Figure

Consent into the HTLV National Register by 12-month period and recruitment source, United Kingdom, July 2003–June 2009, (n=148)



HTLV: human T-lymphotropic virus.

Table 2

Number and proportion of participants having ever experienced various health outcomes as reported on the baseline self-completion health questionnaire, by recruitment type, United Kingdom, July 2003–June 2009 (n=123)

	Asymptomatic clinic attendee (Group E)	Blood donor (Group A)	Blood recipient HTLV-positive (Group B)	Blood recipient HTLV-negative (Group B)	Contact HTLV-positive (Group C)	Contact HTLV-negative (Group C)	Symptomatic patient (Group D)	**Total**
Number returning questionnaire	6	62	4	4	18	15	14	**123**
Operation or serious illness	6	41	4	4	13	7	10	**85 (69.1)**
Uveitis, tuberculosis, thrombosis or thyroid disease	2	11	1	0	3	2	5	**24 (19.5)**
Cystitis or kidney infection treated with antibiotics	1	18	0	0	10	5	5	**39 (31.7)**
Arthritis	3	14	1	0	6	2	7	**33 (26.8)**
Enlarged glands, hepatitis, jaundice or gallstones	2	18	2	0	3	2	5	**32 (26.0)**
Attended a doctor because of shortness of breath	2	17	2	2	5	5	2	**35 (28.5)**
Attended a doctor because of difficulty passing urine, constipation or impotence	3	7	2	2		3	7	**25 (20.3)**
Had treatment (physiotherapy/medication) for back pain	1	22	1	1	2	6	9	**42 (34.2)**
Attended a dermatologist	0	12	0	1	3	4	4	**24 (19.5)**
Had cold sores	1	16	1	2	4	0	1	**25 (20.3)**
Any of these?	6	54	4	5	18	11	14	**112 (90.2)**

HTLV: human T-lymphotropic virus

participants reported having ever had tuberculosis, uveitis or thyroid disease (one, eight and nine, respectively).

Flagging, mortality and cancer

In total 133 (90%) participants consented to flagging; 132 (99%) were successfully flagged, one could not be traced by NHSIC. Of the remaining 15 participants, all but one (an HTLV-negative transfusion recipient) were attending specialist HTLV clinic(s).

Death notifications were received for five participants; two transfusion recipients (both heart disease-related) and three symptomatic patients (incident ATLL, relapsed ATLL and alcohol toxicity). Eleven cancer registration notifications were received for nine participants: one blood donor (HTLV-1: malignant neoplasm of breast), two HTLV-negative contacts (one with malignant neoplasm of bladder, prostate and colon; the other with carcinoma in situ of cervix uteri), two HTLV-1 positive blood transfusion recipients (malignant neoplasm of prostate, and melanoma in unspecified parts of face), and four HTLV-1-positive symptomatic patients (acute myelogenous leukaemia, acute lymphoblastic leukaemia, melanoma in situ of ear and external auricular canal, and neoplasm of uncertain or unknown behaviour).

Discussion

The introduction of HTLV blood donation testing in 2002 meant that asymptomatic carriers, a group previously under-diagnosed and under-reported to routine surveillance [8], could be prospectively identified, recruited and followed up. This is the first prospective cohort study of its kind in Europe. The flexibility of study recruitment has enabled inclusion of other patient groups and contacts to allow descriptions and comparisons of morbidity, mortality and disease progression. These data show that a large proportion of the cohort have a number of sign/symptoms which, when taken together, could indicate HAM/TSP.

HTLV-1 is more frequently detected than HTLV-2 in the UK [8,14] and few study participants had HTLV-2. European blood donors found to be infected with HTLV had generally, where typable, HTLV-1 [15].This is in contrast to a blood donor study in the United States, where 72% had HTLV-2 [16] and 24% reported IDU risk exposure; no participants in our cohort reported to being IDU. Other studies have shown an association between HTLV-2 and IDU [16,17]; it is possible that more detailed questioning of HTLV-2-infected participants might reveal previously undisclosed risks of IDU.

HTLV in the UK is more common among individuals born in endemic areas [13,18,19] or among children born to parents from endemic areas [20], such as the Caribbean [3,4]. Therefore it was unsurprising that a large proportion of register participants were of Black Caribbean ethnicity. Among blood donors in the study, a disproportionate number were non-White; only 5% of the blood donor population is non-White (S Lattimore, personal communication, October 2011). The main risk exposures were mother-to-child transmission and heterosexual sex; many people reported both exposures. This probably reflects the epidemiology of HTLV infection in the UK, and that many of the study participants were born to parents from endemic areas and

Table 3

Number of study participants with possible signs/symptoms of HAM/TSP and Sjorgen's syndrome as reported on the baseline self-completion health questionnaire, by recruitment type, United Kingdom, July 2003–June 2009 (n=123)

	Asymptomatic clinic attendee (Group E)	Blood donor (Group A)	Blood recipient HTLV-positive (Group B)	Blood recipient HTLV-negative (Group B)	Contact HTLV- positive (Group C)	Contact HTLV-negative (Group C)	Symptomatic patient (Group D)	**Total**
Total number of participants with SCQ and in brackets percentage reported as asymptomatic for HTLV on the registration form[a]								
	6 (100.0)	62 (80.7)	4 (50.0)	4 (n/a)	18 (83.3)	15 (n/a)	14 (0)	**123 (59)**
Number of possible signs/symptoms of HAM/TSP[b] reported by the participants								
0	3	9	0	0	3	2	0	**17**
1	1	23	1	2	8	9	1	**45**
2	0	13	1	1	1	1	2	**19**
3	0	8	1	1	3	1	0	**14**
4	0	4	0	0	2	2	4	**12**
5	0	1	0	0	1	0	1	**3**
>5	2	2	1	0	0	0	6	**11**
Reported symptoms indicative of Sjogren's syndrome[c]								
	1	4	0	0	2	1	2	**10**

HAM: HTLV-associated myelopathy; HTLV: human T-lymphotropic virus; SCQ: self-completion questionnaire; TSP: tropical spastic paraparesis.

