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Note from the editors: *Eurosurveillance* online submission system now launched

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Eurosurveillance is now using an online submission system (Editorial Manager): authors should submit their manuscripts via http://eurosurveillance.edmgr.com/ only.

This tool should help us to process the many submissions we receive and improve our interaction with authors and reviewers. For authors, one key advantage is that they can see the current status of their manuscript. For reviewers, responding to review requests and submitting a review should now be a more streamlined procedure.

In conjunction with the launch of the system, we have revised our editorial policy and instructions for authors: most notably, we will share the reviews for a manuscript between the respective referees – anonymously, of course. Also, during online submission, authors are required to outline the contribution of each author to the article and declare any conflict of interest. To date, we have always published any declared conflict of interest, but now, we will also publish any declared lack of conflict of interest. In terms of manuscript preparation, authors should also note a change in reference numbering: any references in figures or tables are now to be numbered after the citations in the text (i.e. the numbering does not take into account the position of the table or figure in the text). Authors must also ensure that all author-identifiable information – authors' names, affiliations and contributions as well as any acknowledgements – are not included in the manuscript or in any file names. See the instructions for further details.

It should, of course, be evident that the submission system is a tool, not a magic wand. While we are always striving to improve our processing times, it is clear that assessment of manuscripts, the peer review process and finalising manuscripts for publication still takes time. Nevertheless, the system will clearly help, and we embrace this new way of interacting with our loyal and new contributors. We look forward to receiving your online submissions!

Simultaneous increase of *Cryptosporidium* infections in the Netherlands, the United Kingdom and Germany in late summer season, 2012

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Starting August 2012, an increase in *Cryptosporidium* infections was reported in the Netherlands, the United Kingdom and Germany. It represented a 1.8 to 4.9-fold increase compared to previous years. Most samples were *C. hominis* IbA10G2. A case–control study was performed in the Netherlands but did not identify an endemic source. A case–case study in the north of England found travel abroad to be the most common risk factor.

In August 2012, an unprecedented increase of *Cryptosporidium* infections, as detected through analysis of faecal samples from patients with gastrointestinal complaints, was independently reported to the regional public health services, and subsequently to the National Institute for Public Health and the Environment (RIVM) by several microbiology laboratories throughout the Netherlands. In the same time period, Germany and parts of the United Kingdom (UK), specifically England, Wales and Scotland, but not Northern Ireland, also identified an unexpected excess of cryptosporidiosis cases compared to former years. Most samples in the UK and the Netherlands were *C. hominis* IbA10G2. No other European countries reported an increase of *Cryptosporidium* infections. Finland reported two ongoing outbreaks caused by *C. parvum*.

In the Netherlands, *Cryptosporidium* infection is not a notifiable disease, therefore there are no solid data on the incidence of human infections. In the UK, surveillance of *Cryptosporidium* was implemented in the 1990s. Positive results from laboratory testing are now notifiable. In Germany, *C. parvum* infection has been notifiable since 2001, but is mostly reported without species determination.

The increased number of cryptosporidiosis infections in three EU countries in the same period of time is unusual and is a great public health concern. In this paper, we present microbiological and epidemiological investigations of this increase in those three countries.

Background

Cryptosporidiosis is a disease caused by the parasite *Cryptosporidium*. The main symptoms in humans are watery diarrhoea, nausea, vomiting, low-grade fever and abdominal pain lasting from a few days to a few weeks. In immunocompromised people such as AIDS patients, the infection can be severe and may result in significant morbidity and mortality [1]. The two predominant species associated with human disease are *Cryptosporidium hominis*, affecting only humans, and *C. parvum*, affecting both humans and animals [2]. The principal reservoirs are humans, cattle and other domestic animals. The oocysts, containing sporozoites

(the infectious form of this parasite) are excreted in the host's faeces. They are transmitted by the faecal-oral route, via person-to-person or animal-to-person spread, or through the ingestion of contaminated water and food.

Methods

Microbiological investigations

Cryptosporidium was detected by medical microbiology laboratories in the Netherlands using standard routine detection methods (microscopy using modified Ziehl Neelsen staining or enzyme immunoassay and/or multiplex PCR). A selection of the positive samples was sent to the RIVM for further investigation and subtyping using *gp60* amplification sequencing. In England and Wales cases were diagnosed in local microbiology laboratories using auramine or modified Ziehl Neelsen staining or enzyme immunoassay, and samples were sent to the *Cryptosporidium* Reference Unit in Swansea for speciation by real-time PCR and subtyping using *gp60* sequencing. In Germany, *Cryptosporidium* was detected by diagnostic laboratories using enzyme immunoassay or microscopy.

Epidemiological investigations of cases in the Netherlands

Data of *Cryptosporidium*-positive cases detected by faecal testing since 2010 were requested from nine large routine microbiology laboratories spread throughout the Netherlands (together servicing approximately 21% of the Dutch population).

In addition, a case–control survey was conducted in four regions. A case was defined as a person who became ill with diarrhoeal symptoms after 1 August 2012 with a stool sample positive for *Cryptosporidium*. Public health services interviewed cases by telephone or posted the questionnaire. Collected data included date of birth, sex, symptoms (profuse and watery diarrhoea), date of onset, and possible sources of infection and exposures in the 10 days prior to onset of symptoms. Controls were randomly selected from a register of residents of 322 Dutch municipalities and were matched by sex and year of birth. The same questionnaire as for cases was send to 316 controls. Univariable and multivariable logistic regression analyses were performed, adjusted by sex and age group.

Epidemiological investigations in the United Kingdom

To examine the descriptive epidemiology of the increase noted from mid-August 2012, *Cryptosporidium* cases reported to national surveillance were compared to those reported over the previous years. A case–case study in the north-east compared risk factors ascertained through routine interviews of cryptosporidiosis cases in weeks 32 to 42 of 2012 with the previous three years.

Epidemiological investigations in Germany

Cryptosporidium cases (without species determination) reported to national surveillance were compared to those reported in the previous years.

International investigation

The RIVM sent out an urgent inquiry on 25 October 2012 on the Epidemic Intelligence Information System for Food and Waterborne Diseases (EPIS-FWD managed by the European Centre for Disease Prevention and Control (ECDC)) to inform other European Union (EU) Members States of this increase.

Results

The Netherlands

The number of *Cryptosporidium* cases from 2010 was readily available for eight laboratories that had had no change in diagnostic procedures since then. For weeks 31 to 42, they reported 524 positive samples for *Cryptosporidium* in 2012 compared with 115 in 2010 and 98 in 2011 (Figure). A peak with 292 *Cryptosporidium* cases occurred in weeks 35 to 38 of 2012, seven times higher than in the same period in 2010 and 2011 (42 and 45 cases, respectively). From weeks 31 to 42 in 2012, 58% of *Cryptosporidium* infections were diagnosed in children under the age of 10 years (comparable to 58% in 2010 and 45% in 2011), and 58% of these children were male. Seventy-two per cent of cases 15 years and older were female. The sex distribution was similar as in the two previous years, but the age distribution was significantly different ($p<0.0001$). Preliminary data showed 80 of 95 stool samples typed contained *C. hominis*, of which 78 belonged to the dominant *gp60* subtype IbA10G2; the remaining 15 samples contained *C. parvum* with six different subtypes.

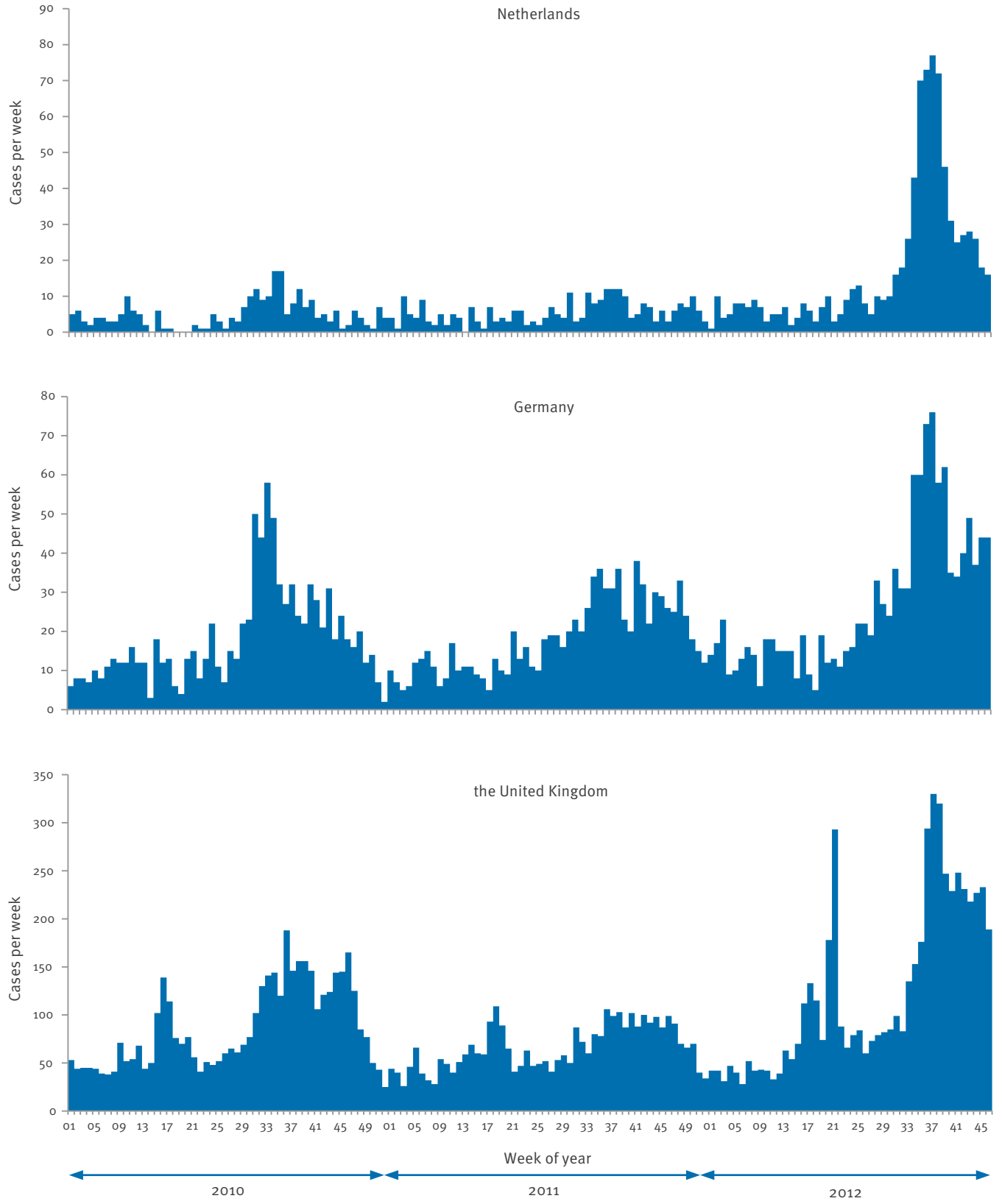
The Dutch case–control survey included 82 cases and 125 controls. More cases (36%) than controls (22%) had travelled abroad, mostly in Europe ($p=0.03$). The most visited countries were France (seven controls and nine cases) and Spain (two controls and nine cases). Seventy per cent of the cases and 66% of the controls had contact with surface water (in a swimming pool, sea, river or lake) in the 10 days before onset of symptoms ($p=0.56$). Contact with farm animals was not significantly different between cases and controls (33% vs. 40%, $p=0.30$). More controls than cases drank tap water on a daily basis (78% vs. 67%, $p=0.07$). In the multivariable logistic regression analysis adjusted for sex and age group, only drinking bottled mineral water remained associated with *Cryptosporidium* infection (odds ratio: 2.72; 95% confidence interval: 1.10–6.76; $p=0.03$), although only 21% of cases had drunk mineral water compared to 11% of controls.

