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Autochthonous *Plasmodium vivax* malaria in Greece, 2011

K Danis (daniscostas@yahoo.com)[1], A Baka[1], A Lenglet[2], W Van Bortel[2], I Terzaki[1], M Tseroni[1], M Detsis[1], E Papanikolaou[1], A Balaska[1], S Gewehr[3], G Dougas[1], T Sideroglou[1], A Economopoulou[1], N Vakalis[4], S Tsiodras[1], S Bonovas[1], J Kremastinou[1]

1. Hellenic Centre for Disease Control and Prevention, Athens, Greece
2. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
3. Ecodevelopment S.A., Thessaloniki, Greece
4. National School of Public Health, Athens, Greece

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Between May and September 2011, twenty cases of *Plasmodium vivax* infection were reported in Greek citizens without reported travel history. The vast majority of those cases were confined to a delimited agricultural area of Evrotas, Lakonia. Conditions favouring locally acquired transmission of malaria, including the presence of competent vectors and migrants from endemic countries exist in Greece, underscoring the need for the development of an integrated preparedness and response plan for malaria prevention.

In 2011, 20 malaria cases without reported travel history to endemic countries have been notified as of 27 September from Evrotas, Lakonia and other geographical areas in Greece. We conducted an investigation to describe the geographical and temporal distribution of those cases, determine the affected area(s) and identify the potential source of infection, in order to better understand the transmission dynamics and implement targeted control measures.

Malaria was officially eliminated from Greece in 1974, following an intense national malaria eradication programme that was implemented between 1946 and 1960 [1]. Between 1975 and 2005 approximately 50 cases of malaria were reported annually, the vast majority of whom were imported cases from countries endemic for malaria. However, sporadic cases of mosquito-transmitted malaria that could have been acquired locally were reported in 1991, 1999 and 2000 [2]. Between 2005 and 2009, 171 cases of malaria were reported in Greece with a mean number of 34 cases per year [3]. Of those, 98% were in people that likely acquired the infection in endemic countries and 78% of all cases were in migrants from those countries.

Between early August and October 2009, a cluster of eight malaria cases was notified to the Hellenic Centre for Disease Control and Prevention (HCDCP) from the Evrotas area of Lakonia district, which is located in the Peloponnese in southern Greece. The first two cases were in migrant workers from Pakistan and Afghanistan who reportedly arrived in Greece during the summer of 2009 and who were working in the agricultural holdings in this particular area. Four of the remaining six cases belonged to the local Roma community and the other two were Greek citizens residing in the area. None of those six cases reported travel history to a malaria endemic country. In 2010, another malaria case was notified from the same area in Evrotas, who also belonged to the local Roma community. Additionally, two Roma children with malaria were notified in Viotia with disease onset on 25 and 30 August 2010 and an unclear travel history.

Surveillance of malaria in Greece

As part of the mandatory notification system, physicians in Greece are asked to notify HCDCP of all cases of laboratory-confirmed malaria infection. Enhanced surveillance is implemented in areas where domestic transmission is suspected (i.e. where no clear recent travel history to a malaria-endemic country can be established), by tracing the reported cases, visiting their homes and if possible conducting face-to-face interviews. When this is not possible, telephone interviews are conducted. Translators are used where appropriate. The case investigation form for enhanced surveillance gathers information on: detailed travel history, potential modes of transmission, clinical manifestations and treatment, previous malaria clinical episodes, possible onward transmission and household characteristics. In addition, active surveillance is implemented by maintaining weekly communication with local laboratories to enquire about recent diagnosed cases of malaria. Residents in the neighbourhoods surrounding the homes of suspected locally-acquired cases are asked to report febrile illnesses to the local public health office and to seek healthcare promptly.

Laboratory investigation

Light microscopic examination of Giemsa stained thick and thin blood smears is used to identify malaria

parasites in local laboratories. Blood smears are routinely analysed when general blood count tests identify anaemia, thrombocytopenia or other abnormal findings. All blood specimens positive for malaria and a number of negative ones are forwarded to the National Malaria Reference Laboratory (MRL) at the National School of Public Health in Athens to be validated with both microscopy and polymerase chain reaction (PCR). Rapid diagnostic antigen tests are not routinely used. Twenty per cent of positive samples are being genotyped at present.

Entomological investigation

Following the 2010 large outbreak of West Nile Virus infection in Greece [4], a study on vector distribution and mapping of risk areas was carried out. The adult mosquito population is monitored using CO_2 or CO_2-light traps at permanent sampling stations that are collected every 14 days. Several additional traps were used at locations of suspected malaria transmission in order to detect *Anopheles* mosquitoes. Collected specimens were counted and morphologically identified.

Situation in 2011

Epidemiological and clinical findings

Up to 27 September 2011, the HCDCP has received reports of 20 cases of *P. vivax* infection in Greek citizens who did not report travel to an endemic country. The majority of those cases (n=14) reside in the agricultural area of Evrotas, Lakonia district (Table, Figure 1). The remaining six Greek cases were reported from four other prefectures, namely Eastern Attiki (n=2), Evia (n=2), Viotia (n=1), and Larissa (n=1). From the area of Evrotas were further reported 16 cases of *P. vivax* infection in migrant workers from endemic countries (mainly from Pakistan) for whom no clear malaria importation status can be determined. In addition, two Romanian workers who had been working and living in the area of Evrotas developed symptoms in July 2011 and were diagnosed with *P. vivax* infection upon their return to Romania [5]. These two cases are not included in further analysis because not all the epidemiological information is available. All 36 cases have been confirmed as *P. vivax* infections, by both microscopy and PCR at the MRL. None of the cases had a history of recent blood transfusion or tissue/organ transplantation.

The first case from Evrotas reported disease onset on 23 May 2011 (Figure 2). An increasing number of cases residing in Evrotas area was observed during September (weeks 35-37). At the time of publication of this report, the outbreak is still ongoing.

The age distribution of the 36 reported cases ranged from 1.5-79 years (median: 36 years). The median age of migrant cases (24 years; range 15-55 years) was significantly lower ($p<0.001$) than of Greek cases (47 years; range 1.5-79 years), possibly reflecting the different age distributions of the two population groups. Seven of the Greek cases were female. As the majority of the migrant worker community is male, women with *P. vivax* infection were not reported among migrants.

Fever was reported as the main symptom by all cases, followed by splenomegaly (n=14) and anaemia (n=14). Three cases had central nervous symptom manifestations. All cases were hospitalised; one was admitted to an intensive care unit and has recovered fully. To date, there has been one fatality in an elderly male case from Evrotas area who had several underlying medical conditions, including cardiac insufficiency, arrhythmias and chronic obstructive pulmonary disease, and developed acute respiratory distress syndrome. This is the first death associated with *P. vivax* infection in the last three years in Greece. All other cases have fully recovered.