[a] Not reported whether asymptomatic/symptomatic on registration form for six blood donors, one HTLV-positive recipient and one HTLV-positive contact.

[b] Possible signs/symptoms of HAM/TSP include: (i) being unable to walk unaided, (ii) legs which feel weak, clumsy, jumpy or stiff, (iii) pain in the lumbar spine/lower back, (iv) passing urine more than five times per day, (v) having to hurry to the toilet to pass urine, (vi) constipation.

[c] Possible symptoms of Sjogren's syndrome included here are dry or itchy eyes and dry mouth.

probably acquired their infection abroad. Many participants therefore may have long-standing infections; interpretation of health data will need to take this into account. The excess of female participants has also been reported previously in other UK-based research studies [14 20] and surveillance data [8] and elsewhere [16,21-23], so was expected.

Estimates suggest that 20-30,000 people have HTLV infection in the UK [14], most are undiagnosed. Blood donors are currently the only population group undergoing regular testing; therefore they are an important source of participants, despite the decline in the number of HTLV-infected donors [9]. Specialist HTLV clinics will become increasingly important in identifying and recruiting other asymptomatic people, through testing of relatives and contacts of positive individuals.

Ever having had cystitis or kidney infection treated with antibiotics was one of the most commonly reported conditions; this was also reported amongst US blood donors [24], although the association in the multivariable models only remained statistically significant in HTLV-2-infected subjects. A range of autoimmune disorders have been associated with HTLV, including polymyositis [25] and arthritis [24]. In our study, a relatively large number of participants reported having had arthritis, although without a suitable control group, it is not possible to say whether this was associated with HTLV infection or not. A number of studies have also found associations between HTLV and uveitis [3], tuberculosis [26] and thyroiditis [27], but few HTLV National Register participants reported these conditions.

Blood donor recruitment was higher during prospective recruitment, which suggests that active recruitment of blood donors during their post-test discussion with blood service staff presents the best opportunity to discuss participation and obtain consent.

A combination of signs and symptoms was used as possible indicators of HAM/TSP. All participants who had been formally diagnosed with HAM/TSP and had returned a baseline SCQ reported four or more signs or symptoms. However, so too did two HTLV-negative contacts and four blood donors, which could suggest that the signs and symptoms used in this study were useful, but not very specific. Whilst each symptom alone does not constitute a significant risk, the constellation of four to five symptoms points towards HAM/TSP. The high level of consent for flagging, as well as regular newsletters, will minimise loss to follow-up and ensure that health, mortality and cancer data will be near complete, and final outcome determined. Combined with follow-up health data, requested every two years, this will provide information on whether these individuals have subclinical disease that will become more manifest.

Recruitment into the register varied by group, being proportionally to its larger size higher for blood donors, the largest group, than for the other recruitment groups, although it was lower than expected. By using routine surveillance data it was estimated that recruitment of symptomatic and asymptomatic individuals of Groups D and E was low, although improved over time. However as many newly diagnosed patients would only be invited to participate on their second or subsequent annual visit to the clinic and only one specialist centre recruited participants until 2008, the proportion of recruited patients is likely to be an underestimate.

From the outset, the planned control group for formal statistical analysis were uninfected blood recipients identified through the HTLV 'lookback' [11]. Unfortunately the sample size was not reached: the majority of transfusion recipients were not infected with HTLV [12] and few agreed to participate. Patients receiving transfusions are often elderly and/or very ill [11], so participating in a study that may be perceived as having little direct benefit may not be their first priority. The HTLV register echoes findings from other cohort studies [28,29], that finding consenting participants for long-term research studies is challenging. Negative contacts could be an alternative control group, but recruitment of these was also low. Therefore recruitment of HTLV-negative individuals was halted by the steering group on ethical grounds. Alternative methods of obtaining data on negative controls need to be identified, including the use of population-level data or recruiting negative blood donors as an alternative; the latter would involve additional ethical approval.

Recruitment into a study of a rare, long-term infection such as HTLV has been challenging. However, follow up of a cohort such as this will enable descriptions of HTLV-associated disease progression to be made amongst people recruited from varying sources. The UK HTLV National Register is the first prospective study of its kind in Europe.

Acknowledgments

We would like to thank the patients for enrolling and participating in the study, NHSBT clinicians for recruiting blood donors and the clinicians and nurses working in specialist HTLV clinics for recruiting patients into the study. We would also like to thank Shirley Cole, Keith Eldridge, Fariba Kirwan and Alan Sheridan for their administrative support.

Steering group members:

Lisa Brant (Health Protection Agency and NHS Blood and Transplant); Su Brailsford (NHS Blood and Transplant and Health Protection Agency); Sally Brearley, Caoimhe Cawley (Health Protection Agency and NHS Blood and Transplant); Katy Davison (Health Protection Agency and NHS Blood and Transplant); Alexandra Fedina(Imperial College Healthcare NHS Trust); Helen Harris (Health Protection Agency); Patricia Hewitt, (NHS Blood and Transplant); Meaghan Kall (Health Protection Agency); Mary Ramsay (Health Protection Agency); Sonia Ribeiro (Health Protection Agency); Graham Taylor (Imperial College Imperial College Healthcare NHS Trust); Jennifer Tosswill (Health Protection Agency).