The United Kingdom

In the UK, there was a two-fold increase in laboratory-confirmed *Cryptosporidium* cases, with 3,230 cases (weeks 33-46) compared to an average of 1,641 cases reported for the same weeks in the previous two years,

Figure

Cryptosporidium cases reported from eight laboratories in the Netherlands and cases notified in Germany and the United Kingdom, January 2010–November 2012



(2,002 cases in 2010 and 1,279 in 2011) (Figure). The percentage of cases over 20 years of age was significantly increased over that seen in the previous two years for weeks 33 to 46, but there was no significant change in age distribution.

Of 2,115 typed samples from weeks 33 to 48 inclusive, 1,577 (75%) contained *C. hominis*, 497 (23%) *C. parvum* and 45 (2%) contained other species/genotypes or were not typable. *Gp60* subtyping was undertaken on 48 not travel-related *C. hominis* cases from weeks 33, 35 and 37 in the age group with most cases, the 5–19 year-olds; of those, 37 (77%) were subtype IbA10G2, five belonged to two other types, and six did not amplify in the PCR. Almost a third of all specimens received at the *Cryptosporidium* Reference Unit and collected in weeks 33 to 37 were reported as travel-related, a proportion that declined after week 37 and from week 42 onwards was ‹10% of cases, which is in line with what has been seen in previous years. Spain and Turkey were the most frequently visited countries.

A case–case study in the north-east of England compared risk factors for weeks 32 to 42 in 2012 with the years 2009 to 2011. Travel abroad was reported in 54% of cases; this proportion had been similar in the previous years but the total case number was 2.2-fold higher. Of the countries visited, Spain and Turkey were most common. Among the cases not related to travel abroad there were significant positive associations with eating at a restaurant (32% in 2012 vs. 4% in 2009–2011, p=0.001) and dog ownership (46% in 2012 vs. 25% in 2009–2011, p=0.02). The difference in consumption of bottled water was not statistically significant (11% vs. 10% in 2009–2011, p=0.44), and swimming pool use was significantly less common in 2012 than between 2009 and 2011 (18% vs. 37%, p=0.02).

Germany

In Germany, there was a 1.8-fold increase of notified cryptosporidiosis cases in weeks 34 to 44 with 584 cases (Figure), compared to 316 cases in 2010 and 333 cases in 2011 in the same period. A peak occurred in week 37 with 76 cases (32 in 2010 and 31 in 2011 in the same week). The median age of cases notified in this time period was 19 years, and 50% of cases were male, similar to the two previous years. Laboratory diagnostic procedures did not include typing.

International investigation

The EPIS alert from the Netherlands identified increases in the UK and Germany. No increase in cryptosporidiosis was reported in Denmark, France, Hungary, Ireland, Lithuania, Malta and Norway. Finland reported two ongoing outbreaks caused by *C. parvum*.

Discussion

An increase in the number of *Cryptosporidium* cases was observed from August 2012 throughout the Netherlands, all regions of England, Wales, Scotland and also Germany. In the Netherlands, the increase lasted from week 31 to 42 while in the UK, the excess cases were reported from week 33 to 46 and in Germany from week 33 to 44. In the Netherlands and the UK, the most frequently isolated species was *C. hominis gp60* subtype IbA10G2, which is the dominant subtype in these countries [3,4].

Cryptosporidium outbreaks have been associated with contaminated drinking water or recreational water [2,5,6], contact with farm animals [7], person-to-person spread in daycare and other institutions [8], food handling [9], or consumption of unpasteurised apple juice [10], milk, fruits or vegetables [11,12]. In the Netherlands, the few published outbreaks have been caused by *C. parvum* [13], while multiple outbreaks in the UK have involved both *C. parvum* and *C. hominis* [14].

In the Netherlands, the heavy rainfall in July and August 2012, followed by an extremely warm period with temperatures up to 35 °C at the end of August, suggested the potential for contamination of surface water [15,16]. The case–control study did not show an association with surface water contact or tap water consumption. However, this risk factor cannot be excluded entirely because the statistical non-significance could be due to a lack of power. Almost 70% of controls and cases reported bathing in surface water in this warm summer holiday period. Travelling abroad before the onset of symptoms was significantly different between cases and controls, but this association did not remain in the multivariate analysis. Drinking bottled mineral water was associated with cryptosporidiosis, but only 21% of cases and 11% of the controls reported daily mineral water consumption. Further questionnaires were administered to cases who drank bottled mineral water, but no particular brand has emerged.

During the period when questionnaires were sent out to Dutch cases and controls, there was also a *Salmonella* Thompson outbreak in the Netherlands [17]. However, there was no significant increase in the number of referred faecal samples, and the increased *Cryptosporidium* cases are unlikely to result from such screening bias.

In the UK, travel abroad was an important risk. However, the percentage of travel-related cases was similar to the previous years and cannot explain all cryptosporidiosis cases. The association with eating out suggests the possibility that transmission of infection in some cases might have been through consumption of contaminated food or drinks.

Because the number of *Cryptosporidium*-positive samples in the Netherlands, the UK and Germany increased during the same period, common exposures or influencing factors might be expected. However, no single source has been found that could explain the increase of cryptosporidiosis seen in these countries. Foreign travel has been an important risk in the UK and

bottled mineral water raised as a hypothesis in the Netherlands. However, plausible factors might include multiple sources, extreme weather conditions, person-to-person transmission and other, still unidentified risk factors. Alternatively, the increase in different countries may have developed independently which could explain the difference in age distribution compared to previous years in the Netherlands but not in the UK and Germany. This increase in cryptosporidiosis across a wider geographic area highlights the need for wider surveillance, development of better subtyping methods, the inadequacy of controls for travel-related infections and a need for further work on bottled waters [18] and foods as potential *Cryptosporidium* risks.

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References

1. Hunter PR, Nichols G. Epidemiology and clinical features of Cryptosporidium infection in immunocompromised patients. Clin Microbiol Rev. 2002;15(1):145-54.
2. Leitch GJ, He Q. Cryptosporidiosis-an overview. J Biomed Res. 2012;25(1):1-16.
3. Wielinga PR, de Vries A, van der Goot TH, Mank T, Mars MH, Kortbeek LM, et al. Molecular epidemiology of Cryptosporidium in humans and cattle in The Netherlands. Int J Parasitol. 2008;38(7):809-17.
4. Chalmers RM, Hadfield SJ, Jackson CJ, Elwin K, Xiao L, Hunter P. Geographic linkage and variation in Cryptosporidium hominis. Emerg Infect Dis. 2008;14(3):496-8.
5. Semenza JC, Nichols G. Cryptosporidiosis surveillance and water-borne outbreaks in Europe. Euro Surveill. 2007;12(5): pii=711. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=711
6. Insulander M, Lebbad M, Stenstrom TA, Svenungsson B. An outbreak of cryptosporidiosis associated with exposure to swimming pool water. Scand J Infect Dis. 2005;37(5):354-60.
7. Smith RP, Chalmers RM, Mueller-Doblies D, Clifton-Hadley FA, Elwin K, Watkins J, et al. Investigation of farms linked to human patients with cryptosporidiosis in England and Wales. Prev Vet Med. 2010;94(1-2):9-17.
8. Artieda J, Basterrechea M, Arriola L, Yague M, Albisua E, Arostegui N, et al. Outbreak of cryptosporidiosis in a child day-care centre in Gipuzkoa, Spain, October to December 2011. Euro Surveill. 2012;17(5):pii=20070. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20070
9. Quiroz ES, Bern C, MacArthur JR, Xiao L, Fletcher M, Arrowood MJ, et al. An outbreak of cryptosporidiosis linked to a foodhandler. J Infect Dis. 2000;181(2):695-700.
10. Blackburn BG, Mazurek JM, Hlavsa M, Park J, Tillapaw M, Parrish M, et al. Cryptosporidiosis associated with ozonated apple cider. Emerg Infect Dis. 2006;12(4):684-6.
11. Robertson LJ, Chalmers RM. Foodborne cryptosporidiosis: is there really more in Nordic countries? Trends Parasitol. 2013;29(1):3-9.
12. Gherasim A, Lebbad M, Insulander M, Decraene V, Kling A, Hjertqvist M, et al. Two geographically separated food-borne outbreaks in Sweden linked by an unusual Cryptosporidium parvum subtype, October 2010. Euro Surveill. 2012;17(46):pii=20318. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20318
13. Yap KB, van der Giessen JW, Brimicombe RW. Cryptosporidium na een bezoek aan de kinderboerderij. [Cryptosporidium after visiting the petting zoo]. Infectieziekten Bulletin. 2003;14:362-5. Dutch. Available from: http://www.rivm.nl/dsresource?type=pdf&objectid=rivmp:59289&versionid=&subobjectname=
14. Chalmers RM, Elwin K, Thomas AL, Guy EC, Mason B. Long-term Cryptosporidium typing reveals the aetiology and species-specific epidemiology of human cryptosporidiosis in England and Wales, 2000 to 2003. Euro Surveill. 2009;14(2):pii=19086. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19086
15. Schets FM, Italiaander R, van den Berg HH, de Roda Husman AM. Rainwater harvesting: quality assessment and utilization in The Netherlands. J Water Health. 2010;8(2):224-35.
16. Schets FM, van Wijnen JH, Schijven JF, Schoon H, de Roda Husman AM. Monitoring of waterborne pathogens in surface waters in amsterdam, the Netherlands, and the potential health risk associated with exposure to cryptosporidium and giardia in these waters. Appl Environ Microbiol. 2008;74(7):2069-78.
17. Friesema IH, de Jong AE, Fitz James IA, Heck ME, van den Kerkhof JH, Notermans DW, et al. Outbreak of Salmonella Thompson in the Netherlands since July 2012. Euro Surveill. 2012;17(43):pii=20303. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20303
18. Nichols RA, Campbell BM, Smith HV. Identification of Cryptosporidium spp. oocysts in United Kingdom noncarbonated natural mineral waters and drinking waters by using a modified nested PCR-restriction fragment length polymorphism assay. Appl Environ Microbiol. 2003;69(7):4183-9.

A verocytotoxin-producing *E. coli* outbreak with a surprisingly high risk of haemolytic uraemic syndrome, Denmark, September-October 2012

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Denmark faced an outbreak of verocytotoxin-producing *E. coli* (VTEC) O157:H7 infections in autumn 2012. Thirteen cases were diagnosed of which eight had haemolytic uraemic syndrome (HUS). Epidemiological investigations suggested ground beef as the vehicle of the outbreak. The outbreak strain had a rare toxin gene subtype profile: *eae*, *vtx1a* and *vtx2a*, and a high proportion of HUS (62%) among cases, a finding previously linked with the outbreak subtype profile. Toxin subtyping can be useful to identify high risk VTEC strains.

In late September 2012, a paediatric department in a Central Copenhagen Hospital notified Statens Serum Institut (SSI) of four cases of haemolytic uraemic syndrome (HUS). This led to the initiation of an outbreak investigation.

HUS and infections with verocytotoxin-producing *E. coli* (VTEC) are individually notifiable in Denmark. Furthermore, VTEC infections are laboratory-notifiable. Around 180 cases are reported each year, of which serogroup O157 constitute 15–20% [1]. Previously, Denmark has experienced only two general outbreaks of VTEC infection. In 2006 an outbreak of VTEC O157 affected 25 cases, with organic pasteurised milk as the source [2]. In 2007, an outbreak of VTEC O26 affected 20 cases, with an organic fermented beef sausage as the source [3]. In addition, Denmark reported 26 cases during the large VTEC O104 outbreak in Germany in 2011 [4]. The annual number of HUS cases in Denmark ranges from two to six [1]. Subtyping of verocytotoxin genes are done at SSI as described in [5].

Outbreak investigation

For this outbreak, we defined a *confirmed case* as an individual with a laboratory-confirmed infection with VTEC O157 *eae*, *vtx1a* and *vtx2a* diagnosed after 1 August 2012, or a person diagnosed with HUS in the same time period and a serology-confirmed VTEC O157 infection. A *probable case* was a person without laboratory-confirmed VTEC infection, diagnosed with HUS after 1 August 2012, or a person diagnosed with VTEC O157 infection in the same period, but without subtyping, or a person diagnosed with VTEC *eae*, *vtx1a* and *vtx2a* infection in the same period, but without O-typing. The date 1 August was chosen in order to identify any early cases.