Almost all cases but three who were prescribed mefloquine and primaquine, received the current treatment regimen for uncomplicated *P. vivax* infection according to the national guidelines [6], which is three-day chloroquine treatment followed by 14-day primaquine treatment. Some cases in Lakonia received the alternative weekly primaquine outpatient regimen (higher dose than the daily regimen) for eight weeks, to achieve a higher compliance rate. Only one case among the reported 36 cases had glucose-6-phosphate dehydrogenase deficiency and did not receive primaquine.

When comparing the date of onset of symptoms to the date of hospitalisation (which is a proxy for receipt of anti-malaria treatment in Greece), the time period for all cases ranged between 0 and 27 days (median: 4 days). The median delay between symptom onset and treatment was shorter in the group of migrant workers (3 days; range 0-19 days) compared to Greek patients (4 days; range 2-27 days). However, this difference was not statistically significant (p= 0.12).

Entomological findings

Fifteen *Anopheles* species occur in Greece, of which five are considered as potential malaria vectors, namely *An. claviger*, *An. hyrcanus*, *An. maculipennis*, *An. sacharovi* and *An. superpictus* [7-9]. In the Evrotas area, *Anopheles* larvae were found in rivers, reed beds, the

Table

Reported *Plasmodium vivax* infections by district of residence, Greece, May–September 2011 (n=36)

District (region)	Number of cases
Lakonia (Peloponnese)	30[a]
Eastern Attiki (Attiki)	2
Evoia (Sterea Ellada)	2
Viotia (Sterea Ellada)	1
Larissa (Thessalia)	1
Total	**36[a]**

[a] This figure includes 16 cases in migrant workers from endemic countries residing in Evrotas area, Lakonia. The remaining cases are in Greek citizens without reported travel history to a malaria-endemic country.

Vivari lake and draining channels, but at very low densities. From 1 June to 15 September, 23 adult *Anopheles* specimens were collected from two sampling stations in the area, most of them *An. sacharovi* (n=21). Two specimens which were determined as *An. plumbeus* need further confirmation as they were not intact.

In the wetland area of Schinias national park in, Eastern Attiki, 19 mosquito species were identified, with *An. claviger* being the dominant *Anopheles* species in the area [9]. Other *Anopheles* species that were collected in that area included: *An. algeriensis*, *An. maculipennis s.s.*, *An. pseudopictus* and *An. sacharovi*. In the remaining affected areas in Greece, *Anopheles* species were identified, but their reported densities were often low. The most commonly identified species there were *An. sacharovi* and *An. claviger*.

Discussion

As of 27 September, 20 malaria cases were reported in Greece, affecting Greek citizens who did not have any reported history of travel to a country endemic for malaria. The vast majority of those cases were confined to a delimited geographical area in Evrotas, Lakonia, where a small number of malaria cases had already occurred in the previous two years. All other areas that reported cases were previously unaffected. In addition, 16 cases in migrant farm workers with unclear malaria importation status were notified in Evrotas. As none of these workers were documented, it is difficult to ascertain when they first arrived in Greece, where they travelled and worked and how long they had been residing in the area. Therefore, based on their self-reported travel, medical history and possibility of relapses, it cannot be determined conclusively whether they were non-imported cases.

Figure 1

Place of residence of reported malaria cases, Greece, May–September 2011 (n=36)

The affected area in Lakonia district is a plain agricultural area of about 20 km² in the delta of the Evrotas river. It was one of the historical hot spots of malaria transmission before elimination of the disease in Greece [10]. The area is characterised by freshwater springs, a complex network of 130 km of irrigation and drainage channels, the Evrotas river delta, the brackish Vivari lake, which seasonally dries out, and coastal wetlands. All other affected sites are located in agricultural areas, often closely associated with river deltas or wetland areas, providing favourable conditions for the presence and reproduction of potential malaria mosquito vectors. None of those areas are tourist destinations.

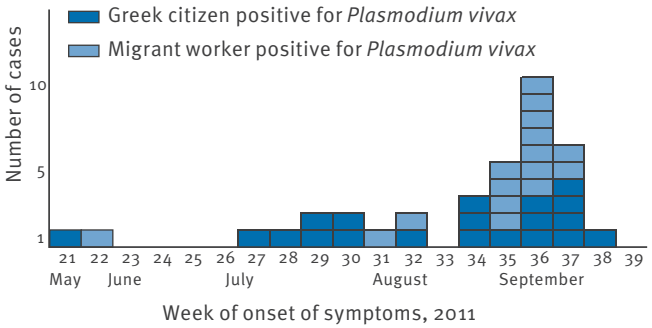
The affected area of Evrotas has a population of 4,485 and a large community of migrant farm workers (estimated between 2,000-4,000 depending on the period of the year), most of whom not registered [11]. Approximately 80% of all migrant workers in the area come from Pakistan, around 15% from Romania and the remaining from Morocco. The other affected areas have high numbers of migrant agricultural workers from malaria-endemic countries, predominantly from the Indian subcontinent.

Following the reports of malaria in Greece, the following control measures were introduced: Guidelines for the recognition, management and diagnosis of malaria were provided to healthcare professionals to improve their awareness of the disease. Interviewed patients were informed that persons in their close environment presenting with fever should get diagnosed as soon as possible. Support was provided to strengthen the laboratory capacity of local health centres in the affected areas to diagnose malaria. Surveillance of mosquitoes was enhanced in the affected areas. Guidance for blood and blood product safety according to European Union directives was implemented, including deferral from blood donation for a period of six months of persons residing or working in the affected areas within a radius of 10 km. Communication and health promotion activities were strengthened encouraging personal protection against mosquito bites in the general population. Intensified vector control activities were implemented using larviciding in breeding sites, ultra-low volume spraying in the affected villages and outdoor residual spraying in a zone of 50 meters around the houses of the cases, including backyards, neighbouring stockyards and other installations favourable for the resting of *Anopheles* adults. Furthermore, all households in the area have been visited fortnightly since 30 September to detect people with fever and to ensure early detection and prompt treatment of all malaria cases. During those visits, multidisciplinary health teams screened blood smears from all persons with fever of 37.5 °C or higher, current or reported during the previous 15 days.

Since the malaria eradication in 1974 in Greece, sporadic cases of probable local mosquito-borne transmission have occurred. Because of its climate, proximity of human and mosquito populations, and the increased number of migrants from malaria-endemic countries, Greece and possibly other Mediterranean countries might be vulnerable to the re-establishment of endemic malaria [12,13]. However, provided that current healthcare, mosquito control and public health infrastructures remain intact in Greece, the re-establishment of endemic areas for malaria remains unlikely. Nevertheless, conditions may exist for small clusters of locally acquired mosquito-borne transmission to occur sporadically. The development of an integrated preparedness and response plan for malaria that covers all aspects from surveillance, clinical management, laboratory diagnosis, entomological surveillance, vector control and communication is necessary to prevent transmission and control the disease on the long term. Such a plan should not only address the most affected area of Evrotas, Lakonia, but also other parts of Greece where ecological parameters are favourable for malaria transmission.