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Food poisoning outbreaks linked to mussels contaminated with okadaic acid and ester dinophysistoxin-3 in France, June 2009

V Hossen (virginie.hossen@anses.fr)[1], N Jourdan-da Silva[2], Y Guillois-Bécel[2], J Marchal[3], S Krys[1]
1. Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES; French Agency for Food, Environmental and Occupational Health), Maisons-Alfort Laboratory for Food Safety (National Reference Laboratory for the control of marine biotoxins), Maisons-Alfort, France
2. Institut de Veille Sanitaire (InVS, National Institute for Public Health Surveillance), Saint Maurice, France
3. General Directorate for Food, Ministry of Agriculture, Paris, France

Citation style for this article:
Hossen V, Jourdan-da Silva N, Guillois-Bécel Y, Marchal J, Krys S. Food poisoning outbreaks linked to mussels contaminated with okadaic acid and ester dinophysistoxin-3 in France, June 2009.
Euro Surveill. 2011;16(46):pii=20020. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20020

Article published on 17 November 2011

In June 2009, 11 outbreaks of food poisoning occurred in France, involving 45 individuals who had consumed mussels harvested in Vilaine Bay (Northwestern France). Because the toxic dinoflagellate *Dinophysis* spp. had been detected in the area from mid-May, okadaic acid (OA) and dinophysistoxins were suspected to be the cause of these outbreaks, although the weekly monitoring tests by mouse bioassay had been negative. With the help of the French reporting system for food-borne disease outbreaks, the detailed data on epidemiology, mussel consumption and complete product traceback, were collected for 11 individuals involved in three reported outbreaks. The batch of mussels identified as the source of these three outbreaks contained concentrations of toxins of the okadaic acid group that were approximately eight times higher than the European regulatory limit. Moreover, based on the consumption data available for the 11 cases, a lowest observable adverse effects level (LOAEL) was deduced. The LOAEL calculated from this study, although based on a very limited number of individuals, was in the same range, i.e. approximately 50 µg OA equivalents per person, as the LOAEL established by the European Food Safety Authority in 2006.

Introduction

Diarrhoeic shellfish poisoning (DSP) is a gastrointestinal illness caused by the consumption of shellfish contaminated with algal toxins produced by marine dinoflagellates belonging to the genera *Dinophysis* spp. (*D. fortii, D. mitra, D. rotundata, D. tripos, D. acuta, D. norvegica* and *D. acuminata*) and *Prorocentrum* spp. (*P. lima, P. maculosum, P. concavum,* and *P. hoffmannianum*) [1,2]. The DSP toxins, including okadaic acid (OA) and its analogues dinophysistoxin-1 (DTX-1), dinophysistoxin-2 (DTX-2) and dinophysistoxin-3 (DTX-3), belong to the larger group of lipophilic toxins which also includes the azaspiracid, yessotoxin and pectenotoxin group toxins [3,4]. Since the discovery of DSP toxins in the late 1970s, DSP outbreaks have been reported worldwide [5]. To date, documented DSP cases including an exposure estimate, i.e. with consumption and contamination data collected at the same time, remain scarce. To a certain extent, this may be due to underdiagnosis and/or underreporting. Indeed, many consumers suffering from mild gastrointestinal disorders do not consult a physician, and even if they do so, physicians might fail to diagnose DSP, since gastrointestinal symptoms are not specific. In July 2006, the European Commission requested the European Food Safety Authority (EFSA) to issue a scientific opinion assessing the current regulatory limits in the European Union (EU) with regard to human health and analytical methods for marine biotoxins. On 27 November 2007, the EFSA opinion on okadaic acid and its analogues was adopted [6]. Considering the acute toxicity of OA-group toxins, the expert panel on contaminants in the food chain decided to establish an acute reference dose (ARfD), which represents the amount of a substance that can be ingested in a period of 24 hours or less without appreciable health risk. The lowest observable adverse effects level (LOAEL) deduced from available human case reports was used to derive the ARfD. This LOAEL is about 50 µg OA equivalents (eq) per person, which approximates to 0.8 µg OA eq/kg bodyweight (bw) for a 60 kg adult. An uncertainty factor of 3 was applied to extrapolate this LOAEL to a no observed adverse effect level (NOAEL). The panel considered that it was not necessary to apply an additional uncertainty factor for the variation among humans as the data were based on observations in several hundreds of affected shellfish consumers, originating from various countries, and considered to account for the most sensitive individuals (i.e. the young children and elderly) [6,7]. Finally, the ARfD was calculated by dividing the LOAEL of about 0.8 µg OA eq/kg bw by the uncertainty factor of 3; it resulted in an ARfD of 0.3 µg OA eq/kg bw. Based on the ARfD, and assuming that this amount of

toxin could be contained in a single large portion of shellfish of 400 g, EFSA advised that a concentration of 45 µg OA eq/kg shellfish flesh would not result in risks to the consumer, whereas the EU limit is currently at 160 µg OA eq/kg shellfish flesh [8].

The Panel noted however that information on the doses and profiles of OA-related toxins provided in the majority of reports on DSP outbreaks is very limited. Indeed, the toxin concentrations cannot be unequivocally established, particularly if the tested shellfish are not from the same batch as those consumed. Moreover, these studies rarely provide precise information on the amount of contaminated shellfish that has been consumed by intoxicated people.

In June 2009, 11 DSP outbreaks were reported in France within a few days (from 3 to 9 June), involving 45 individuals who had consumed mussels. Following EFSA recommendations for detailed reports on shellfish consumption and collection of reliable data on toxin content in the event of DSP outbreaks [6], a thorough investigation of human cases was conducted with the help of the stakeholders involved in the French reporting system for food-borne disease outbreaks. Data on epidemiology, mussel consumption, complete product traceback and toxin content of the suspected mussel batch were examined for three of the 11 outbreaks. The aim of our study was to establish a dose-response relationship by calculating the LOAEL from this case study and to compare it to the one previously established by EFSA in 2006 [6].