On 22 October, after laboratory confirmation of VTEC O157 in two patients, SSI notified Danish clinical laboratories of a possible VTEC outbreak to increase case ascertainment and reporting. We interviewed patients (or their parents for children under 15 years of age) by telephone, using a structured trawling questionnaire. Early investigations had pointed to ground beef as the possible outbreak source, and information on purchase dates and other possible labelling information of ground beef was collected and presented to the supermarkets for further tracing of possible batch identification. The Danish Veterinary and Food Administration traced back the ground beef.

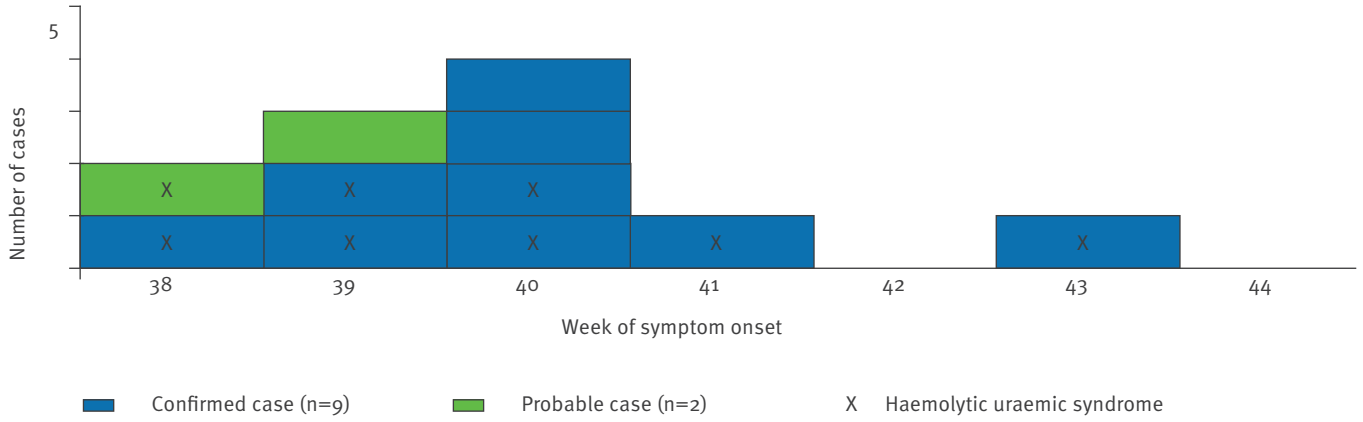
SSI performed live-slide agglutination on the submitted isolates upon arrival, and all VTEC O157-positive isolates were typed immediately with the PCR protocol for subtyping of *vtx* genes [5]. Further testing included conventional (and confirmatory) O:H serotyping, Vero cell assay, fermentation of sorbitol, production of beta-glucuronidase, presence of additional virulence genes by dot blot hybridisation and/or PCR, and pulsed-field gel electrophoresis (PFGE). We asked patients who were culture-negative for VTEC O157 to submit a serum specimen for serology testing for antibodies against VTEC O157.

Findings

We identified 13 cases of VTEC O157 (11 confirmed and two probable). Eight cases had HUS. The cases belonged to nine families. Eleven reported symptoms,

Figure

Probable and confirmed cases of symptomatic verocytotoxin-producing *E. coli* O157 by date of onset, Denmark, September –October 2012 (n=11)



The two asymptomatic cases found by screening are not depicted in the figure.

whereas two were diagnosed when we screened healthy family members. Date of disease onset ranged from 18 September to 28 October 2012 (Figure). The cases were distributed throughout the country, eight were female, and the median age was 14 years (range: 3–68 years).

Hypothesis-generating interviews suggested that the source of the outbreak was food served in the households. Most affected families had young children, ate traditional (non-vegetarian) Danish food and lived in provincial towns. The most frequent food exposure reported was ground beef: all cases had eaten ground beef during the incubation period, six in the form of pan-fried ground beef ("hakkebøffer"). Two households mentioned the beef still being red in the centre when eaten. No other food items were common to all cases. The families had purchased food in a variety of different supermarket chains. Trace-back of the beef indicated that it was of Danish origin and narrowed the possibilities down to two major Danish slaughterhouses and to two consecutive slaughter days. However, identification of a single food producer was impossible and no further action was taken.

We compared interview information from the current outbreak with that of a salmonella outbreak occurring in 2011 in the same months (to account for possible changes in eating habits with the seasons) [6], where a comparable hypothesis-generating questionnaire was used. The nine families involved in the 2012 VTEC outbreak reported similar frequencies of consumption as the 2011 salmonella cases for almost all food items. However, all nine case-families in the 2012 VTEC outbreak reported eating ground beef, compared with 14 of 24 case-families in the salmonella outbreak (p=0.03; Fisher's exact-test).

The outbreak strain was a typical VTEC O157:H7, *eae* positive, non-sorbitol fermenting, negative for beta-glucuronidase. However, it had a rare toxin subtype profile including the genes *vtx1a* and *vtx2a*. All strains had the same PFGE profile, which had not been reported previously among Danish VTEC isolates. The Table shows the distribution of the total number of VTEC O157 cases diagnosed and sub-typed in Denmark from 1997 to 2012, stratified by toxin profile. For each toxin profile, the proportion of cases with HUS is shown. VTEC infections containing the *vtx2a* toxin profile were associated with a higher number of HUS cases (from 3% to above 20%), and VTEC infections containing the *eae* + *vtx1a* + *vtx2a* profile were associated with even higher frequencies of HUS cases (33%).

Discussion

The present outbreak represents the first food-borne outbreak of a highly virulent VTEC O157 in Denmark. Subtyping of the toxin genes allowed rapid identification and classification of cases. In addition, toxin subtyping was of relevance for the overall risk assessment. The combination of *vtx1a* and *vtx2a* in the toxin profile of the outbreak strain is rare and appears to be associated with a high risk of progression to HUS as also indicated by previously subtyped VTEC O157 strains. This emphasises that within the VTEC O157 group, there is a diversity of strains with different potential of causing HUS.

As a surrogate for an analytical epidemiological investigation, we compared case exposure to ground beef

Table

Verocytotoxin-producing *E. coli* O157 cases and proportion of haemolytic uraemic syndrome by toxin profile, Denmark, 1 January 1997–31 July 2012 (n=212)

Toxin profile	Total number of cases	Number of HUS cases	Proportion of HUS
eae + vtx1a	8	0	0
eae + vtx1a + vtx2c	85	0	0
eae + vtx2c	31	1	3%
eae + vtx2a + vtx2c	45	11	24%
eae + vtx2a	37	11	30%
eae + vtx1a + vtx2a	6	2	33%

HUS: haemolytic uraemic syndrome.

with similar exposure in a recent salmonella outbreak. This case¬–case comparison suggested that more families than expected had consumed ground beef in the present outbreak. In addition, these families had prepared it in a way that allowed for part of the beef to remain uncooked. This suggests that this outbreak was caused by ground beef, a common source of VTEC outbreaks. Ground beef has a short shelf life (seven days), which may have limited the size of this outbreak. If the vehicle of the outbreak had been a food item with longer shelf life, the public health impact of this high risk HUS-associated VTEC outbreak could have been much larger.

Based on the findings of this outbreak we suggest performing toxin subtyping in similar outbreak situations in order to quickly identify high risk VTEC strains and thereby aid risk assessment of the outbreak.

References

1. VTEC, laboratorieanmeldelsespligtige sygdomme. [VTEC, laboratory-notifiable diseases]. Copenhagen: Statens Serum Institut. [Accessed December 2012]. Danish. Available from: http://www.ssi.dk/Smitteberedskab/Sygdomsovervaagning/Sygdomsdata.aspx?sygdomskode=STEC&xaxis=Aar&show=&datatype=Laboratory&extendedfilters=False#HeaderText
2. Jensen C, Ethelberg S, Gervelmeyer A, Nielsen EM, Olsen KE, Molbak K. First general outbreak of Verocytotoxin-producing Escherichia coli O157 in Denmark. Euro Surveill. 2006;11(2):pii=597. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=597
3. Ethelberg S, Smith B, Torpdahl M, Lisby M, Boel J, Jensen T, et al. Outbreak of non-O157 Shiga toxin-producing Escherichia coli infection from consumption of beef sausage. Clin Infect Dis. 2009;48(8):e78-e81.
4. Müller L, Ethelberg S, Kjelsø C, Mølbak K, Scheutz F, et al. VTEC O104 outbreak in Germany. EPI-NEWS. 2011;27-33. Available from: http://www.ssi.dk/English/News/EPI-NEWS/2011/No%2027-33%20-%202011.aspx
5. Scheutz F, Teel LD, Beutin L, Pierard D, Buvens G, Karch H, et al. Multicenter evaluation of a sequence-based protocol for subtyping shiga toxins and standardizing Stx nomenclature. J Clin Microbiol. 2012;50(9):2951-63.
6. Müller L. Copenhagen: Statens Serum Institut. Outbreak of salmonella Strathcona. 2012. EPI-NEWS. 2012;4. Available from: http://www.ssi.dk/English/News/EPI-NEWS/2012/No%204%20-%202012.aspx

Mycobacterium tuberculosis Beijing outbreak in a school in Marseille, France, 2012

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Between January and September 2012, a teacher and four students at a technical college in Marseille, France, developed pulmonary tuberculosis. All *Mycobacterium tuberculosis* isolates from these cases were identical and belonged to the Beijing strain family, multispacer sequence type 72, a rare genotype identified only once in our laboratory in the previous two years. This report highlights once more the potential for *M. tuberculosis* Beijing strains to cause outbreaks, this time in a school setting.

Among the different genotypes of *Mycobacterium tuberculosis* pathogenic to humans, the Beijing strains - first described 20 years ago in the Chinese capital – are now known to have a global distribution [1,2]. The Beijing strain family is characterised by its potential to cause epidemics and its association with drug resistance [3,4]. Several outbreaks of pulmonary tuberculosis (TB) due to *M. tuberculosis* Beijing have been reported in congregate settings such as homeless shelters [5] and prisons [6]. We report on a recent outbreak of pulmonary TB cases attributed to *M. tuberculosis* Beijing genotype in a school.

Outbreak description

In January 2012, a 20-year-old male (Case 1) attending a technical school in Marseille, in southern France, was diagnosed with pulmonary TB and mediastinal lymph node involvement. Direct microscopy examination of three sputum specimens did not detect acid fast bacilli (AFB) but *M. tuberculosis* was cultured from the sputa and broncho-alveolar fluid. The strains were susceptible to rifampicin and isoniazid and the patient was successfully treated using a combination of rifampicin, isoniazid, pyrazinamide and ethambutol. In mid-June 2012, a 42-year-old teacher at the same school (Case 2) was also diagnosed with pulmonary TB. He presented with fever and weight loss as well as a cough that had lasted for the previous six months. Radiology showed extensive lesions in both lungs with multiple cavitations. Three sputum samples yielded an average of 100 AFB per microscopy field and *M. tuberculosis* susceptible to first-line anti-tuberculosis drugs was cultured. Response to first-line drug combination therapy was favourable and no AFB were detectable on sputum microscopy after two months. In early July 2012, as part of the investigation of these two cases by the local public health authorities for TB control, pulmonary TB was diagnosed in a second student in the same school (Case 3) who presented both clinical and radiological signs. The diagnosis was confirmed by culture from sputum specimens, which also isolated drug-susceptible *M. tuberculosis*.

Contact tracing

These cases of pulmonary TB clustered in time and place led to a broader investigation including a total of 334 individuals associated with this school in 2012, comprising students, teachers and administrative personnel. All were tested with interferon gamma release assays (IGRA) and 30 tests were interpreted as positive. Those who tested positive were put on prophylactic medication with isoniazid. Family members of the three patients who had been in regular contact with the three and 20 other persons in a factory where Case 1 was a trainer were also examined by symptom screening, followed by X-ray, and then sputum microscopy. In September 2012, this investigation led to the detection of subclinical pulmonary TB in two students (Cases 4 and 5) attending the same class as Case 3. In both cases, culture of respiratory tract samples yielded drug-susceptible *M. tuberculosis* isolates.