Figure 2

Reported cases of malaria by week of symptom onset and region of residence, Greece, May–September 2011 (n=36)



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Preliminary report on an ongoing outbreak of hepatitis A in Estonia, 2011

I Dontšenko (irina.dontsenko@terviseamet.ee)[1], N Kerbo[1], J Pullmann[2], S Plank[3], N Võželevskaja[4], K Kutsar[1]
1. Health Board, Tallinn, Estonia
2. Southern Service of the Health Board, Viljandi, Estonia
3. Southern Service of the Health Board, Tartu, Estonia
4. Northern Service of the Health Board, Tallinn, Estonia

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Since the beginning of August 2011, an outbreak of hepatitis A has been detected in Estonia. The majority of laboratory-confirmed cases (n=66) were notified between 4 August and 3 October 2011 and were linked to Viljandi county. The outbreak is still ongoing.

Outbreak description

Since the beginning of August 2011, an increase in the number of hepatitis A notifications has been observed in Estonia. The majority of cases were notified in Viljandi county or epidemiologically linked to Viljandi county.

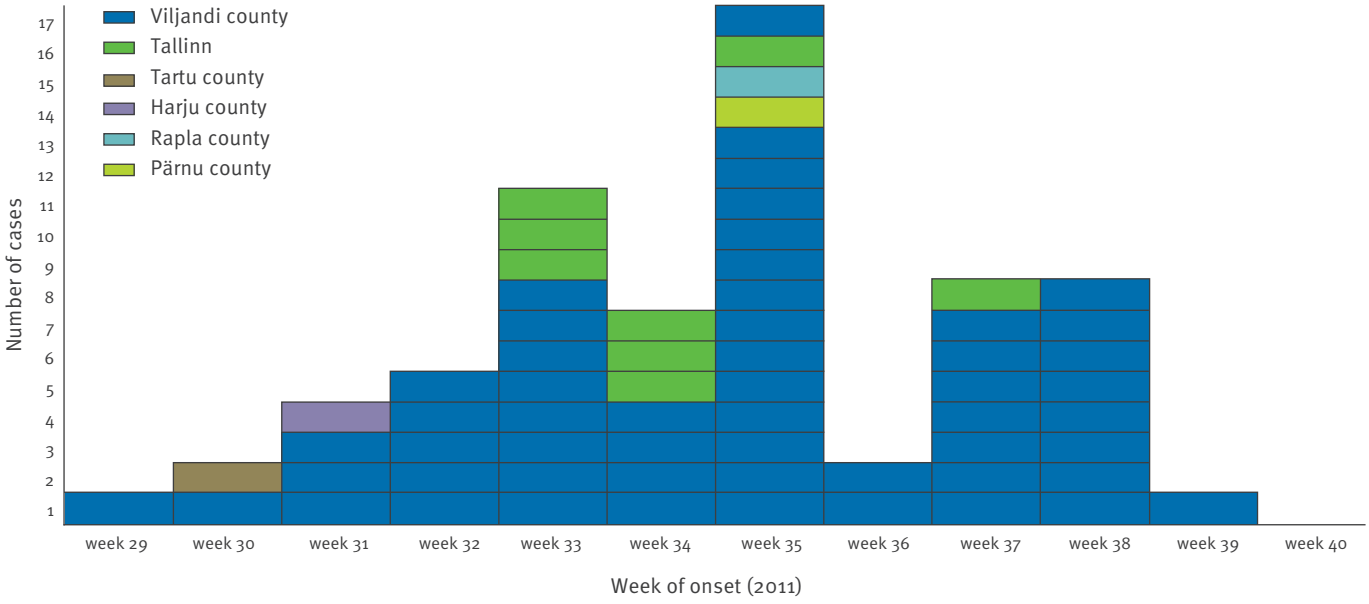
In the epidemiological investigation, a case was defined as a person with an acute illness including symptoms clinically compatible with hepatitis A, such as fever, fatigue, nausea, vomiting, abdominal pain, dark urine and jaundice, and positive for IgM anti-hepatitis A virus (HAV) identification. In addition, a case was either a resident of Viljandi county, or a resident from another county, who had visited Viljandi city or had had contact with a Viljandi county resident from 4 June 2011 onwards.

Between 4 August and 3 October 2011, 66 confirmed cases of hepatitis A, linked to Viljandi county were notified. This constituted the majority of 71 cases of hepatitis A notified during the same period in Estonia, the highest number of cases (n=51) was notified in September.

The first case notified on 4 August, had onset of symptoms on 24 July and the most recent case, who was notified on 3 October, had symptom onset on 29 September. The majority of cases had onset of symptoms in the period between 18 August and 3 September (33 cases) with peaks in week 33 and 35, suggesting person-to-person transmission. The epidemic curve of the 66 confirmed cases of hepatitis A by date of onset is shown in Figure 1.

Figure 1

Hepatitis A cases by week of symptom onset and county of residence, Estonia, 18 July–9 October (n=66)



Of a total of 66 cases, 54 were reported from Viljandi county, eight from Tallinn, and one from Tartu, Pärnu, Harju and Rapla counties, respectively. The 12 cases who were not from Viljandi county had either visited Viljandi county or had been in contact with a Viljandi city resident. For Viljandi county, 47 of the cases were Viljandi city residents and seven were part of the rural population.

The age and sex distribution of cases is shown in Figure 2.

The mean age was 33 years (range: 2–78 years), including 15 cases (23%) in children under 14 years of age. Men and women were equally affected.

Due to severe disease and not for isolation purposes, 39 persons were hospitalised with 12 patients in the age group 40–49 years old. Except for one patient, none of the patients had been vaccinated against hepatitis A.

Up to 3 October, no acute liver failures or deaths occurred.

Epidemiological situation of hepatitis A in Estonia

Hepatitis A is a notifiable disease in Estonia. The European Union hepatitis A case definition is used [1]. Laboratory-confirmed cases of hepatitis A are reported by the clinicians to the national surveillance system for communicable diseases NAKIS. Laboratory confirmation of acute HAV infection is performed based on IgM anti-HAV identification. Every confirmed case of hepatitis A is interviewed by the Health Board local service epidemiologist to identify possible common risk factors.

The overall incidence of hepatitis A in Estonia has decreased over the last 13 years from 68.0 per 100,000 population in 1998 to 0.4 per 100,000 in 2010 [2]. The decreasing trend has been attributed to continued improved sanitary and living conditions, including for example improvement of drinking water quality.