Methods

Food poisoning outbreaks associated with mussels: reporting and investigation

Notification of food-borne outbreaks has been mandatory in France since 1987 [9]. Food poisoning outbreaks are notified to the regional public health authority and to the regional veterinary services and forwarded to the Health Emergency Mission of the Ministry of Agriculture. The regional veterinary services (Direction Départementale de la Protection des Populations, DDPP) are in charge of carrying out the food traceback investigation, withdrawing the incriminated food from the market and destroying the contaminated food. When shellfish are suspected of being contaminated, a sample is sent to the national reference laboratory (NRL) for the control of marine biotoxins of Maisons-Alfort for analysis. Regional veterinary services report the results of their investigations to the regional public health authorities which depend on the Ministry of Health. The Ministry of Health, with support from the regional offices of the National Institute for Public Health Surveillance (InVS), is in charge of the epidemiological investigation (see Figure 1).

An outbreak is defined as an incident in which two or more cases had shared a common meal. For this investigation, the meal should include mussels. A case was defined as a patient with diarrhoea, i.e. at least three liquid stools in a day after having consumed mussels, in the period from 1 to 15 June 2009.

Data relating to the number of cases, onset dates, symptom identification, symptom severity and recovery time were collected through interviews of cases and exposed persons. On request of our laboratory, since our intention was to deduce a LOAEL from the outbreak cases, the quantity of mussels consumed and also personal information (sex, age and weight) of the affected persons were added to the standard questionnaire.

Analysis of lipophilic toxins (okadaic acid and dinophysistoxins)

A 10 kg shellfish sample from the same batch as the one suspected to be involved in three outbreaks was collected by the DDPP of the département Morbihan and sent to NRL for the control of marine biotoxins of Maisons-Alfort for analysis of lipophilic toxins. A homogenate of the digestive glands of mussels was analysed by the mouse bioassay (MBA) described by Yasumoto et al. [3] to determine DSP toxicity according to EU Regulation 2074/2005/EC [10]. The MBA measures the total toxicity based on the biological response of the animals to the toxins. In order to determine the toxin profile of the sample, an in-house liquid chromatography-tandem mass spectrometry (LC-MS/MS) validated test, based on a method developed by McKenzie et al. [11] and further adapted by the European Union Reference Laboratory [12], was used as an additional test to investigate these outbreaks. The LC-MS/MS analysis specifically detects, identifies and quantifies OA and its dinophysistoxins, as well as other lipophilic toxin groups for which a toxin standard per group is available (i.e. pectenotoxins, azaspiracids, yessotoxins, gymnodimine, spirolides). It became the reference method in the EU on 1 July 2011 [13].

Results

From 1 to 9 June 2009, 11 outbreaks involving a total of 45 individuals were reported through the food-borne outbreak reporting system in three départements of western France: Morbihan, Loire Atlantique and Gironde (Figure 2).

The investigation revealed that all of the intoxicated people had consumed mussels harvested from one production area (Vilaine bay) located in Morbihan, Brittany, between 29 May and 3 June 2009. They suffered from diarrhoea, i.e. at least three liquid stools in a day, in some cases accompanied with abdominal cramps, as well as nausea and vomiting. In one case, fever (>37 °C) was also reported. The onset of symptoms ranged from three to 20 hours after consuming the mussels and recovery time was one to four days (Table 1).

Detailed investigation of Outbreaks 1, 2 and 3

Shellfish traceback

The traceback investigation showed that Outbreaks 1, 2 and 3, involving at least 18 individuals in the

département Morbihan, were linked to a single batch of mussels from the Vilaine Bay. In this bay, a high risk period for *Dinophysis* has been defined between May and August [14]. During this period, both water and shellfish are sampled on a weekly basis, i.e. each Monday or Tuesday depending on the tide, at five predefined sampling points for shellfish and six points for water. The MBA results are available by the end of the week, on Thursday or Friday, and communicated without delay to the local authorities for a decision on whether to open or close the harvesting areas. The harvested mussels incriminated in the three outbreaks came from an area where the presence of toxic dinoflagellates *Dinophysis* spp. was detected from mid-May during the routine phytoplankton monitoring, but the weekly MBA were negative. Thus, the area remained open when 210 kg of mussels were harvested on 1 June. Shellfish harvesting in the area was suspended on 3 June when the outbreaks became known. On 4 June, the area was closed when the MBA result from that week showed a positive result. The distribution of the contaminated batch of mussels is described in Figure 3. The batch of 210 kg was separated into two parts: 10 kg were sold to a family (Outbreak 1) and 200 kg were sold to a dispatch centre. Of these 200 kg, 50 kg were sold to Restaurant A (Outbreak 2), 40 kg were sold to a family (Outbreak 3) and 10 kg were sold to Restaurant B. After notification of the outbreaks, the dispatch centre destroyed the remaining 100 kg. The 10 kg sample distributed to Restaurant B was not consumed and was sent to the NRL for the control of marine biotoxins of Maisons-Alfort for analysis. As the presence of toxic dinoflagellate *Dinophysis* spp. in the water had been detected during the routine phytoplankton monitoring, the sample was initially screened for OA and dinophysistoxins.