The investigation led to the hypothesis that the teacher (Case 2) was the source case of this outbreak. The source case had no identified risk for TB from significant contact outside the school or a previous history of TB. Given that his clinical signs and symptoms were initially attributed to chronic obstructive pulmonary disease secondary to heavy smoking, the diagnosis of TB was delayed and only confirmed after that of Case 1. Cases 3 and 4 were considered to have been exposed in the class in which the teacher taught. In addition, the teacher gave truck-driving lessons to the students of this class three times per week with each session lasting four consecutive hours. No direct contact between Case 1 and the teacher was established.

Laboratory investigations

M. tuberculosis isolates collected in all five cases were sent to our reference laboratory for further analyses. Molecular testing using a marketed assay (GenExpert, Cepheid, Maureus-Scoport, France) [7] confirmed the identification of *M. tuberculosis* and detected no mutations associated with rifampicin resistance. Susceptibility testing using conventional liquid culture showed no resistance to all first-line antimycobacterials. Real-time PCR genotyping targeting the intergenic region Rv0927c-pstS3 [8] and a second region specific to the Beijing family [9] confirmed a Beijing genotype for all isolates. Multispacer sequence-typing (MST) [10] identified a genotype MST72 and confirmed that the isolates were indistinguishable. Our laboratory had only detected this genotype once previously among 174 strains of *M. tuberculosis* genotyped since 2010 (data not shown) in a patient born in Thailand and residing in France who had no known contacts with the cases reported in the current outbreak.

Conclusions

To our knowledge, this is the first report of an outbreak of *M. tuberculosis* Beijing genotype infections occurring in a school. This is also the largest outbreak of pulmonary TB detected in Marseille area in the last 15 years: in this area, the other outbreaks have only occurred in penitentiary establishments. This report illustrates the highly pathogenic and highly contagious nature of the Beijing strain family, which requires a quick laboratory confirmation. This outbreak was characterised by the high contagiousness of the source case and a clinically-severe picture in three of the five cases detected. Prolonged contact within the confines of a truck cabin (with an approximate volume of six cubic metres) may confer a risk of TB infection not very different from that in a long-haul airplane flight [11]. This outbreak also illustrates the importance of contact tracing and laboratory investigation in improving the early detection of linked cases of TB and the need to maintain a high index of suspicion for this disease even in the presence of other conditions leading to chronic cough. As in this report, most cases of TB today are caused by organisms which are not drug-resistant and which can be cured using a standard treatment with combination of anti-TB drugs for at least six months [12]. Patients on treatment only require isolation until they are no longer infectious. Given that Beijing strains are particularly transmissible and often exhibit multi-drug resistance, France and other European countries are concerned with Beijing strain family of *M. tuberculosis* [13]. Schools should be integrated in nation-wide surveillance systems for TB in France.

References

1. Van Soolingen D, Qian L, de Haas PE, Douglas JT, Traore H, Portaels F, et al. Predominance of a single genotype of Mycobacterium tuberculosis in countries of East Asia. J Clin Microbiol. 1995;33(12):3234-8.
2. Bifani PJ, Mathema B, Kurepina NE, Kreiswirth BN. Global dissemination of the Mycobacterium tuberculosis W-Beijing family strains. Trends Microbiol. 2002;10(1):45-52.
3. Glynn JR, Whiteley J, Bifani PJ, Kremer K, van Soolingen D. Worldwide occurrence of Beijing/W strains of Mycobacterium tuberculosis: a systematic review. Emerg Infect Dis. 2002;8(8):843-9.
4. Hanekom M, Gey van Pittius NC, McEvoy C, Victor TC, Van Helden PD, Warren RM. Mycobacterium tuberculosis Beijing genotype: a template for success. Tuberculosis (Edinb). 2011;91(6):510-23.
5. Munsiff SS, Nivin B, Sacajiu G, Mathema B, Bifani P, Kreiswirth BN. Persistence of a highly resistant strain of tuberculosis in New York City during 1990-1999. J Infect Dis. 2003;188(3):356-63.
6. Ignatova A, Dubiley S, Stepanshina V, Shemyakin I. Predominance of multi-drug-resistant LAM and Beijing family strains among Mycobacterium tuberculosis isolates recovered from prison inmates in Tula Region, Russia. J Med Microbiol. 2006;55(Pt10):1413-8.
7. Dorman SE, Chihota VN, Lewis JJ, Shah M, Clark D, Grant AD, et al. Performance characteristics of the Cepheid Xpert MTB/RIF test in a tuberculosis prevalence survey. PLoS One. 2012;7(8):e43307.
8. Leung ET, Zheng L, Wong RY, Chan EW, Au TK, Chan RC, et al. Rapid and simultaneous detection of Mycobacterium tuberculosis complex and Beijing/W genotype in sputum by an optimized DNA extraction protocol and a novel multiplex real-time PCR. J Clin Microbiol. 2011;49(7):2509-15.
9. Hillemann D, Warren R, Kubica T, Rüsch-Gerdes S, Niemann S. Rapid detection of Mycobacterium tuberculosis Beijing genotype strains by real-time PCR. J Clin Microbiol. 2006;44(2):302-6.
10. Djelouadji Z, Arnold C, Gharbia S, Raoult D, Drancourt M. Multispacer sequence typing for Mycobacterium tuberculosis genotyping. PLos One. 2008;3(6):e2433.
11. Kenyon TA, Valway SE, Ihle WW, Onorato IM, Castro KG. Transmission of multidrug-resistant Mycobacterium tuberculosis during a long airplane flight. N Engl J Med. 1996;334(15):933-8.
12. World Health Organization (WHO). Treatment of Tuberculosis: guidelines for national programmes. 4th edition. Geneva: WHO. 2009. Available from: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf
13. Cohen-Bacrie S, Ben Kahla I, Botelho-Nevers E, Million M, Parola P, Brouqui P, et al. Imported extensively drug-resistant Mycobacterium tuberculosis Beijing genotype, Marseilles, France, 2011. Euro Surveill. 2011;16(16):pii=19846. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19846

Hospital-acquired infections due to multidrug-resistant organisms in Hungary, 2005-2010

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Healthcare-associated infections caused by multidrug-resistant organisms are associated with prolonged medical care, worse outcome and costly therapies. In Hungary, hospital-acquired infections (HAIs) due to epidemiologically important multidrug-resistant organisms are notifiable by law since 2004. Overall, 6,845 case-patients (59.8% men; median age: 65 years) were notified in Hungary from 2005 to 2010. One third of case-patients died in hospital. The overall incidence of infections increased from 5.4 in 2005 to 14.7 per 100,000 patient-days in 2010. Meticillin-resistant *Staphylococcus aureus* (MRSA) was the most frequently reported pathogen (52.2%), but while its incidence seemed to stabilise after 2007, notifications of multidrug-resistant Gram-negative organisms have significantly increased from 2005 to 2010. Surgical wound and bloodstream were the most frequently reported sites of infection. Although MRSA incidence has seemingly reached a plateau in recent years, actions aiming at reducing the burden of HAIs with special focus on Gram-negative multidrug-resistant organisms are needed in Hungary. Continuing promotion of antimicrobial stewardship, infection control methodologies, reinforced HAI surveillance among healthcare and infection control practitioners, and engagement of stakeholders, hospital managers and public health authorities to facilitate the implementation of existing guidelines and protocols are essential.

Introduction

Healthcare-associated infections are infections arising from any aspect of healthcare management, most commonly during hospitalisation in acute care facilities (hospital-acquired infections, HAI) where the patient receives treatment for another medical or surgical condition. These infections are a significant cause of morbidity and mortality worldwide, primarily among immunocompromised and elderly people, especially if the causative organism has developed resistance to a number of antimicrobial agents. Patients infected with multidrug-resistant organisms usually have a significantly longer hospital stay, are more likely to be in need of intensive care, costly therapies and treatments, and have a worse prognosis [1]. While the burden of HAIs due to multidrug-resistant organisms may vary widely according to geographical region, healthcare setting, type of pathogen and antimicrobial substance, its relevance to patient safety and public health continues to increase both nationally and internationally. Therefore surveillance of HAIs caused by multidrug-resistant organisms, epidemiological, microbiological or both, has been established in most industrialised countries [2-6], and the need for a global approach has been recognised [7].

Data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) are worrisome. The proportion of strains of major pathogens isolated from blood or cerebrospinal fluid (CSF) with resistance to important antimicrobial agents exceeds 10% or even 25% in several countries, with the highest figures seen in southern and eastern Europe [8,9]. Recently, national efforts in infection control in the European Union (EU) have led in some countries to a plateau or even a reversal of the trend of increasing resistance to antimicrobial agents, for example for meticillin-resistant *Staphylococcus aureus* (MRSA), penicillin- and/or macrolide-resistant *Streptococcus pneumoniae* and aminoglycoside-resistant *Enterococci*; however, increasing trends are still being observed for multidrug-resistant *Escherichia coli* and *Klebsiella pneumoniae* [9].

Carbapenems are currently considered as last-line antibiotics for the treatment of many infections caused by certain multidrug-resistant organisms. In particular, carbapenem resistance among Gram-negative microorganisms such as *K. pneumoniae* [9,10], *Pseudomonas aeruginosa* [9] and *Acinetobacter baumannii* [11] has recently increased in Europe.

In Hungary (population ca. 10 million), HAIs due to epidemiologically important multidrug-resistant organisms are notifiable by law through the national surveillance system for nosocomial infections (Nemzeti Nosocomiális Surveillance Rendszer, NNSR) which was established in October 2004. Reporting is mandatory for all hospitals. We aimed at describing the patient population and infections due to multidrug-resistant

organisms reported to the relevant surveillance module of the NNSR, and assessing the epidemiological trends during the period from 2005 to 2010 and the recent situation of reported HAIs caused by multidrug-resistant organisms in Hungary.

Methods

Data source and reporting method

The NNSR, operated by the National Center for Epidemiology in Budapest, Hungary, is a national surveillance network and a database of nosocomial infections. Data on incident cases are collected, using surveillance methodology and HAI case definitions of the United States Centers for Disease Control and Prevention (US CDC) [12]. As of December 2010, the NNSR consisted of three compulsory modules (nosocomial outbreaks, HAI caused by multidrug-resistant organisms/*Clostridium difficile*, and nosocomial bloodstream infections), four voluntary modules (surgical site infections, intensive care unit- and perinatal intensive care unit-based surveillance, device-associated infections) and a disinfectant database [13]. Reporting of the compulsory elements is continuous.

The relevant surveillance module of the NNSR contains records from patients with HAI caused by a given multidrug-resistant organism at one or more anatomical sites, acquired during a given hospital stay. HAI is defined as a localised or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s), with no evidence that the infection was present or incubating at the time of admission [12].

HAIs caused by the following multidrug-resistant organisms were included in the period studied: meticillin-resistant *S. aureus* (MRSA), vancomycin-resistant *Enterococcus* sp. (VRE), multidrug-resistant *Enterobacter* sp., multidrug-resistant *Escherichia coli*, multidrug-resistant *Klebsiella* sp., multidrug-resistant *A. baumannii*, multidrug-resistant *P. aeruginosa*, co-trimoxazole-resistant *Stenotrophomonas maltophilia*, and intermediate vancomycin-resistant *S. aureus* (VISA). The pathogens and key antibiotics to which resistance was monitored were selected through national expert consultations (Table 1). Throughout the period studied, resistance thresholds defined by the Clinical and Laboratory Standards Institute (CLSI) were used in laboratories in Hungary [14-19].