The last outbreak of hepatitis A in Estonia occurred in Lääne-Virumaa county in 1993. It was caused by contaminated water and affected 614 people [3].

During the period from 2006 to 2010, between 60% and 89% of hepatitis A cases in Estonia were imported. In 2008, hepatitis A outbreaks were notified in the Czech Republic, Slovakia and Latvia [4-6]. The same year, six cases of hepatitis A, notified in Estonia, were related to travel to Latvia, which also resulted in two cases in 2009

Between 1 January and 3 August 2011 only three cases of viral hepatitis A were notified, all travel related. Between 4 August and 3 October 2011, 71 confirmed cases of hepatitis A were reported in Estonia. Of those, three were travel-related with two cases related to travelling to India and one to Belarus.

Measures to contain the outbreak

The Health Board has prepared HAV prevention guidelines for hospitals, general practitioners, blood centres, food handlers, schools and pre-school establishments. The public is being kept regularly informed about the epidemiological situation via the Health Board website and the media. Increased hand hygiene is recommended for the whole population and for people travelling to affected countries [7].

Post-exposure vaccination of close contacts of confirmed cases within 14 days after the last contact, and traveller's vaccination is recommended [8]. It is of note that vaccination against hepatitis A is not included in the national immunisation schedule and is not free of charge. Vaccination against hepatitis A is only reimbursed by employers, for employees with an occupational risk of infection (for example healthcare workers).

The Health Board has recommended to temporarily stop blood donations from Viljandi county residents during this increase of hepatitis A incidence.

Figure 2

Hepatitis A cases linked to Viljandi county, by age and sex, hepatitis A outbreak, Estonia, 4 August–3 October 2011 (n=66)

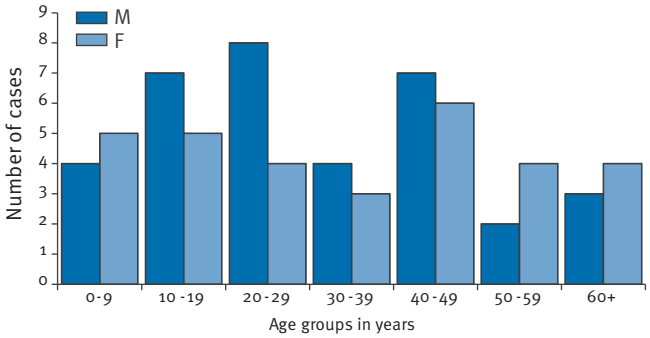
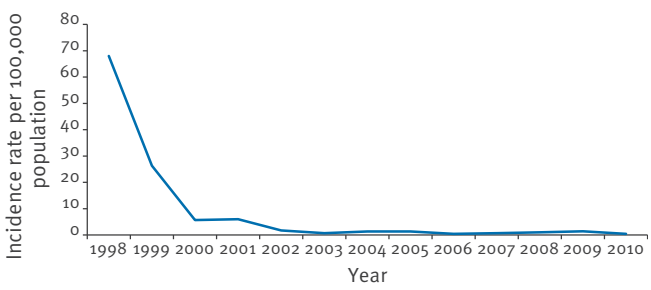


Figure 3

Annual incidence of notifications of hepatitis A per 100,000 population in Estonia, 1998–2010



Investigation to find the source of the outbreak

The Health Board has an agreement with the National Institute for Public Health and the Environment of the Netherlands (RIVM) for molecular sequencing. The results of this investigation will provide an opportunity to identify a potential source of infection and to compare the genotypes in this outbreak to those circulating in the previous years in Estonia and to those that are circulating in other countries at the present time.

Suspected modes of transmission in Viljandi are person-to-person transmission and environmental exposure. Drinking water quality and sanitation conditions in Viljandi city met the requirements of national legislative acts. Eighty per cent of citizens are served by a central water supply system based on deep wells and the rest of the citizens are supplied by shallow wells. There was no non-compliance of drinking water quality as well as no accident on the water supply system as well as waste water treatment plant. Therefore contaminated water was excluded as a possible vehicle. Based on veterinarian and epidemiological preliminary investigation results, there is no evidence that contaminated food could be the possible vehicle. The Health Board is planning to conduct a case-control study for cases linked to Viljandi to identify possible common risk factors.

Discussion

Hepatitis A continues to be one of the most frequently reported vaccine-preventable disease in the world [9]. The virus is present worldwide, and the risk of infection is inversely proportional to levels of sanitation and personal hygiene. With improved sanitation and hygiene, the age of infection shifts to older age groups and consequently the number of persons susceptible to the disease increases over time [10].

The current outbreak of hepatitis A in Estonia, affecting mainly adults over 20 years of age, can be partly explained by the high susceptibility of the population due to a reduced HAV circulation with consecutive lower immunity in the population in the past years that, in the absence of a national vaccination policy, has lead to an accumulation of susceptible individuals [10]. There is a higher risk of more severe disease when hepatitis A is acquired as an adult [9]. This can be relevant for outbreaks in settings where hepatitis A is not endemic. The fact that the biggest age group among hospitalised patients in the current outbreak was between 40 to 49 years old underlines this, however no deaths or acute liver failures were noted so far.

As neither the source of infection nor the mode of transmission have yet been identified, epidemiological investigations by the Health Board are still ongoing in collaboration with hospitals, general practitioners, the Veterinary and Food Board local service, the Ministry of education, the water supply company and the Viljandi county government.

The Health Board has stressed the significance of vaccination against hepatitis A as post-exposure prophylaxis. As HAV vaccination is not included in the national immunisation schedule and many people do not have economical means to cover vaccination expenses, the other main measure taken is to increase awareness of hand hygiene.

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Vibrio alginolyticus-associated wound infection acquired in British waters, Guernsey, July 2011

G D Reilly[1], C A Reilly[2], E G Smith[3], C Baker-Austin (craig.baker-austin@cefas.co.uk)[4]
1. Department of Dermatology, Princess Elizabeth Hospital, Guernsey
2. Barts and The London Medical School, London, United Kingdom
3. Health Protection Agency, Public Health Laboratory, Birmingham, West Midlands, United Kingdom
4. Centre for Environment Fisheries and Aquaculture Science, Weymouth, Dorset, United Kingdom

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In July 2011, a *Vibrio alginolyticus* infection was diagnosed in a woman from Guernsey in the Channel Islands, British Isles after sea bathing and application of a natural seaweed dressing to a pre-existing leg wound. Microbiological investigation confirmed *Vibrio* in the wound and the species of seaweed used for the dressing. The washing of open wounds in seawater and use of unsterilised seaweed dressings should be discouraged, particularly in individuals with underlying risk conditions.