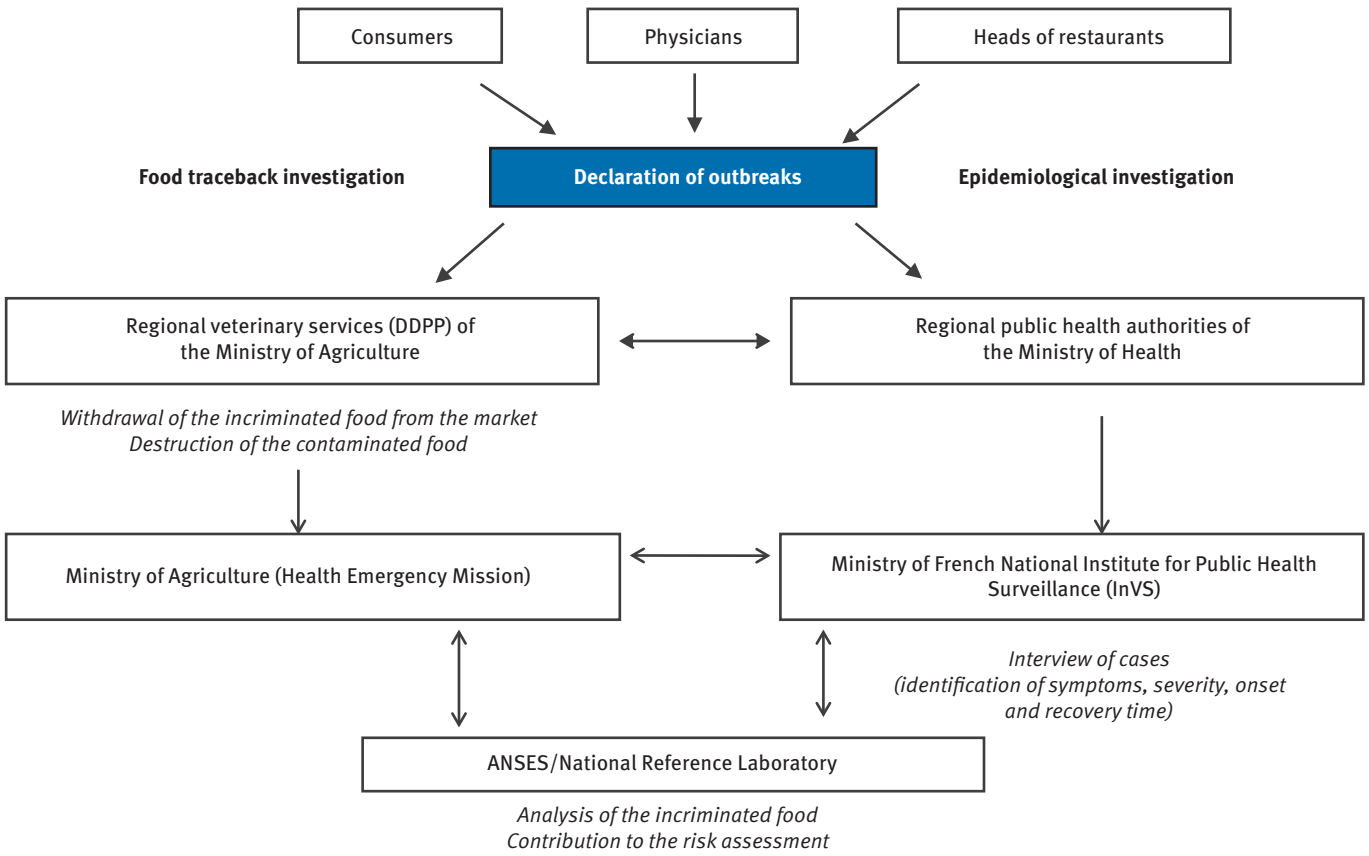
Epidemiological and consumption data

The detailed results of the epidemiological investigation are summarised in Table 2. Information on the number of cases, including sex, age and weight, symptom onset, reported symptoms and recovery time were available for 13 of the 18 ill individuals of Outbreaks 1, 2 and 3.

The age of the cases ranged from 11 to 65 years (mean age: 39.5 years) and their weights ranged from 38 to 95 kg (mean weight: 63 kg). The mean weight observed in this case study was close to the 60 kg body weight frequently used in risk assessment studies. Most of

Figure 1

Reporting system for food poisoning outbreaks in France

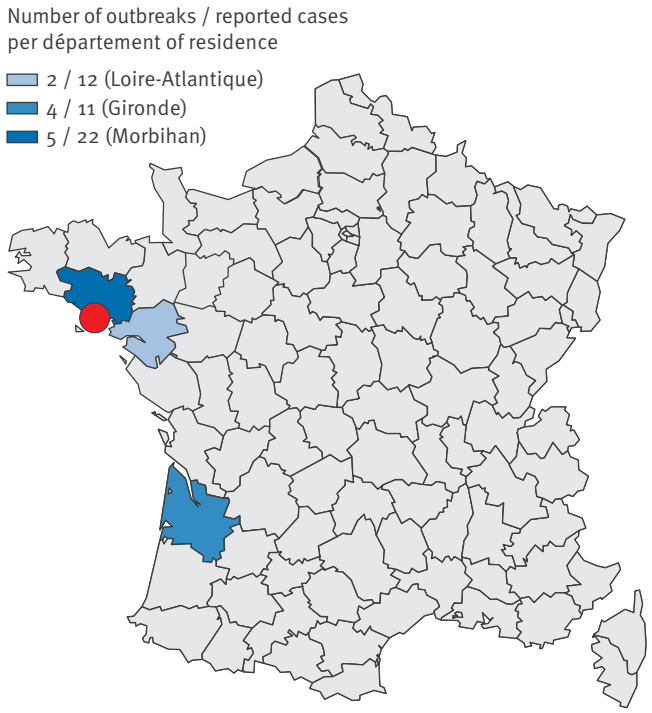


ANSES: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail; DDPP: Direction Départementale de la Protection des Populations; InVS: Institut National de Veille Sanitaire.

the intoxicated individuals were women (9/13). The reported symptoms included abdominal cramps and diarrhoea (13/13), nausea (8/13), vomiting (5/13) and fever (1/13). The symptoms occurred between three and 15 hours after shellfish consumption. In most cases, symptoms resolved one to four days after consumption. None of the people were hospitalised. Quantities of mussel consumption were reported for 11 of 18 individuals, with the reported amounts varying from 150 to 900 g.