Variables required included information on patients' demographics (age, sex), lifestyle characteristics (smoking, alcohol consumption, drug abuse), medical history (concomitant diseases, recent surgeries), hospital stay (hospital ward, diagnosis upon admission, therapies or medical procedures applied as well as use of catheters before the recognition of HAI), outcome at discharge (recovered, transferred to another hospital, deceased), and healthcare-associated infection caused by a multidrug-resistant organism (pathogen, type of infection, date of microbiological confirmation). Data on admission diagnosis, concomitant diseases and lifestyle characteristics were gathered from International Classification of Diseases (ICD-10) diagnosis codes documented in the medical records. Case-based data were entered in the internet-based surveillance tool by infection control (IC) nurses and, if available, approved by IC doctors when the patient affected was discharged from the hospital or dies. No post-discharge data are collected.

Study design and study population

We conducted a descriptive study including all notified cases of HAI due to multidrug-resistant organisms in Hungary until 2010. We defined a case-patient as a patient who was infected with one or more multidrug-resistant organisms at one or more anatomical sites during a given hospital stay. Data from 2004 were

Table 1

Pathogens included in the module for hospital-acquired infections due to multidrug-resistant organisms of the national surveillance system for nosocomial infections in Hungary, 2005–10

Microorganism	Antibiotic resistance
Staphylococcus aureus (MRSA)	Meticillin/oxacillin
Klebsiella sp.	Third generation cephalosporins for ESBL-production, imipenem and/or meropenem
Acinetobacter baumannii	Imipenem and/or meropenem
Escherichia coli	Third generation cephalosporins for ESBL-production, imipenem and/or meropenem
Pseudomonas aeruginosa	Sensitive to maximum two of the following agents: piperacillin/tazobactam, ceftazidin, cefepim, imipenem, meropenem, ciprofloxacin, gentamicin, tobramycin, amikacin, aztreonam
Enterobacter sp.	Third generation cephalosporins for ESBL-production, imipenem and/or meropenem
Stenotrophomonas maltophilia	Cotrimaxazol (sumetrolim)
Staphylococcus aureus (VISA)[a]	Intermediate sensitivity to vancomycin
Enterococcus sp. (VRE)	Vancomycin

ESBL: extended spectrum beta-lactamase; MRSA: meticillin-resistant *Staphylococcus aureus*; VISA: intermediate vancomycin-resistant *S. aureus*; VRE: vancomycin-resistant *Enterococcus* sp.

[a] VISA was added to the surveillance module in 2008.

discarded because the surveillance system was established and launched in that year, and the reported data are incomplete. Furthermore we excluded case-patients for whom date of admission, date of discharge or microbiological tests were not available.

Descriptive and analytical methods

We estimated the yearly coverage of the surveillance system by means of three indicators: proportion of all hospitals included in the system (hospitals notifying at least one multidrug-resistant organism/all hospitals in Hungary), proportion of hospitalisations (hospitalisation in the notifying hospitals/hospitalisations in all hospitals in Hungary), and proportion of patient-days (patient-days in the notifying hospitals/patient-days in all hospitals in Hungary).

We described HAI case-patients in terms of the following variables: sex, age at admission, lifestyle characteristics, underlying medical conditions, type of healthcare institution, hospital ward, medical procedures and devices applies, outcome, type of infection and type of multidrug-resistant organism.

We classified healthcare institutions into five categories: primary (typically city hospitals with essential medical specialties), secondary (typically county hospitals and large hospitals in the capital city with highly differentiated clinical functions), tertiary (central referral hospitals and university clinics with highly differentiated clinical functions, specialised staff and technical equipment), specialised hospitals (single clinical specialty, possibly with sub-specialties) as well as chronic care/rehabilitation hospitals.

Distributions of categorical variables between patient groups (e.g. case-patients with versus those without prior operation) were compared using the chi-square test. A p-value of 0.05 was considered to be statistically significant. For continuous variables, interquartile ranges (IQR) were calculated.

Annual incidence densities of reported HAIs were calculated as: (number of HAIs notified to NNSR during a given year) / (patient-days from all hospitals notifying at least one HAI that year) x 100,000. Incidence densities were calculated overall and stratified by multidrug-resistant organism. Denominator data were retrieved from official annual reports on hospital beds and patient turnover issued by the National Health Insurance Fund in Hungary [20].

The analyses were performed using Stata v10 (StataCorp LP).

Results

Reporting hospitals

The proportion of hospitals that reported at least one patient with HAI due to a multidrug-resistant organism to the NNSR gradually increased from 27.8% (50 of 180) in 2005 to 43.6% (75 of 172) in 2010. In 2005, reporting hospitals received 64.0% of hospitalisations and accounted for 58.5% of patient-days in Hungary, while in 2010 the corresponding figures were 87.8% and 78.7%.

Table 2

Selected characteristics[a] of patients with reported hospital-acquired infection due to multidrug-resistant organism in Hungary, 2005–10 (n=6,845)

Patient characteristics	Number	Proportion of study population (%)
Sex		
Male case-patients	4,095	59.8
Female case-patients	2,750	40.2
Age group (age at admission)		
0–10 years	211	3.1
11–20 years	93	1.4
21–30 years	189	2.8
31–40 years	291	4.2
41–50 years	556	8.1
51–60 years	1,315	19.2
61–70 years	1,614	23.6
71–80 years	1,715	25.1
81–90 years	807	11.8
91–100 years	54	0.8
Lifestyle characteristics		
Smoking	597	8.7
Alcohol abuse	538	7.9
Concomitant diseases		
Cardiovascular disease	3,015	44.0
Chronic respiratory disease	1,072	15.7
Cancer	970	14.2
Chronic kidney disease	545	8.0

[a] Based on relevance and frequency.

Patient population

Overall, 8,673 case-patients were reported between 2004 and 2010. After applying exclusion criteria, 6,845 case-patients (59.8% men; median age at admission: 65 years, range: 1–98 years) were included in the analysis as study population (Table 2). The most frequently reported concomitant diseases were cardiovascular (44.0%) and chronic respiratory diseases (15.7%). The number of reported case-patients increased from 590 in 2005 to 1,807 in 2010. The median length of hospital stay was 25 days (IQR: 14–42 days) in the study population. The proportion of case-patients infected with more than one multidrug-resistant organism during the same hospital stay was around 18% each year; the median length of their hospital stay was 39 days

Table 3

Characteristics of hospital stay of case-patients with reported hospital-acquired infection due to multidrug-resistant organism in Hungary, 2005–10 (n=6,845)

Characteristics of hospital stay	Number	Proportion of study population (%)
Ward at admission		
Surgical ward	2,523	36.9
Intensive care unit	2,082	30.4
Medical ward	1,754	25.6
Rehabilitation ward	256	3.7
Obstetrics and gynaecology ward	47	0.7
Paediatrics ward	41	0.6
Psychiatry ward	39	0.6
Other/mixed	38	0.6
Missing	65	1.0
Medical interventions and devices		
Prior surgical intervention	3,762	55.0
Urinary catheter	3,888	56.8
Peripheral catheter	3,711	54.2
Central venous catheter	2,706	39.5
Endotracheal tube	2,029	29.6
Parenteral nutrition	1,671	24.4
Tracheostomy	1,007	14.7
Gastrostomy	150	2.2
External ventricular drain	143	2.1

(IQR: 24–61 days). The median number of days elapsed between date of admission and date of first microbiological confirmation of an HAI due to a multidrug-resistant organism was 12 (IQR: 6–21 days).

The number of case-patients notified by primary, secondary, tertiary, specialised and chronic care/rehabilitation hospitals was 1,163 (17.0%), 3,099 (45.3%), 2,433 (35.5%), 104 (1.5%) and 46 (0.7%), respectively. Fourteen hospitals accounted for more than half (3,560 of 6,845) of all reported case-patients. Almost one third of all case-patients (1,950 of 6,845) were reported from hospitals located in the capital city, Budapest.

In Table 3, data on hospital stay (ward at admission, medical procedures and devices applied) are reported. Among surgical specialties, the most frequently reported wards were general surgery (40.7%), traumatology (24.7%) and urology (11.5%), and among medical specialties general internal medicine (46.8%), haematology-oncology (12.1%) and infectious diseases (9.7%). Fifty-five per cent of case-patients underwent prior surgical intervention, most commonly gastrointestinal and liver surgery (24.4%, excluding transplantations), orthopedic surgery (19.0%), neurosurgery (5.1%) and head and neck surgery (4.6%).

Case-patients with prior surgery had a lower prevalence of cardiovascular disease (41% versus 47%, p<0.001), chronic respiratory disease (11% versus 21%, p<0.001) and chronic kidney disease (5% versus 11%, p<0.001) compared to those without. No difference was found in age and sex distribution between the two groups. Among case-patients who underwent prior surgery the most common types of HAI were 54.6% surgical site infection (SSI), 9.7% bloodstream infection and 9.6% urinary tract infection (UTI). The most frequent types of infection among those without prior surgery were bloodstream infection (21.9%), UTI (17.2%) and pneumonia (13.9%).

Information on the outcome during the current hospital stay was available for 6,388 case-patients (93.3%). Of them, 2,772 (43.4%) recovered, 1,470 (23.0%) were transferred to another hospital, and 2,146 (33.6%) died. Patients infected with multidrug-resistant *P. aeruginosa* and *A. baumannii* had the highest case-fatality (43.8% and 40.2%, respectively); case fatality for MRSA infection was 32.6%. Patients infected with more than one multidrug-resistant organism had a case-fatality of 48.7%. Among all deaths, according to the reports, 14.2% were related directly or indirectly to the HAI.

Reported hospital-acquired infections

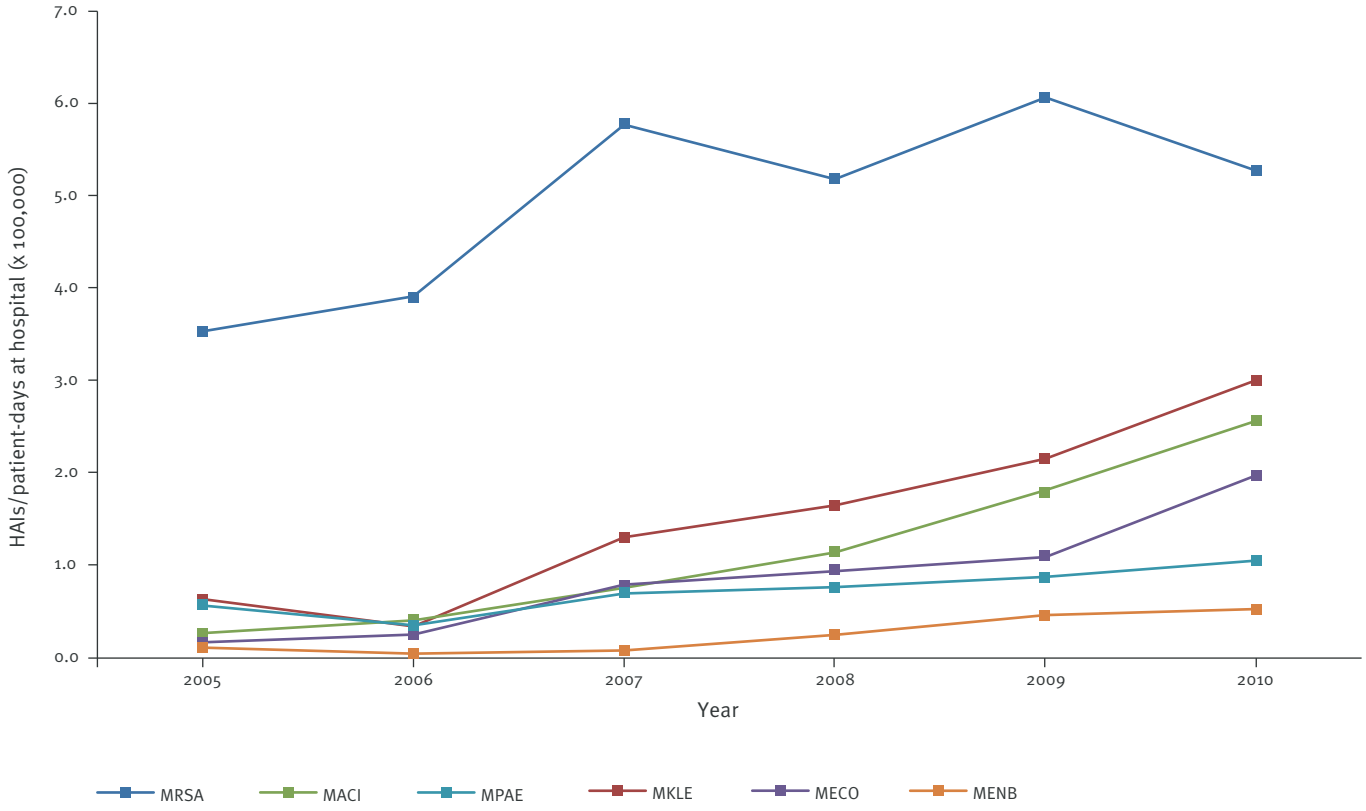
Of the 6,845 case-patients, 5,482 (80.1%) were infected with one multidrug-resistant organism at one anatomical site, 1,094 (16.0%) with one multidrug-resistant organism at more than one anatomical site, 129 (1.9%) with more than one multidrug-resistant organism at one anatomical site, and 140 (2.0%) with more than one multidrug-resistant organism at more than one anatomical site. The overall number of individual HAIs reported was 8,732. The overall incidence of HAI due to multidrug-resistant organisms increased from 5.4 in 2005 to 14.7 per 100,000 patient-days in 2010. The overall yearly incidence (per 100,000 patient-days) of HAI in primary, secondary, tertiary, specialised and chronic care/rehabilitation hospitals was 9.4, 9.1, 11.2, 7.5 and 3.2, respectively.