Background

Vibrio alginolyticus is a halophilic (salt-tolerant) Gram-negative bacterium found naturally in temperate marine and estuarine environments. This species is recognised as a human pathogen, and the incidence of infection significantly increases during summer months [1]. *V. alginolyticus* is ubiquitous in seawater and tends to cause superficial wound and ear infections (otitis media and otitis externa) [2]. Most reports of *V. alginolyticus* wound infections result from exposure of cuts or abrasions to contaminated seawater. *V. alginolyticus*-associated infections may be resolved using appropriate antibiotics, however, very rarely these infections can progress to bacteraemia and necrotising fasciitis, particularly in the immunocompromised.

Case report

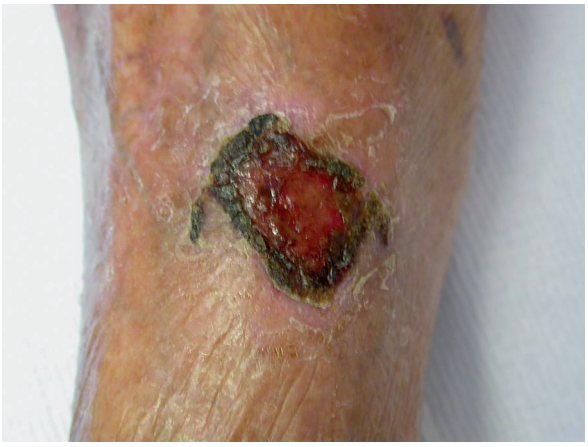
In July 2011, a woman in her 70s presented to the dermatology clinic in Guernsey in the Channel Isles, British Isles, with a non-healing infected wound on her lower leg. The patient was not receiving any medication, was otherwise healthy and had no past history of diabetes or other chronic conditions. Two weeks previously the patient had injured her leg on a plant pot in the garden. The patient continued her habit of swimming regularly in the sea off Guernsey and also cleaned the wound with a salt water solution made up at home and applied a seaweed dressing. The patient used a gel dressing which she had extracted from the receptacles of spiral wrack (*Fucus spiralis*), a seaweed collected locally from the beach at low tide, which was used to cover the wound under cling film. After two or three days the wound scabbed over and was left to heal. Ten days later the scab fell off whilst swimming in the sea. The wound reopened and she reapplied the dressing as before using seaweed gel under cling film for a further three days. As the wound was failing to heal, the patient presented to the clinic. On examination crusting erythema surrounding the wound was noted, indicative of an infection (Figure).

Laboratory analysis

A charcoal swab was taken for bacteriological culture, and this resulted in a pure growth of a Gram-negative bacterium. Based on colony morphology, tolerance to NaCl and case history, a pathogenic marine *Vibrio* was suspected, and a preliminary identification of *V. alginolyticus* was made after biochemical analysis using API 20E (Biomerieux, Marcy l'Etoile, France). The patient was treated with doxycycline (100 mg twice daily) for two weeks. At a subsequent follow up three weeks later the wound was completely healed.

Figure

Post-exposure aspect of leg wound, with crusting and surrounding erythema showing evidence of infection, Guernsey, June 2011



Microbiological analysis was subsequently performed on the isolated bacterial strain encompassing culture-based, molecular, and biochemical testing for unambiguous identification and characterisation. The bacterial cultures were subcultured on marine agar, thiosulfate citrate bile sucrose (TCBS) agar and chromID *Vibrio* agar (Biomerieux, Marcy l'Etoile, France) overnight at 30 °C and 37 °C. The distinctive morphology and colour of isolated colonies (yellow/orange on TCBS and chromID agar and cream colouration on marine agar), coupled to biochemical analysis (97.8% species-level confirmation), were indicative of *V. alginolyticus*. Ten single colonies of presumptive *V. alginolyticus* strains from each set of agar plates were subsequently analysed by PCR, using primers recognising two separate *V. alginolyticus* species-specific targets, collegenase and the DNA replication gene *gyrB*, essentially as previously described [2,4]. In both cases, positive results were obtained confirming that the bacterium isolated was a *V. alginolyticus* strain.

Analysis of the seaweed and seawater samples obtained from the beach where the patient had bathed was also performed. Seaweed samples (25 g mechanically disrupted in a laboratory blender with 25 ml of alkaline saline peptone water) were found positive for *V. alginolyticus* by PCR, however no *V. alginolyticus* strains were identified in analysed water.

Discussion and conclusions

V. alginolyticus wound infections are rare in Europe, with sporadic cases previously reported in the UK [5], the Netherlands [6] and Denmark [7]. Strikingly, as with other pathogenic *Vibrio* species, cases appear to be correlated with warm surface seawater temperatures, and it has been suggested that the number of infections may increase with warming of coastal regions attributed to climate change [8]. Although the summer of 2011 was not anomalously warm by recent standards, the infection corresponded with peak surface seawater temperatures (circa 18 °C) experienced at the end of June/beginning of July 2011. It is striking that these infections are now beginning to be reported in temperate and 'non-endemic' regions, such as in European waters. To our knowledge, this is the first *Vibrio* wound infection reported in the UK in over 20 years. Recent reports have suggested that the number of bathing water-associated *Vibrio* cases in northern Europe are increasing [8], and other studies in Europe have reported *Vibrio* wound infections acquired through the intentional washing of wounds in seawater [9]. Previous work has suggested that alginate gels derived from seaweed are highly absorbent and biodegradable dressings that can be successfully applied to cleanse a wide variety of secreting lesions, facilitating healing [10]. To date, little reliable data is available to demonstrate the safety of home-prepared alginate dressings used in this context. Here the dressing used probably represented an effective route of exposure of an open wound to pathogenic *Vibrio* species, initiating infection. Although the patient described here did not have underlying medical conditions, this report highlights the potential health risks associated with the practice of using of non-sterile seawater and seaweed for wound cleansing purposes. Given the recent increase in reports of more serious *Vibrio* wound infections in northern Europe [8], including cases associated with *V. vulnificus* and non-O1 *V. cholerae*, this practise should be discouraged, particularly in vulnerable groups such as the elderly and individuals with underlying risk conditions. Medical Practitioners should be aware and consider marine *Vibrio* species as a possible cause of non healing wound infections in this group of patients.