Figure 2

Geographic distribution of mussel food poisoning outbreaks and reported cases, France, June 2009 (n=45 cases)



The red circle indicates the area where contaminated mussels were harvested.

Content of lipophilic toxins in the suspected batch of mussels

The sample of mussels from the batch suspected to be involved in Outbreaks 1, 2 and 3 (Table 2) tested positive in the MBA indicating the presence of DSP toxins at a concentration higher than the regulatory limit of 160 µg OA eq/kg shellfish flesh. The three mice tested died respectively in 47, 49 and 56 minutes. They exhibited symptoms typical of the OA group of toxins i.e. apathy, general weakness, difficulty to move, spasms, respiratory distress and death. The analysis of the sample by the informative LC-MS/MS method showed that it contained 681 µg of free OA/kg and 580 µg of DTX-3/kg. Hydrolysis of DTX3 toxins (esterified forms of parent toxins, which can be OA, DTX1 or DTX2) gave free OA only. As indicated in the scientific opinion document by EFSA, the toxicity equivalence factor (TEF) values for DTX3 are equal to those of the corresponding unesterified toxins [6]. Consequently, the total concentration of OA was calculated at 1,261 µg OA eq/kg shellfish flesh, which is approximately eight times higher than the European regulatory limit for OA group toxins. This high concentration explains the very short survival time of the mice and the rapid appearance of the symptoms following the consumption of the mussels by those who had been intoxicated.

Discussion

From 1 to 9 June 2009, 11 DSP outbreaks involving a total of 45 individuals were reported. In comparison, a single DSP outbreak involving two individuals was confirmed in 2006, seven outbreaks involving 109 individuals in

Table 1

Epidemiological data of reported disease outbreaks associated with the consumption of mussels harvested in Vilaine bay, France, June 2009 (n=45 cases)

Outbreak	Département	Number of individuals ill/exposed	Date of meal	Symptoms	Time between meal and approx. symptom onset	Recovery time
1[a]	Morbihan	3/3	1 Jun 2009	AC, D	12–15 h	1-3 days
2[a]	Morbihan	7/7	1 Jun 2009	N, AC, V, D, F	6–10 h	2-4 days
3[a]	Morbihan	at least 8 /UNK[b]	2 Jun 2009	N, AC, D	3–13 h	1 day
4	Morbihan	2/2	5 Jun 2009	N, V, AC, D	8–20 h	at least 3 days
5	Morbihan	2/2	5 Jun 2009	UNK	UNK	UNK
6	Gironde	3/7	3 Jun 2009	D	4–16 h	UNK
7	Gironde	3/3	4 Jun 2009	D	4 h	2 days
8	Gironde	2/2	4 Jun 2009	V, D	4–12 h	UNK
9	Gironde	3/3	5 Jun 2009	V, D	8h	UNK
10	Loire-Atlantique	10/10	1 Jun 2009	V, D	UNK	UNK
11	Loire-Atlantique	2/2	3 Jun 2009	UNK	UNK	UNK

AC: abdominal cramps, D: diarrhoea, N: nausea, V: vomiting, UNK: unknown.

[a] Outbreaks 1, 2 and 3 are described in full detail in Table 2.

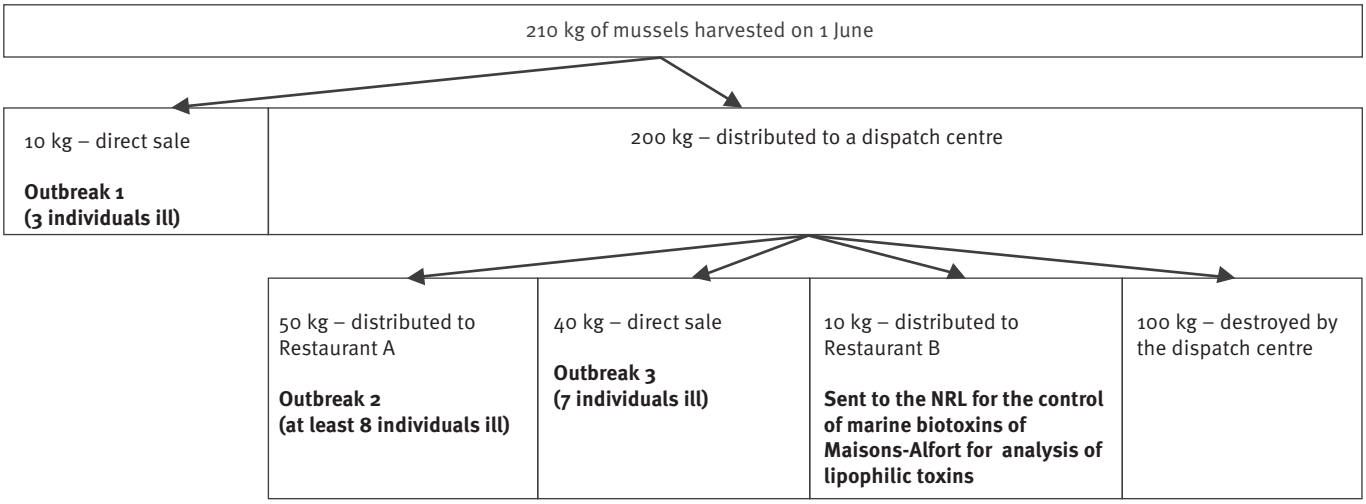
[b] This outbreak occurred in a restaurant. The owner was informed that eight people fell ill after consuming mussels, only three of whom reported the intoxication to their physician. The total number of people who consumed the contaminated mussels is not known; consequently, the number of ill individuals may be underestimated.