MRSA was the most frequent single cause of HAI during the study period (n=4,477, 52.2%), but while MRSA numbers stabilised after 2007 (annual notifications were 471 in 2005, 826 in 2007 and 824 in 2010), notifications of all the other multidrug-resistant organisms kept increasing during 2005 to 2010 from 247 to 1,468. As a result, MRSA represented 65.6% and 36.0% of all HAIs in 2005 and 2010, respectively. Incidence rates of reported HAIs by type of multidrug-resistant organism (excluding vancomycin-resistant *Enterococcus* sp., cotrimoxazole-resistant *S. maltophilia* and intermediate vancomycin-resistant *S. aureus*, which never exceeded an annual incidence rate of 0.1 per 100,000 patient-days in any given year) are shown in Figure 1.

SSI and bloodstream infection were the two most frequently reported sites during the whole study period;

Figure 1

Annual incidence rates of reported hospital-acquired infections due to multidrug-resistant organisms in Hungary, 2005–10 (n=8,732)



HAI: healthcare-associated infection; MACI: multidrug-resistant *Acinetobacter baumannii*; MECO: multidrug-resistant *Escherichia coli*; MENB: multidrug-resistant *Enterobacter* sp.; MKLE: multidrug-resistant *Klebsiella* sp; MPAE: multidrug-resistant *Pseudomonas aeruginosa*; MRSA: methicillin-resistant *Staphylococcus aureus*.

yet their proportion among all reported HAIs due to multidrug-resistant organisms decreased from 31.9% to 25.1% and from 25.9% to 21.7%, respectively, from 2005 to 2010. The proportion of reported urinary tract infections increased from 7.7% in 2005 to 19.3% in 2010.

Considerable differences were found in the distribution of the type of infections by multidrug-resistant organism (Figure 2). MRSA was the most frequently reported multidrug-resistant organism for all sites of infection in 2010 except for urinary tract and lower respiratory tract (Figure 3). However, the proportion of MRSA as cause of HAI decreased at each site of infection between 2005 and 2010, while an increase was seen in the proportion of multidrug-resistant *A. baumannii* (at all infection sites, except for urinary tract), *E. coli* (particularly bloodstream and urinary tract infections) and *Klebsiella* sp. (particularly surgical site and soft tissue infections).

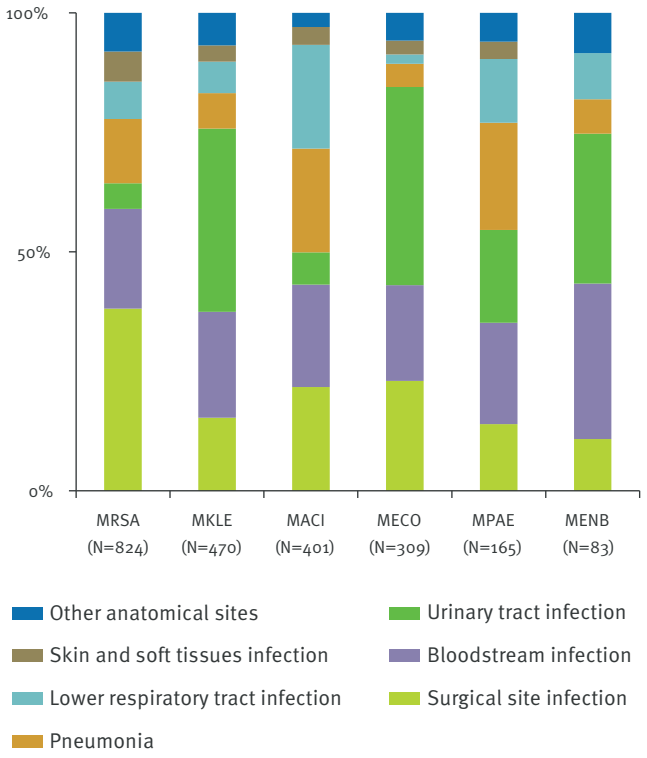
Discussion

The coverage of Hungarian hospitals by the NNSR has constantly grown over the years. Although less than half of all hospitals notified at least one infection due to multidrug-resistant organisms in 2010, these healthcare institutions accounted for the vast majority of hospitalisations and patient-days in the country during that year. Efforts to further expand the coverage of the surveillance system should focus on those hospitals not currently reporting: mainly smaller facilities and chronic care hospitals.

The proportion of reports sent by primary, specialised and chronic care/rehabilitation hospitals was lower than their relative proportion of overall number of acute and chronic beds in Hungary. The opposite was observed for tertiary-level hospitals, while no difference was found for secondary-level hospitals. Varying compliance with reporting, case-mix of patients and presence or absence of high-risk specialties are the most plausible explanations for these differences.

Figure 2

Most frequent types of reported hospital-acquired infections due to multidrug-resistant organisms in Hungary in 2010 (n=2,252)



MACI: multidrug-resistant *Acinetobacter baumannii*; MECO: multidrug-resistant *Escherichia coli*; MENB: multidrug-resistant *Enterobacter* sp.; MKLE: multidrug-resistant *Klebsiella* sp; MPAE: multidrug-resistant *Pseudomonas aeruginosa*; MRSA: meticillin-resistant *Staphylococcus aureus*.

Surgical departments were the most frequent hospital wards concerned, and further investigations are needed to disentangle the possible impact of parallel surveillance activities linked to the SSI module of the NNSR, and specific issues in perioperative care. ICUs were the second in line which is likely due to the presence of high-risk patients, better patient monitoring, including higher frequency of sampling and more timely microbiological diagnosis. Similarly, an influence of the dedicated ICU surveillance module cannot be excluded. A more in-depth description should assess differences by region, individual hospitals and ward types.

The population of case-patients affected by HAI due to multidrug-resistant organisms was characterised by old age at admission, a high prevalence of comorbidities, and a large proportion of prior surgical interventions and indwelling medical devices. All these are known risk factors for developing an HAI, either by impairing the immune system or by facilitating the entry of a multidrug-resistant organism through a medical procedure [21].

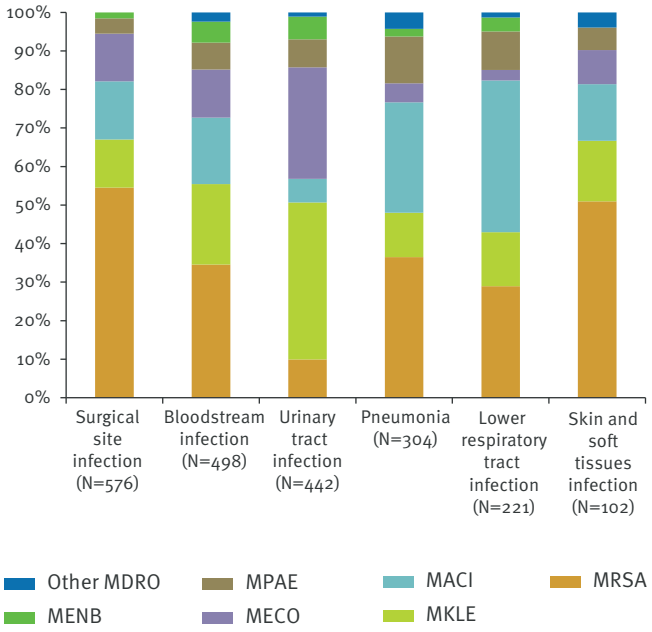
One third of the case-patients died during their hospitalisation. This figure is probably biased downwards considering that no information on final outcome is available for patients who were transferred to another hospital. According to the notification data, 14.2% of deaths could directly be ascribed to the HAI; however, no definition of HAI-related death exists in the NNSR to which reporting personnel must adhere.

MRSA was the most frequent cause of HAI at most anatomical sites except for UTIs and lower respiratory tract infections (LRTIs), exceeding 50% of all reported HAIs at surgical site as well as skin and soft tissues. Multidrug-resistant *A. baumannii* was the most frequent cause of LRTI, probably linked to ventilation and oral care practices. Extended-spectrum beta-lactamase (ESBL)-producing bacteria are increasingly causing UTI in inpatients and outpatients worldwide [22]. Also in Hungary, the proportion of reported UTIs due to multidrug-resistant organisms more than doubled over the study period; multidrug-resistant *K. pneumoniae* and multidrug-resistant *E. coli* accounted for approximately 70% of reports. This is most likely due to both the increased occurrence, spread and microbiological diagnoses of these pathogens. Improved awareness can also be a contributing factor since the issue has been extensively discussed at infection control meetings in Hungary since 2009, and a recommendation on the prevention of catheter-associated urinary tract infections was published in the same year.

The overall incidence of reported HAIs due to multidrug-resistant organisms in Hungary has shown a significant increase in recent years, but different tendencies are seen for Gram-positive and Gram-negative pathogens. Concerning Gram-positive pathogens, the incidence of MRSA infections has lately reached a plateau in some European countries [23] and in the United States [24]. Similarly in Hungary, MRSA incidence seemed to have stabilised around six infections per 100,000 patient-days over the last four years of the study period, when the reporting system was already established in major hospitals. In other words, at the beginning of surveillance, the continuously improving reporting of MRSA infections could have been the reason for the increase in observed incidence. After this initial period, we assume that the observed incidence approached the true incidence which has remained stable since then. Nonetheless, this figure is lower than those reported by most other European [3,25-27] and non-European countries [23,28,29]. For instance, the incidence of hospital-onset MRSA in Germany was 23 per 100,000 patient-days in 2009, approximately four times higher than the Hungarian result [3]. In Canada [28], the figure was 34.3 per 100,000 patient-days in 2007, around six times higher than in Hungary. The

Figure 3

Most frequently reported multidrug-resistant organisms by type of hospital-acquired infection in Hungary in 2010 (n=2,143)



MACI: multidrug-resistant *Acinetobacter baumannii*; MECO: multidrug-resistant *Escherichia coli*; MENB: multidrug-resistant *Enterobacter* sp.; MKLE: multidrug-resistant *Klebsiella* sp; MPAE: multidrug-resistant *Pseudomonas aeruginosa*; MRSA: meticillin-resistant *Staphylococcus aureus*.

number of reported cases per 100,000 population in 2010 was 8.8 in Norway [27] and 16.8 and Sweden [26], to be compared with a value of 8.24 in Hungary. How much this is due to underreporting or true differences in incidence is hard to establish; differences in the frequency of microbiological sampling, availability of microbiological services, structure of surveillance systems and general compliance with reporting may also play an important role.