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The European gonococcal antimicrobial surveillance programme, 2009

M J Cole (michelle.cole@hpa.org.uk)[1], M Unemo[2], S Hoffmann[3], S A Chisholm[1], C A Ison[1], M J van de Laar [4]
1. Health Protection Agency, London, United Kingdom
2. Örebro University Hospital, Örebro, Sweden
3. Statens Serum Institut, Copenhagen, Denmark
4. European Centre for Disease Prevention and Control, Stockholm, Sweden

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Neisseria gonorrhoeae **antimicrobial susceptibility is monitored in the European Union (EU) and the European Economic Area (EEA) by the European gonococcal antimicrobial surveillance programme (Euro-GASP). Results from 17 EU/EEA Member States in 2009 showed that 5% of isolates had decreased susceptibility to cefixime, an upward trend in the minimum inhibitory concentrations of ceftriaxone and a high prevalence of resistance to ciprofloxacin (63%) and azithromycin (13%). These results are of public health value and highlight the need for healthcare professionals to be aware of possible cefixime treatment failures. Euro-GASP is being implemented in additional EU/EEA Member States to achieve greater representativeness. In addition, Euro-GASP aims to set up a system which will allow biannual reporting of antimicrobial resistance in the EU/EEA, with a transition from centralised towards decentralised testing, and will link epidemiological data to laboratory data to enhance surveillance. The benefits of this approach include more timely detection of emerging trends in gonococcal resistance across the EU/EEA and the provision of a robust evidence base for informing national and European guidelines for therapy.**

Introduction

Surveillance systems to detect the emergence and spread of *Neisseria gonorrhoeae* antimicrobial resistance (AMR) are essential to ensure patients receive the most appropriate therapy for gonorrhoea treatment. Over the years, the gonococcus has demonstrated the ability to develop resistance to antimicrobial drugs used for therapy [1,2], and the subsequent worldwide spread of resistant strains [3-8] has shown that the antimicrobial susceptibility of this bacterium needs to be monitored closely to inform public health control. The current European recommended therapy for gonorrhoea [9] consists of the extended-spectrum cephalosporins (ESCs) ceftriaxone and cefixime, which are also used in most other countries worldwide [1]. Decreased susceptibility to ESCs was first recognised in 2001 in Japan [10] and subsequent reports of worldwide spread [1,11,12], including reports from Europe [6,13] are becoming more common. The loss of ESCs for the treatment of gonorrhoea would be a major public health concern. The danger that gonorrhoea may become untreatable is real, particularly in light of treatment failure of cefixime first documented in Japan [14] and more recently in Norway and the United Kingdom [15,16] as well as the decreasing susceptibility to ceftriaxone globally [1,2].

Six countries within the European Union and the European Economic Area (EU/EEA) perform national surveillance of *N. gonorrhoeae* AMR and regularly publish their results [6,17-21]. A European approach is however useful to obtain valid and comparable data, to encompass countries without a surveillance system, and to monitor the movement of resistant strains throughout Europe. The European gonococcal antimicrobial surveillance programme (Euro-GASP) was established in 2004 [22] and continued until 2008 [7] as part of the European Commission-funded European surveillance of sexually transmitted infections (ESSTI) project. Their results from 2004 to 2008 [7] revealed a high mean prevalence of ciprofloxacin resistance (›30%) across the participating countries, a varying mean annual prevalence of azithromycin resistance (2–8%), along with high-level azithromycin resistance (›256 mg/L) in Scotland and Ireland. Of utmost concern was the upward trend in the minimum inhibitory concentration (MIC) of ceftriaxone [7]. These results, along with the lack of alternative treatment options, highlight the need for a pan-European and international approach monitoring the emergence and spread of gonococcal resistance to ensure the most appropriate therapies are administered and preserved.

In 2009, the European Centre for Disease Prevention and Control (ECDC) took over the responsibility of coordinating the enhanced surveillance of sexually transmitted infections (STI) in the EU/EEA. The European STI surveillance expert network was established, consisting of nominated experts in epidemiology and microbiology. The first European STI surveillance report on the period from 1990 to 2009 has been published recently

and showed that the number of gonorrhoea cases per 100,000 population exceeded five per 100,000 population in many European countries [23], a sign that gonorrhoea remains a public health problem also in the EU/EEA. The objectives of the enhanced STI surveillance in the EU/EEA include strengthening the laboratory diagnostics for bacterial STIs, and ECDC has launched and funds an STI microbiology project which focuses on the surveillance of gonococcal antimicrobial susceptibility (Euro-GASP). Its main purpose is to agree on a new protocol for a European gonococcal antimicrobial surveillance programme, including an external quality assessment (EQA) scheme, and to provide training in STI laboratory diagnostics. Euro-GASP, aims to provide susceptibility data for a range of therapeutically relevant antimicrobial drugs in a timely manner by reporting trends and developments in gonococcal antimicrobial resistance in the EU/EEA and by linking susceptibility data with epidemiological information.

This article summarises the first gonococcal susceptibility data generated from Euro-GASP in 2009, as published by ECDC [24].

Material and methods

Members of the European STI surveillance network were invited to participate in Euro-GASP during 2009. Seventeen EU/EEA Member States (Austria, Belgium, Denmark, France, Germany, Greece, Italy, Latvia, Malta, the Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom) agreed to participate and to collect isolates for susceptibility testing from a number of laboratories. Two participating countries collected specimens from laboratories with a comprehensive coverage of all diagnosed gonorrhoea in their country (Denmark and Sweden). Eight laboratories had good national coverage, defined as representations from all areas of the country but not every case of diagnosed gonorrhoea (Belgium, France, Greece, Latvia, Malta, Norway, Portugal and Spain). Seven laboratories had good coverage of a particular region of the country (Austria, Germany, Italy, the Netherlands, Slovakia, Slovenia and the United Kingdom).

Each country was asked to contribute 110 consecutive isolates of *N. gonorrhoeae* with the aim of retrieving 100 isolates from each country. Isolates were collected from 1 October 2009 until 110 isolates were collected, ending latest on 31 December 2009. Some countries (Austria, Germany, Greece, Italy, Latvia, Malta, Norway, Portugal and Slovenia) started collecting isolates before the start date, to compensate for a low collection rate. Isolates from the United Kingdom were collected during the collection period of the national gonococcal resistance to antimicrobials surveillance programme (GRASP) [6] in June and July 2009 as national isolates were not available outside of the GRASP collection period. Laboratories were requested to collect only one isolate per patient from those who were infected at multiple sites or at multiple times within a four week period; rectal followed by urethral specimens were preferred from males and cervical specimens from females. Pure cultures of *N. gonorrhoeae* were sent frozen on dry ice to one of three laboratories for susceptibility testing (Health Protection Agency (HPA), London, UK; Statens Serum Institut, Copenhagen, Denmark and Örebro University Hospital, Örebro, Sweden). Isolates were recovered from the frozen stock and confirmed to be *N. gonorrhoeae* by Gram staining, oxidase test, and Microtrak test (Trinity Biotech, Wicklow, Ireland).