2007, and none in 2008 [15]. These outbreaks had been caused either by French mussels contaminated with OA group toxins or by Irish mussels contaminated with azaspiracides. As was the case in June 2009, most of these earlier DSP outbreaks occurred within a period of a few days because the regional veterinary services of the Ministry of Agriculture had withdrawn the incriminated food from the market and closed the production area following the results of the traceback investigation. If the shellfish are exchanged or exported, the Health Emergency Mission of the Ministry of Agriculture immediately notifies the European Commission using the Rapid Alert System for Food and Feed (RASFF). The goal of the notification is to give all RASFF members the information so that they can confirm whether the product in question is on their market and take the necessary measures. In the case of the DSP outbreaks in June 2009, no RASFF alert was issued since the contaminated shellfish were only distributed on French territory. The production area was closed by prefectoral order on 3 June when the first three outbreaks were reported, and the suppliers and consumers were informed immediately in order to withdraw and/or recall the unconsumed shellfish.

The described outbreaks were the result of an unusually rapid shellfish contamination, occurring within one week in which *Dinophysis* density increased by a factor

Figure 3

Distribution of the batch of mussels involved in three outbreaks of diarrhoeic shellfish poisoning, France, June 2009



NRL: national reference laboratory

Table 2

Epidemiological and consumption data in three outbreaks of diarrhoeic shellfish poisoning, France, June 2009 (n=18 cases)

Outbreak	Date of consumption	Number of individuals ill/exposed and sex and age of the ill (in ascending order)	Weight of the intoxicated person	Quantity of mussels consumed (weight including shell)	Symptoms	Approx. symptom onset/ recovery time
1	1 June 2009	3/3 1 male, 2 female 32, 35, and 55 years-old	59 kg	400 g	AC, D	15h / 1 day
			64 kg	400 g	AC, D	12h / 3 days
			70 kg	400 g	AC, D	12h / 3 days
2	1 June 2009	7/7 3 male, 4 female 11, 17, 18, 39, 40, 63, and 65 years-old	90 kg	600–700 g	N, V, AC, D	6h / 3 days
			58 kg	700 g	N, V, AC, D	6h / 3 days
			67 kg	ca. 900 g	N, V, AC, D	6h / 4 days
			58 kg	ca. 150 g	N, V, AC, D	6-7h / 2 days
			48 kg	ca. 400 g	AC, D	6-10h / UNK
			61 kg	ca. 900 g	N, V, AC, D, F	6-7h / 3 days
			38 kg	ca. 150 g	N, AC, D	6-7h / UNK
3	2 June 2009	at least 8 / UNK 3 female 28, 39, and 62 years-old	58 kg	ca. 900 g	N, AC, D	3h / 1 day
			95 kg	UNK	AC, D	4h / 1 day
			58 kg	UNK	N, AC, D	13h / 1 day

AC: abdominal cramps, D: diarrhoea, F: fever (>37 °C), N: nausea, UNK: unknown, V: vomiting.

of 5 in the harvesting area, quickly contaminating the mussels with a high toxin level. At the time of the outbreaks, the MBA was used for monitoring DSP toxins in shellfish; the result of the weekly test performed on the mussel sample harvested on 25 May was found negative on 29 May, whereas the result of the test on sample harvested on 1 June was found positive on 4 June. The occurrence of these outbreaks demonstrates that even if an efficient monitoring system is in place, rapid shellfish contamination may appear suddenly and cause health problems. The following factors could be responsible for the failure of the monitoring system to detect the contamination: the level of contamination of the sample harvested on 25 May may not have been representative of the contamination within the production area due to heterogeneity, and the MBA may have suffered from a lack of sensitivity for this sample [6]. This sudden toxic event could have been prevented by increasing the frequency of the sampling and/or the number of sampling points and/or by a quantitative method to follow the increase of the toxins content in shellfish. The implementation of the LC-MS/MS method as the reference method for monitoring lipophilic toxins [11] will make such quantification possible, and preventive actions can be taken to avoid the harvesting of shellfish in areas where a toxic episode is likely to occur.

Information in reports of DSP outbreaks rarely provide data on the actual quantities of toxin ingested by the intoxicated individuals since the tested shellfish samples often come from a batch different from the one consumed. Based on the concentration and consumption data detailed here, the minimum amount of OA causing symptoms was estimated for 11 intoxicated individuals involved in three of the 11 reported outbreaks. It was possible to deduce a LOAEL from this study. The 10 kg of mussels, from the same batch as the one involved in the three outbreaks, represented 2.4 kg of raw flesh, thus the flesh/whole shellfish ratio was estimated to be 24%. Although the flesh ratio varies from batch to batch, the value of 24% is consistent with information released by the Food Safety Authority of Ireland (18–24%) and the Food and Agriculture Organization of the United Nations (24%) [16,17].

In the outbreaks described here, the portion size ranged from 150 to 900 g of mussels, which translates to 36 to 216 g of mussel flesh. This is consistent with the data provided by the EU Member States to EFSA and the information included in EFSA's comprehensive database indicating that a portion size of 400 g of shellfish flesh has been identified as an appropriate estimate of a large portion [18].

Given that the toxin concentration in the incriminated batch was 1,261 µg OA eq/kg mussel flesh and that DSP symptoms were observed after consuming 36 to 216 g of mussel flesh, the toxin intake inducing symptoms in the intoxicated individuals ranged from 45 to 272 µg OA eq. The lowest toxin intake referred to two persons with a bodyweight of 38 and 58 kg, respectively. It corresponds to 1.2 µg and 0.8 µg OA eq/kg bw, respectively. Therefore, the LOAEL deduced from our study was 45 µg OA eq/person or 0.8 µg OA eq/kg bw for the most sensitive person.