Prevention and control of infections caused by meticillin/oxacillin resistant *S. aureus* has been facilitated by a national guidance available in Hungary since 2001. Due to improved knowledge over time, not only infection control practitioners, but also healthcare workers have become familiar with necessary actions to be taken in case of MRSA in hospitals. Nonetheless it serves as a warning that the proportion of *S. aureus* resistant to meticillin isolated from blood is currently around 30% in Hungary, with a significant increase seen between 2007 and 2010 [9].

In contrast to the incidence pattern of Gram-positive MRSA, the incidence of infections caused by multidrug-resistant Gram-negative organisms has continuously increased since the establishment of NNSR. The magnitude of this increase is striking (the ratio of incidences in 2010 versus 2005 is 11 for multidrug-resistant *E. coli*, 9 for multidrug-resistant *A. baumannii*, 6 for co-trimoxazole-resistant *S. maltophilia*, 5 for multidrug-resistant *Enterobacter* sp. and 5 for multidrug-resistant *Klebsiella* sp.), similarly to what has been observed in the EU [9] and also countries outside the EU [30-33] in the same time period. Therefore there appears to be a true increase in their incidence in Hungary, whereas the impact of improved reporting due to better awareness of the problem may obviously play a role, too. Recent surveillance results show that incidences of most multidrug-resistant organisms in 2011 are comparable to their respective values observed in 2010, except for multidrug-resistant *A. baumannii*, whose incidence further increased.

While extensive or inappropriate antimicrobial use may be the key factor in the striking emergence of multidrug-resistant Gram-negative organisms, their current successful spread, compared to MRSA, could also be attributed to particular microbiological characteristics (e.g. a successful decolonisation strategy is not available) and more efficient survival strategies through dissemination of acquired mechanisms of antibiotic resistance. Interestingly, Hungary is in the lower third of European countries regarding the quantity of outpatient antimicrobial consumption and had the lowest hospital use of antimicrobials for systemic use in 2009, nevertheless quality indicators of antibiotic use suggest issues need to be addressed both in ambulatory and hospital care [34-36]. We hypothesise that limited collecting of appropriate and early microbiological samples before initiating empiric antibiotic therapy, and therefore limited streamlining of antibiotic treatment based on culture results, may be the most relevant problem areas in practice.

A comprehensive evaluation of the National Nosocomial Surveillance System is planned in 2013 to assess its impact on the prevention and control of HAI in Hungary. At national level, surveillance results formed the basis for a decree issued by the Ministry of Health in 2009 (extended in its scope in 2012) on the prevention and control of HAI, surveillance of antimicrobial consumption and professional minimum requirements [37]. Governmental bodies and institutions with public health function were involved in the organisation of national campaigns linked to the European Antibiotic Awareness Day targeting both professionals and the public. National recommendations have already been issued for MRSA, VISA, ESBL-producing Gram-negative pathogens, VRE, and carbapenemase-producing *Enterobacteriaceae* [38-44]. However, partially as a reaction to the current epidemiological trends, a new comprehensive recommendation on prevention of infections caused by Gram-positive and emerging Gram-negative multidrug-resistant pathogens is being developed.

While national actions are essential, prevention efforts will have the desired effect only if existing guidelines and protocols are effectively and efficiently implemented in hospitals and followed in routine practice, tailored to the situation described by local surveillance results. Measures implemented at hospital level over the years also have to be reviewed and evaluated. Additional financial resources are needed for hospitals to be able to meet all legal requirements and provide continuous training for their personnel. Promotion of microbiological diagnosis would also be highly relevant. A number of obstacles should be addressed, for example healthcare reimbursement through diagnosis-related groups without separate budget for diagnostics and treatment, which may currently act as a disincentive to taking samples for microbiological tests.

In summary, our results highlight that, in addition to the efforts made until now, further actions are needed in Hungary, both at locally and nationally to reduce the burden of HAIs due to multidrug-resistant organisms.

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References

1. Ben-David D, Novikov I, Mermel LA. Are there differences in hospital cost between patients with nosocomial methicillin-resistant Staphylococcus aureus bloodstream infection and those with methicillin-susceptible Staphylococcus aureus bloodstream infection? Infect Control Hosp Epidemiol. 2009;30(5):453-60.
2. Centers for Disease Control and Prevention (CDC). National Healthcare Safety Network (NHSN). Atlanta: CDC. [Accessed: 19 Dec 2012]. Available from: http://www.cdc.gov/nhsn/
3. Nationales Referenzzentrum für Surveillance von nosokomialen Infektionen (NRZ) [German National Reference Center for the Surveillance of Nosocomial Infections]. MRSA-KISS Reference Data, 2009. Berlin: NRZ. [Accessed: 19 Dec 2012]. Available from: http://www.nrz-hygiene.de/en/surveillance/hospital-infection-surveillance-system/mrsa-kiss/
4. Geffers C, Gastmeier P. Nosocomial infections and multidrug-resistant organisms in Germany: epidemiological data from KISS (the Hospital Infection Surveillance System). Dtsch Arztebl Int. 2011;108(6):87-93.
5. Centres de Coordination de la Lutte contre les Infections Nosocomiales (CCLIN) [Infection Control Coordinating Centres]. Homepage. Nancy: CCLIN. [Accessed: 19 Dec 2012]. French. Available from : http://www.cclin-france.fr/
6. Carlet J, Astagneau P, Brun-Buisson C, Coignard B, Salomon V, Tran B, et al. French national program for prevention of healthcare associated infections and antimicrobial resistance, 1992-2008: positive trends, but perseverance needed. Infect Control Hosp Epidemiol. 2009;30(8):737-45.
7. Transatlantic Taskforce on Antimicrobial Resistance (TATFAR). Recommendations for future collaboration between the U.S. and EU. TATFAR; 2011. Available from: http://www.cdc.gov/drugresistance/pdf/tatfar-report.pdf
8. European Centre for Disease Prevention and Control. Annual Epidemiological Report 2011. Reporting on 2009 surveillance data and 2010 epidemic intelligence data. Stockholm: ECDC; 2011. Available from: http://www.ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=767
9. European Centre for Disease Prevention and Control (ECDC). Antimicrobial resistance surveillance in Europe 2010. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2011. Available from: http://ecdc.europa.eu/en/publications/Publications/1111_SUR_AMR_data.pdf.pdf
10. Vatopoulos A. High rates of metallo-beta-lactamase-producing Klebsiella pneumoniae in Greece--a review of the current evidence. Euro Surveill. 2008;13(4):pii=8023. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8023
11. Durante-Mangoni E, Zarrilli R. Global spread of drug resistant Acinetobacter baumannii: molecular epidemiology and management of antimicrobial resistance. Future Microbiol. 2011; 6(4):407-22.
12. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008;36(5):309-32.
13. Országos Epidemiológiai Központ [National Center for Epidemiology]. Tájékoztató a Nemzeti Nosocomialis Surveillance Rendszer (NNSR) és a Nemzeti Bakteriológiai Surveillance (NBS) 2010. évi eredményeiről [Annual Reports of the National Surveillance System for Nosocomial Infections (NNSR) and the National Bacteriological Surveillance System (NBS), 2010] Epinfo. 2011;6. supplement. Hungarian. Available from: http://www.oek.hu/oek.web?to=839,1890&nid=964&pid=1&lang=hun
14. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing: Fifteenth Informational Supplement M100-S15. Wayne: CLSI; 2005.
15. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing: Sixteenth Informational Supplement M100-S16. CLSI Wayne: CLSI; 2006.
16. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing: Seventeenth Informational Supplement M100-S17. Wayne: CLSI; 2007.
17. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing: Eighteenth Informational Supplement M100-S18. Wayne: CLSI; 2008.
18. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing: Nineteenth Informational Supplement M100-S19. Wayne: CLSI; 2009.
19. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing: Twentieth Informational Supplement M100-S20. Wayne: CLSI; 2010.

20. Országos Egészségbiztosítási Pénztár [National Health Insurance Fund Administration of Hungary]. Kórházi Ágyszám- és Betegforgalmi Kimutatás. [Hospital beds and patient turnover account]. [Date of access: 19 Dec 2012] Hungarian. Available from http://www.gyogyinfok.hu/magyar/archiv.html
21. Puhto T, Ylipalosaari P, Ohtonen P, Syrjala H. Point prevalence and risk factors for healthcare-associated infections in primary healthcare wards. Infection. 2011;39(3):217-23.
22. Coque TM, Baquero F, Canton R. Increasing prevalence of ESBL-producing Enterobacteriaceae in Europe. Eurosurveill. 2008;13(47):pii=19044. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19044
23. Pearson A, Chronias A, Murray M. Voluntary and mandatory surveillance for methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-susceptible Staphylococcus aureus (MSSA) bacteraemia in England. J Antimicrob Chemother. 2009;64 Suppl 1:i11-7.
24. Kallen AJ, Mu Y, Bulens S, Reingold A, Petit S, Gershman K, et al. Health care-associated invasive MRSA infections, 2005-2008. JAMA. 2010;304(6):641-8.
25. Health Protection Agency (HPA). Quarterly epidemiological commentary: mandatory MRSA, MSSA and E. coli bacteraemia, and C.difficile infection data (up to July-September 2012). London: HPA; 13 Dec 2012. Available from: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1284473407318
26. Smittskyddsinstitutet (SMI) [Swedish Institute for Communicable Disease Control]. Statistik för meticillinresistenta gula stafylokocker (MRSA). [Statistics for meticillin-resistant Staphylococcus aureus (MRSA)) Swedish. Available from: http://www.smittskyddsinstitutet.se/statistik/meticillinresistenta-gula-stafylokocker-mrsa/
27. Elstrøm P, Kacelnik O, Bruun T, Iversen B, Hauge SH, Aavitsland P. Meticillin-resistant Staphylococcus aureus in Norway, a low-incidence country, 2006-2010. J Hosp Infect. 2012;80(1):36-40.
28. Simor AE, Gilbert NL, Gravel D, Mulvey MR, Bryce E, Loeb M, et al. Methicillin-resistant Staphylococcus aureus colonization or infection in Canada: National Surveillance and Changing Epidemiology, 1995-2007. Infect Control Hosp Epidemiol. 2010;31(4):348-56.
29. Lessa FC, Mu Y, Davies J, Murray M, Lillie M, Pearson A, et al. Comparison of incidence of bloodstream infection with methicillin-resistant Staphylococcus aureus between England and United States, 2006-2007. Clin Infect Dis. 2010;51(8):925-8.
30. Lautenbach E, Synnestvedt M, Weiner MG, Bilker WB, Vo L, Schein J, et al. Epidemiology and impact of imipenem resistance in Acinetobacter baumannii. Infect Control Hosp Epidemiol. 2009;30(12):1186-92.
31. Lautenbach E, Synnestvedt M, Weiner MG, Bilker WB, Vo L, Schein J, et al. Imipenem resistance in Pseudomonas aeruginosa: emergence, epidemiology, and impact on clinical and economic outcomes. Infect Control Hosp Epidemiol. 2010;31(1):47-53.
32. Ramsey AM, Zilberberg MD. Secular trends of hospitalization with vancomycin-resistant enterococcus infection in the United States, 2000-2006. Infect Control Hosp Epidemiol. 2009;30(2):184-6.
33. Lee K, Kim MN, Kim JS, Hong HL, Kang JO, Shin JH, et al. Further increases in carbapenem-, amikacin-, and fluoroquinolone-resistant isolates of Acinetobacter spp. and P. aeruginosa in Korea: KONSAR study 2009. Yonsei Med J. 2011;52(5):793-802.
34. European Surveillance of Antimicrobial Consumption (ESAC). ESAC Yearbook 2009. Antwerp: ESAC. [Accessed: 19 Dec 2012]. ISBN: 9789057283307. Available from: http://www.ecdc.europa.eu/en/activities/surveillance/ESAC-Net/publications/Pages/documents.aspx
35. Adriaenssens N, Coenen S, Versporten A, Muller A, Vankerckhoven V, Goossens H; ESAC Project Group. European Surveillance of Antimicrobial Consumption (ESAC): quality appraisal of antibiotic use in Europe. J Antimicrob Chemother. 2011;66Suppl 6:vi71-77. doi: 10.1093/jac/dkr459.
36. Benko R, Matuz M, Peto Z, Bogár L, Viola R, Doró P, et al. Variations and determinants of antibiotic consumption in Hungarian adult intensive care units. Pharmacoepidemiol Drug Saf. 2012;21(1):104-9.
37. 20/2009. (VI. 18.) EüM rendelet az egészségügyi ellátással összefüggő fertőzések megelőzéséről, e tevékenységek szakmai minimumfeltételeiről és felügyeletéről. [Decree of the Ministry of Health on prevention of healthcare-associated infections, related professional minimum requirements and control activities]. [Accessed: 18 Dec 2012]. Hungarian. Available from: http://www.complex.hu/jr/gen/hjegy_doc.cgi?docid=A0900020.EUM
38. Országos Epidemiológiai Központ [National Center for Epidemiology]. Módszertani levél a Methicillin/Oxacillin Rezisztens Staphylococcus Aureus (MRSA) fertőzések megelőzésére. [Methodological letter on the prevention of infections caused by meticillin/oxacillin-resistant Staphylococcus aureus (MRSA)].Epinfo. 2001;8(5. különszám). Hungarian. Available from: http://www.oek.hu/oek.web?nid=444&pid=2&to=16&lang=hun
39. Országos Epidemiológiai Központ [National Center for Epidemiology]. A széles spektrumú béta-laktamázokat termelő Gram-negatív baktériumok jelentősége és az általuk okozott nosocomialis járványok leküzdése. [The importance of extended-spectrum beta-lactamase producing Gram-negative bacteria and control of such nosocomial outbreaks]. Epinfo. 2002;30:349-52. Hungarian. Available from: http://www.oek.hu/oek.web?nid=1080&pid=1
40. Országos Epidemiológiai Központ [National Center for Epidemiology]. Vancomycin-rezisztens Enterococcus (VRE) fertőzések megelőzése az egészségügyi intézményekben. [Prevention of infections caused by vancomycin-resistant enterococci (VRE) in healthcare facilities]. Epinfo. 2004;42:522-26. Hungarian. Available from: http://www.oek.hu/oek.web?nid=1080&pid=1
41. Országos Epidemiológiai Központ [National Center for Epidemiology]. A multirezisztens kórokozók felügyelete az egészségügyi intézményekben. [Control of multidrug-resistant pathogens in healthcare facilities]. Epinfo. 2007;10-11:89-98. Hungarian. Available from: http://www.oek.hu/oek.web?nid=1080&pid=1
42. Országos Epidemiológiai Központ [National Center for Epidemiology]. Ajánlás a hVISA/VISA azonosítása esetén szükséges teendőkről és a kórokozó terjedésének megelőzését célzó infekciókontroll intézkedésekről. [Recommendations on actions required upon the detection of hVISA/VISA and on infection control measures to prevent its spread]. Epinfo. 2008;15:173-6. Hungarian. Available from: http://www.oek.hu/oek.web?to=1493,1494,1495,1480&nid=41&pid=8&lang=hun
43. Országos Epidemiológiai Központ [National Center for Epidemiology]. A S. aureus vancomycinnel szembeni rezisztenciája. [Vancomycin resistance of S. aureus]. Epinfo. 2008;15:177-9. Hungarian. Available from: http://www.oek.hu/oek.web?to=1493,1494,1495,1480&nid=41&pid=8&lang=hun
44. Országos Epidemiológiai Központ [National Center for Epidemiology]. Ajánlás a karbapenemáz-termelő Enterobacteriaceae törzsek azonosítására és terjedésük megelőzésére az egészségügyi intézményekben. [Recommendation on identification of carbapenemase-producing enterobacteriaceae strains and prevention of their spread in healthcare facilities]. Epinfo. 2011;47:541-50. Hungarian. Available from: http://www.oek.hu/oek.web?to=839,1866&nid=41&pid=11&lang=hun