The antibiotic susceptibility of the isolates was assessed using the agar dilution breakpoint technique for ciprofloxacin, azithromycin, and spectinomycin as previously described [7]. Susceptibility to gentamicin was determined by the full agar dilution technique as previously described [25], and isolates exhibiting an MIC to gentamicin of >8 mg/L were additionally tested by Etest (AB bioMérieux, Solna, Sweden). Furthermore, Etests were used for MIC determination of ceftriaxone and cefixime. Etests were also performed for azithromycin, i.e. if isolates displayed azithromycin resistance by the agar dilution breakpoint technique. World Health Organization (WHO) quality assurance and control strains (A, G, J, K, M, O and P) specifically chosen for gonococcal susceptibility testing were used for quality control [26]. All isolates were tested for penicillinase production using the chromogenic reagent Nitrocefin (Oxoid, Basingstoke, UK). Breakpoints, which are the MICs defined for determining category of resistance, are shown in Table 1.

Results

Over the 2009 collection period, 1,471 isolates were collected and 1,367 isolates were successfully recovered from the frozen cultures and confirmed to be *N. gonorrhoeae* (93% retrieval rate). A total of 1,366 isolates were included in the analysis after the removal of one duplicate isolate. The number of isolates tested from

Table 1

Neisseria gonorrhoeae breakpoints used to determine category of resistance, Euro-GASP, 2009

Antimicrobial	MIC breakpoint (mg/L)		
	R ≥	I	S ≤
Azithromycin	1	-	0.5
Cefixime	TBD		0.125[a]
Ceftriaxone	TBD		0.125[a]
Ciprofloxacin	1	0.12 - 0.5	0.06
Gentamicin	TBD		
Spectinomycin	128		64

I: intermediate; MIC: minimum inhibitory concentration; R: resistance; S: susceptible; TBD: to be determined.

European Committee on Antimicrobial Susceptibility Testing (EUCAST) [27] breakpoints were used, except for ciprofloxacin, and azithromycin intermediate resistance where breakpoints used in GRASP were adhered to [6].

[a] Strains with MIC >0.125mg/L were defined as having decreased susceptibility/resistance (appropriate laboratory and clinical correlates are lacking for evidence-based determination for this breakpoint).

each country varied from nine (Latvia) to 120 (United Kingdom) (Table 2).

Data from all countries were combined to determine the overall resistance rates to azithromycin, ciprofloxacin and penicillin (plasmid mediated high-level resistance) in 2009 (Table 2). Overall 63% of all isolates displayed resistance to ciprofloxacin, with a prevalence of ciprofloxacin resistance of more than 5% in any given country (Table 2). Azithromycin resistance was shown to be 13%, with the most frequently occurring MIC of azithromycin-resistant isolates being close to the breakpoint of 1.0 mg/L. None of the isolates displayed high-level resistance to azithromycin (>256 mg/L). High-level resistance to penicillin (penicillinase-producing *N. gonorrhoeae*) was seen in 12% of isolates, and no resistance to spectinomycin (>64 mg/L) was detected in 2009.

Five per cent (70/1,366) of the isolates displayed decreased susceptibility (>0.125 mg/L) to cefixime (Table 3, Figure 1). All 70 isolates additionally harboured resistance to ciprofloxacin. The decreased susceptibility to cefixime was detected in 10 countries, in five of which more than 5% of isolates had decreased susceptibility to cefixime (Table 3).

No decreased susceptibility to ceftriaxone (>0.125 mg/L) was detected in 2009 and the most frequently occurring (modal) MIC to ceftriaxone in the isolates was 0.008 mg/L (Figure 2).

The MIC distribution of gentamicin in European isolates from 2009 has previously been described; both the MIC_{50} and MIC_{90} of gentamicin was 8 mg/L with an MIC range of 1–16 mg/L [25].

Discussion

Five per cent of all *N. gonorrhoeae* isolates collected in the 17 countries had decreased susceptibility to cefixime. Cefixime was included in the list of antimicrobial drugs monitored by Euro-GASP for the first time in 2009, so it is not known if this proportion of 5% is an increase from previous years. Even though the majority of isolates (58%) showed low MICs (≤0.016 mg/L), it is of concern that isolates displaying higher MICs (>0.125 mg/L) exist. Even though the relationship between the MIC for cefixime and treatment failure remains poorly understood and appropriate resistance breakpoints are yet to be described, treatment failure could become an increasing problem in Europe if MICs continue to increase. Therefore all European countries that use cefixime for treatment should alert appropriate health professionals to monitor for treatment failure. Advisory

Table 2

Neisseria gonorrhoea resistance to azithromycin, ciprofloxacin, and high-level resistance to penicillin, and strains fully susceptible to all antimicrobial drugs, 17 EU/EEA countries, 2009 (n=1,366)

Country	Number of isolates tested[a]	Resistance			Fully susceptible
		Azithromycin n (%)	Ciprofloxacin n (%)	PPNG n (%)	
Austria	104	30 (29)	83 (80)	9 (9)	21 (20)
Belgium	110	16 (15)	74 (67)	24 (22)	32 (29)
Denmark	119	55 (46)	83 (70)	7 (6)	30 (25)
France	104	19 (18)	45 (43)	6 (6)	53 (51)
Germany	45	0	33 (73)	3 (7)	12 (27)
Greece	110	9 (8)	74 (67)	4 (4)	32 (29)
Italy	70	20 (29)	53 (76)	5 (7)	16 (23)
Latvia	9	0	1 (11)	0	8 (89)
Malta	22	1 (5)	20 (91)	0	0
The Netherlands	114	3 (3)	56 (49)	5 (4)	58 (51)
Norway	110	2 (2)	88 (80)	41 (37)	14 (13)
Portugal	79	0	27 (34)	13 (16)	46 (58)
Slovakia	15	1 (7)	15 (100)	1 (7)	0
Slovenia	24	2 (8)	19 (79)	3 (13)	3 (13)
Spain	103	6 (6)	67 (65)	7 (7)	33 (32)
Sweden	108	11 (10)	77 (71)	37 (34)	25 (23)
United Kingdom[b]	120	5 (4)	42 (35)	7 (6)	76 (63)
Total	**1,366**	**180 (13)**	**857 (63)**	**172 (13)**	**459 (34)**
95% CI		(11.4–15)	(60.2–65.3)	(10.8–14.4)	(31.1–36.1)

CI, confidence interval of the total % mean; EU/EEA: European Union and European Economic Area; PPNG: penicillinase-producing *Neisseria gonorrhoeae*.

[a] Number of isolates tested varied due to differences in test methodology, laboratory structure within each country and total number of reported gonorrhoea cases [23]

[b] 2009 isolates from the United Kingdom were only from England and Wales.

groups who recommend treatment options, should consider higher doses or alternative regimes [28]. The loss of cefixime as an oral treatment option for gonorrhoea across the EU/EEA may have severe implications because the use of the parenterally administered ceftriaxone is more expensive and there are currently no new alternative treatments.