Finally, the data collected in our study, although based on a limited number of individuals, support the LOAEL for human illness of approximately 50 µg OA eq/person or 0.8 µg OA eq/kg bw for a 60 kg adult established by the EFSA in 2006 [6].

Acknowledgments

The authors would like to thank M. Retho from IFREMER at La Trinité sur Mer for providing information on the phytoplankton and phycotoxin monitoring plan in the Vilaine Bay area, and C. Alves and P. Leroy from the national reference laboratory for the control of marine biotoxins of Maisons-Alfort for their skillful technical assistance.

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European Antibiotic Awareness Day provides platform for campaigns on prudent use of antibiotics for the fourth time

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

Citation style for this article:
Eurosurveillance editorial team. European Antibiotic Awareness Day provides platform for campaigns on prudent use of antibiotics for the fourth time. Euro Surveill. 2011;16(46):pii=20018. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20018

Article published on 17 November 2011

Antibiotic resistance restricts therapeutic options for treatment of bacterial infections and may put patients at risk. It is thus a major public health issue in Europe and globally. The European Antibiotic Awareness Day (EAAD) is a European health initiative coordinated with the involvement of the European Centre for Disease Prevention and Control (ECDC) that aims to provide a platform and support for national campaigns about prudent antibiotic use [1]. It falls in the week of 18 November every year and sets the date for the launch of national campaigns.

On the occasion of the upcoming fourth EAAD, the surveillance data on antibiotic resistance, gathered by the European Antimicrobial Resistance Surveillance Network (EARS-Net, a network coordinated by ECDC), are released in a new report [2] and a European Commission five-year action plan to tackle antimicrobial resistance is launched [3].

According to the new data from the EARS-Net report, the percentage of carbapenem-resistant *Klebsiella pneumoniae* is on the increase in Europe. Between 2005 and 2010, a total of 140 laboratories from 18 countries continuously reported results on the susceptibility to carbapenems of invasive *K. pneumoniae* isolates. During this period, the number of laboratories reporting continuously per country ranged from one laboratory in the Czech Republic, Iceland, Malta and Sweden, to 33 laboratories in France. Trend analysis was performed only on the results from these 140 laboratories. Results from this analysis show that in Europe the proportion of *K. pneumoniae* isolates resistant to carbapenems increased from 8 % to 15 % between 2005 and 2010. This increase was found to be highly significant ($p < 0.001$) but this is mainly due to a substantial increase in a few countries. Twelve European Union (EU) countries, reported resistance to carbapenems in 2010 [2]. Many EU Member States report that between 15 to nearly 50 per cent of *K. pneumoniae* from bloodstream infections are carbapenem-resistant. Carbapenems are the major last-line class of broad-spectral antibiotics to treat infections with multidrug-resistant Gram-negative bacteria such as *K. pneumoniae*, a frequent cause of pneumonia and urinary tract infections in hospitals.

For a large part, antibiotic resistance is being driven by misuse of antibiotics in humans and animals. According to the latest data from the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [4] the vast majority of human consumption of antibiotics occurs in the community. Resistance to last-line antibiotics like the carbapenems, however, cannot be explained only by the use of antibiotics outside hospitals. This growing problem of resistance against major last-line antibiotics could also indicate that misuse of antibiotics may take place in hospitals. ESAC-Net is a Europe-wide network of national surveillance systems, providing European reference data on antimicrobial consumption. It collects and analyses data on antimicrobial consumption from EU and EEA/EFTA countries, both in the community and in the hospital sector.

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The European Union provides funding to strengthen the protection against zoonoses and animal diseases

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

Citation style for this article:
Eurosurveillance editorial team. The European Union provides funding to strengthen the protection against zoonoses and animal diseases.
Euro Surveill. 2011;16(46):pii=20019. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20019

Article published on 17 November 2011

On 9 November 2011, the European Union (EU) adopted measures to support programmes across the EU aimed at monitoring, controlling and eradicating zoonoses and animal diseases. A EUR 203 million envelope has been earmarked to support annual and multi-annual programmes aimed at assisting Member States in fighting animal diseases that affect human and animal health.

The money will go to programmes aimed at reducing, among other diseases, salmonellosis, rabies and transmissible spongiform encephalopathies (TSE's), as well as avian influenza, bovine tuberculosis, bluetongue, brucellosis and classical swine fever.

The notification rate of salmonellosis in humans has decreased steadily over the past five years but it is still the second most commonly reported zoonosis and eradication programmes will need support for the foreseeable future. Some EUR 16 million will be set aside to assist Member States in the fight against salmonellosis.

The rabies situation in the EU is improving but Member States will receive continued financial support to help them with the fight to eradicate rabies and to increase public health protection. The Member States provide their own funding and the programmes to combat rabies are therefore co-funded by themselves and the EU. Vaccination programmes in the areas of Belarus, Ukraine and Russia will be funded to reduce the risk of introduction of rabies from these countries into the EU.

As the incidence of TSE's continues to fall, largely due to strict risk management measures, monitoring requirements for bovines have been relaxed. Member States will receive EUR 54 million from the EU budget to ensure continued support against TSE's.

Member States will also continue to carry out surveillance for avian influenza in poultry and wild birds in 2012 with the financial assistance of € 2.3 million from the EU budget. The implementation of the surveillance programmes is the most effective way to detect early outbreaks and is extremely useful in preventing the spread of this disease, which can have serious economic repercussions on poultry farming.

For more information, please see:
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