Increased norovirus activity in Scotland in 2012 is associated with the emergence of a new norovirus GII.4 variant

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To the editor: Since late 2012, Scotland has seen a significant increase in norovirus activity and the norovirus season began earlier than usual [1]. The article by van Beek et al. published in last week's issue of *Eurosurveillance* described the emergence of a new variant of norovirus GII.4 (Sydney strain) in a number of countries [2]. To examine whether this was also the case in Scotland, we examined representative samples from norovirus outbreaks in hospitals submitted to the West of Scotland Specialist Virology Centre (WoSSVC) in Glasgow between 8 and 20 November 2012. This time period was chosen as it was after the point when the increased norovirus activity was first reported by Health Protection Scotland [1].

In the time period we examined, there were a total of 13 norovirus positive outbreaks reported by the WoSSVC, 12 were GII-positive and one was GI-positive [3]. We selected a representative sample from 10 of the 12 GII-positive outbreaks for this study (two GII outbreaks were not examined due to low Ct values in real-time PCR). The method used to carry out this analysis targets the ORF 2 gene and has been described previously [4].

The results show that nine of the 10 outbreaks investigated were caused by the Sydney GII.4 strain (Hu/GII.4/Sydney/NSW0514/2012/AU), i.e shared more than 99.5% homology with that strain in ORF2. The remaining outbreak was attributed to a GII.7 strain. As far as we are aware this is the first time this Sydney variant has been described in Scotland [5].

Most norovirus outbreaks world-wide are caused by variants of noroviruses belonging to the genogroup II genotype 4 lineage (GII.4) [6]. Compared to other noroviruses, those belonging to this lineage undergo an influenza-like antigenic drift (due to a combination of rapid replication, evolution and selection through herd immunity) which results in the selection of new pandemic variants [7]. The emergence of a new norovirus GII.4 pandemic variant occurs every two to three years and is often associated with an increase in disease activity [6,7]. For example, this has been the case in 2002 (Farmington Hills virus), 2004 (Hunter virus), 2006 (2006a/2006b viruses), 2007 (2006b virus) and 2010 (New Orleans virus). Since 2010, the predominant GII.4 variant in Scotland [5] and world-wide [8] has been the New Orleans strain.

As the emergence of a new GII.4 norovirus variant is often associated with increases in norovirus activity and the data presented here suggest that this may be the reason for the increase in norovirus activity seen in 2012.

There are limitations to our study. Firstly, we only looked at a small number of outbreaks reported to us at the beginning of the norovirus season. It is possible that, if we were to sequence subsequent samples, we may not see this same predominance. We plan to examine previous outbreaks including samples from the end of the 2011/12 season and subsequent outbreaks in 2012/13 in order to determine when this virus emerged in Scotland and whether it remains the predominant strain throughout 2013.

References

1. Increase in norovirus reports. Health Protection Scotland Weekly Report. 2012;46(2012/4721).Available from: http://www.documents.hps.scot.nhs.uk/ewr/pdf2012/1247.pdf
2. van Beek J, Ambert-Balay K, Botteldoorn N, Eden JS, Fonager J, Hewitt J, et al. Indications for worldwide increased norovirus activity associated with emergence of a new variant of genotype II.4, late 2012. Euro Surveill. 201;18(1):pii=20345. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20345
3. Gunson RN, Carman WF. Comparison of two real-time PCR method for diagnosis of norovirus infection in outbreak and community settings. J Clin Microbiol. 2005;43(4):2030-1.
4. Adamson WE, Gunson RN, Maclean A, Carman WF. Emergence of a new norovirus variant in Scotland in 2006. J Clin Microbiol. 2007;45(12):4058-60.
5. McAllister G, Holmes A, Garcia L, Cameron F, Cloy K, Danial J, et al. Molecular epidemiology of norovirus in Edinburgh healthcare facilities, Scotland 2007-2011. Epidemiol Infect. 2012;140(12):2273-81.
6. White PA, Eden JS, Hansman GS. Molecular epidemiology of noroviruses and sapoviruses and their role in Australian outbreaks of acute gastroenteritis. Microbiology Australia. 2012;33(2):70-3. Available from: http://journals.cambridgemedia.com.au/UserDir/CambridgeJournal/Articles/08white409.pdf
7. Bull RA, Eden JS, Rawlinson WD, White PA. Rapid evolution of pandemic noroviruses of the GII.4 lineage. PLoS Pathog. 2010;6(3):e1000831.
8. Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention. Updated Norovirus Outbreak Management and Disease Prevention Guidelines. MMWR Recomm Rep. 2011:60(RR-3):1-1

Letter to the editor: Ongoing outbreak of dengue type 1 in the Autonomous Region of Madeira, Portugal

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To the editor: We read with great interest the article by Sousa et al. [1] in *Eurosurveillance* on the recent *Aedes aegypti*-mediated dengue fever outbreak in the Portuguese autonomous small island of Madeira. An internationally coordinated response is indeed needed in view of the challenges posed not only by this outbreak, but also by outbreaks in other islands of similar size that share characteristics like a tourism-dependent economy and vulnerability to vector-borne diseases and where, in addition, the globally expanding *Ae. albopictus* may be the mosquito vector of dengue viruses [2]. In this letter, we wish to highlight some similarities with the situation in Mauritius.

Mauritius is another small island which has recently suffered from outbreaks of mosquito-borne viral infections. Like Madeira, Mauritius has an influx of tourists which makes it particularly vulnerable to the entry and development of these infections. The large epidemic outbreak of chikungunya which affected about 30% of the Mauritian population in 2006 was followed by a minor outbreak of dengue fever in 2009 [3]. *Ae. albopictus* was the suspected mosquito-vector for both these outbreaks. Currently, Mauritius has embarked on an Integrated Vector Management (IVM) [4] strategy as part of a prevention programme targeting a number of different moquito-borne diseases. With the decreasing recourse to insecticides, IVM provides an environmentally-friendly way for the control of mosquito populations which could be particularly applicable on small islands. The precepts of IVM are advocacy, social mobilisation and legislation, collaboration within the health sector and with other sectors, an integrated approach, evidence-based decision making, and capacity building [4].

The long-term response of Madeiran authorities to the threat of dengue fever include public awareness and participation in vector control activities, and research [5]. Comparatively, the Mauritius IVM strategy is strongly community-based with a projected decentralisation of vector surveillance activities to local communities via a process of empowerment through capacity building. The implementation of the strategy relies to a great extent on the mapping and optimisation of the resources (social, economic and others) needed to ensure community participation and the sustainability of this participation.

A number of caveats have been noticed in the implementation of IVM in Mauritius. These include a slow development of programme ownership at various levels, the reliance of communities on the ability of authorities to control outbreaks, the challenges in involving nuclear families in community-based projects, and delays in providing timely incentives to participants. Despite these caveats, IVM provides a strong framework for significantly reducing the risk of vector-borne infections such as dengue fever in Mauritius and in other small islands, provided that these caveats are dealt with in a timely manner.

References

1. Sousa CA, Clairouin M, Seixas G, Viveiros B, Novo MT, Silva AC, et al. Ongoing outbreak of dengue type 1 in the Autonomous Region of Madeira, Portugal: preliminary report. Euro Surveill. 2012;17(49):pii=20333. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20333
2. Reiter P. Yellow fever and dengue: a threat to Europe? Euro Surveill. 2010;15(10):pii=19509. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19509
3. Ramchurn SK, Moheeput K, Goorah SS. An analysis of a short-lived outbreak of dengue fever in Mauritius. Euro Surveill. 2009;14(34):pii=19314. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19314
4. World Health Organization (WHO): Global strategic framework for Integrated Vector Management. WHO document WHO/CDS/CPE/PVC/2004.10. Geneva: WHO; 2004. Available from: http://whqlibdoc.who.int/hq/2004/WHO_CDS_CPE_PVC_2004_10.pdf
5. Funchal avança com plano de combate à dengue. [Funchal moves forward with plan to fight dengue]. [Accessed 3 Jan 2013]. Portuguese. Available from: http://europe.openleech.org/index.php/component/k2/item/92463-robben-dacht-aan-stoppen.