Ceftriaxone continues to be an appropriate treatment for gonorrhoea in the EU/EEA as all tested isolates were susceptible. However the modal MIC of isolates to ceftriaxone has increased to 0.008 mg/L in 2009 compared with ≤0.002 mg/L in 2004 [22]. In addition, the proportion of isolates that display MICs of ≥0.094 mg/L for ceftriaxone has been increasing annually (2.9% in 2009). This upward trend and recent identification of ceftriaxone treatment failure for pharyngeal infection [29,30] make it clear that emerging resistance to ceftriaxone needs to be carefully monitored.

There is no overall trend in the azithromycin resistance of *N. gonorrhoeae* isolates: the level of azithromycin resistance increased from 2008 to 2009 (2% to 13%), but had decreased from 2007 to 2008 (7% to 2%) [7]. This is most probably due to the fact that the modal MIC of resistant isolates falls on a breakpoint, as previously described [7]. Azithromycin is not a recommended treatment for gonorrhoea in Europe, however it is important to continue monitoring for resistance as azithromycin may be a therapeutic option in particular situations or in combination therapy [31]. The high prevalence of ciprofloxacin resistance, previously reported by ESSTI [7,22], continued and further increased by 12% (51% to 63%) in 2009 in spite of changes to the European treatment guidelines [9] that recommend that ciprofloxacin should not be used as first line therapy, and that, together with azithromycin, it should not be used for empirical treatment, unless isolates are known to be susceptible or local resistance rates are known to be less than 5%.

The ECDC in close collaboration with the STI expert network has established Euro-GASP as a programme for sentinel surveillance of *N. gonorrhoeae* AMR across the EU/EEA. The programme aims to provide longitudinal robust data to inform treatment guidelines at this crucial time when gonorrhoea is becoming difficult to treat. Describing the prevalence of resistance or decreased

Table 3

Prevalence of decreased susceptibility to cefixime among *Neisseria gonorrhoea* isolates from 10 EU/EEA countries, 2009 (n=908)

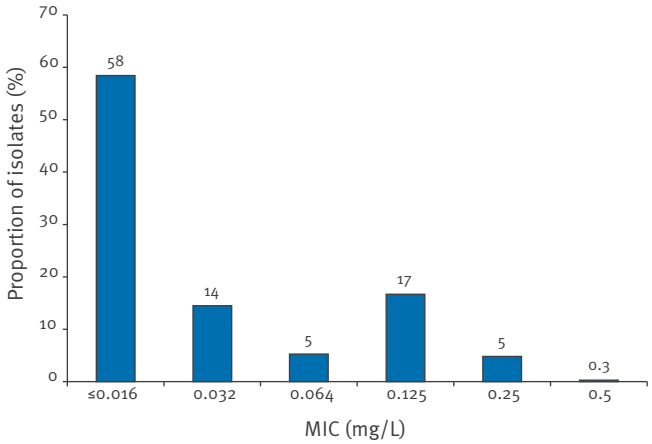
Country (total number of isolates tested)	Isolates with DS-cefixime Number (%)
Austria (104)	22 (21.2)
Italy (70)	13 (18.6)
Denmark (119)	18 (15.1)
Slovenia (24)	2 (8.3)
Belgium (110)	7 (6.4)
Sweden (108)	3 (2.8)
Germany (45)	1 (2.2)
France (104)	2 (1.9)
The Netherlands (114)	1 (0.9)
Norway (110)	1 (0.9)

DS: decreased susceptibility; EU/EEA: European Union and European Economic Area.

Overall level of decreased susceptibility to cefixime in the 17 countries participating in Euro-GASP: 5.1% (70/1,366). Seven countries are not included in the table as no isolates displaying decreased susceptibility to cefixime were detected.

Figure 1

Distribution of minimum inhibitory concentrations of *Neisseria gonorrhoea* isolates for cefixime, 17 EU/EEA countries, 2009 (n=1,366)

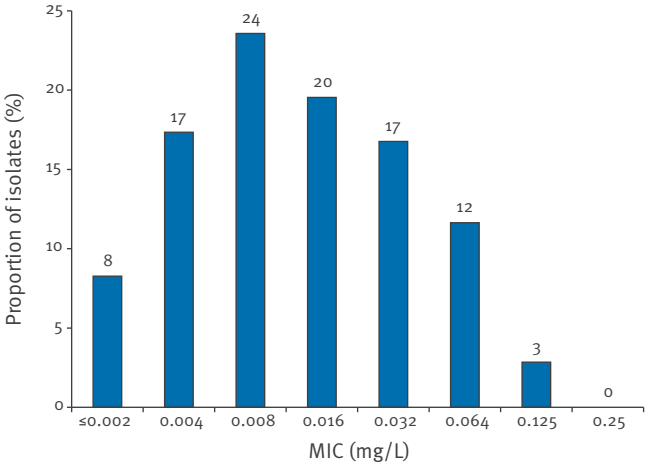


MIC: minimum inhibitory concentration.

Etest MIC values inbetween two-fold dilutions have been rounded up to next two-fold dilution.

Figure 2

Distribution of minimum inhibitory concentrations of *Neisseria gonorrhoea* isolates for ceftriaxone, 17 EU/EEA countries, 2009 (n=1,366)



MIC: minimum inhibitory concentration.

Etest MIC values inbetween two-fold dilutions have been rounded up to next two-fold dilution.

susceptibility across Europe by combining countries gives the study more power due to the larger sample size (n>1,000). However the low number of isolates collected from some countries limits the conclusions that can be drawn for individual countries. Increasing the number of isolates to obtain a representative sample is a priority for Euro-GASP. The reasons for low collection numbers vary from a lack of resources, and differences in clinical and diagnostic practices such as molecular testing, to a low number of gonorrhoea cases. Ultimately, the success of Euro-GASP depends upon the availability of *N. gonorrhoeae* cultures, and it is extremely important that the countries' capacity for collection of *N. gonorrhoeae* cultures is strengthened to obtain adequate numbers of isolates. Coverage will be extended to sample gonococcal isolates from as many EU/EEA countries as possible and a system of combined centralised and decentralised testing will be implemented to allow biannual reporting of AMR and improve timeliness of trend data. Furthermore, the surveillance of gonococcal AMR will be enhanced by linking laboratory data to appropriate epidemiological data. This will facilitate the future improvement of sample representativeness by providing information on the patients sampled in individual countries and the better understanding of risk factors associated with emerging resistance patterns. Euro-GASP will support countries in producing sustainable gonococcal resistance surveillance programmes by providing EQA and training. As resistance continues to emerge, the panel of antimicrobial agents tested will be constantly reviewed and may need to include new or old drugs. For example, gentamicin, a potential future treatment option (for use in single therapy or especially in combination therapy), has been included in Euro-GASP since 2009. An evaluation of the current programme is foreseen in 2011. The modernisation and development of Euro-GASP has shown how a surveillance system can remain agile to keep up with the ever changing, versatile gonococcus.

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